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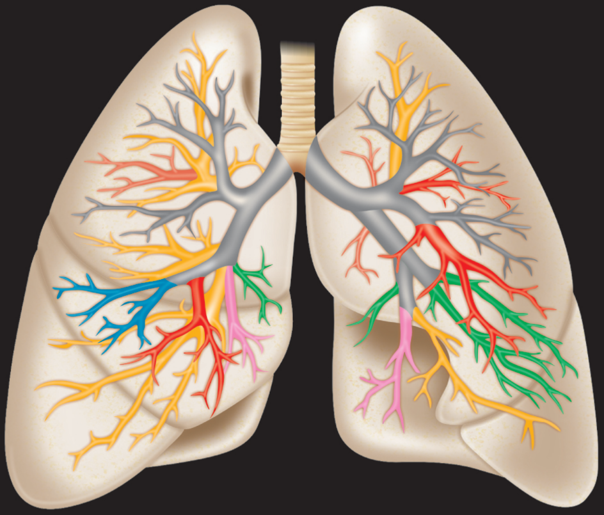

TEXTBOOK OF
PULMONARY & CRITICAL CARE MEDICINE

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Ashutosh N Aggarwal
Ritesh Agarwal

Foreword
Sidney Braman

With Archives of Rare Pictures

JAYPEE

Textbook of
Pulmonary and
Critical Care Medicine

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Pulmonary and Critical Care Medicine

Volume 1

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Textbook of Pulmonary and Critical Care Medicine

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Foreword

In reading through the *Textbook of Pulmonary and Critical Care Medicine* edited by Professor SK Jindal of the Postgraduate Institute of Medical Education and Research, Chandigarh, my thoughts drifted to a recent best-selling book authored by Thomas Friedman, titled, *The World is Flat: A Brief History of the Twenty-first Century*. The author argues that the world is shrinking from a size small to a size tiny and this has been accompanied by a flattening of the playing field. The dynamic forces of recent globalization give a unique quality to our flat world today—the power of individuals to collaborate and compete globally. Using this 21st century power and the tools of the flat world, namely the personal computer, the fiberoptic cable, and modern publishing house software, Professor Jindal has fostered an outstanding collaboration among experts spanning several continents. He has also produced a practical, authoritative and comprehensive resource for students, physicians in training and seasoned clinicians alike, that rivals any standard textbook on this subject and can compete on equal footing with other educational tools.

However, as globalization flattens the playing field, and countries leap to industrialization, cultural beliefs, natural resources, climate and geography have slowed the pace of development in many parts of the world. Poverty leads to malnutrition, homelessness, lack of education, and poor access to health care. Overcrowded cities and rural underdevelopment are other challenges that impact health in the various parts of the world. Moreover, epidemics of HIV, drug abuse and smoking addiction take a greater toll on the population. Yes, the world is flat, but the terrain is filled with mountains and valleys and local problems demand local solutions. And these local problems need to be explored and presented with a scholarly perspective. The *Textbook of Pulmonary and Critical Care Medicine* has successfully incorporated these sociodemographic factors into the subject matter.

The text is well-written and the chapters are carefully referenced with subjects found in all traditional pulmonary and critical care textbooks, e.g. airway diseases, interstitial lung disease, pleural disease, pulmonary neoplasia, pulmonary infection, sleep and critical care. There are several nontraditional sections as well that are practical and especially helpful to the practicing physician. These include a section on the symptom approach to lung disease, an overview of the pharmacologic agents used to treat lung disease, and a comprehensive review of methods in lung diagnosis from the simple history and physical examination to the latest complex tools of interventional pulmonology. The textbook is especially unique because of the abundance of illustrations, flow charts and tables. Their clarity and at times simplicity make them especially valuable for the novice. There are many radiographic and pathologic reproductions that are especially helpful.

The textbook also offers a unique exposure to the problems in many parts of the world. Tuberculosis, the "number one" treatable condition has been extensively covered; and special topics such as multi-drug resistance, directly observed therapy, TB prevention, nonpharmacologic approaches and extapulmonary tuberculosis are particularly relevant. Many countries are facing a growing burden of noncommunicable respiratory diseases. They have become the second leading cause of death after injuries, and their impact on indirect costs such as loss of work and home productivity is enormous. These problems are addressed and measures of prevention such as smoking cessation are included. Other special challenges including topics such as indoor and outdoor air pollution, climate change, poisoning with pesticides, snakebite toxicity, pulmonary manifestations of tropical infections and industrial accidents such as the tragedy seen in Bhopal, Madhya Pradesh, with methyl isocyanate, have been well covered.

What is most impressive about this textbook is how comprehensive and practical it is for the reader. Topics range from the history of respiratory medicine to the approach to end-of-life issues with critically ill patients. It is hard to think of a topic that is missing. While this textbook will have a special appeal and value to the physicians of the South-Asian continent, clinicians around the globe will benefit from Professor Jindal's extensive efforts.

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Preface

It was merely a quarter of a century ago when the specialty of Pulmonary Medicine was factually recognized as an important division of Medicine. Until then, the lung diseases were generally dismissed as tuberculosis, or nondescriptive pneumonias and infections. Most of the nontuberculous lung diseases remained either undiagnosed or unknown. Of course, several stalwarts of the sixties and seventies had clearly identified this deficiency and made efforts to define the pulmonary problems and plan their solutions.

It was in 1989 that the first independent, postdoctoral DM Fellowship Program in Pulmonary Medicine was started at Chandigarh. Subsequently, the program was expanded to include the Critical Care as an essential component of the DM training. In addition, there were several postgraduate MD and/or diploma courses in tuberculosis and chest diseases, and/or respiratory diseases at different medical colleges. Unfortunately, most of the postgraduate programs lacked in their curricula especially for nontuberculous diseases and other systemic disorders. Moreover, the on-hand training in diagnostic and treatment modalities had been highly inadequate in the postgraduate courses. It is rather enigmatic that we still continue to lack the dedicated thoracic surgery courses and texts in the various countries.

The increased importance and scope of respiratory and critical care medicine had also necessitated the need to develop the indigenous teaching and training materials including the texts with incorporation of local problems and possible solutions. Undeniably, the science is the same all over the world, but the experiences are different. Excellent texts and reference materials on the subject are available for long which continues to guide the students, the teachers and the practicing physicians. In the present literature, quite a few textbooks of pulmonary medicine have been published and continue to remain available. Ours is one more attempt in this direction to add to the existing literature on lung diseases available worldwide. This book contains contributions by approximately hundred international esteemed pulmonary medicine consultants and teachers.

There are, however, a few important additions in the present textbook. It is fairly comprehensive with contributions from several internationally eminent authors. It includes the basic principles as well as the recent advances related to different subjects. We have also attempted to incorporate allied clinical sciences relevant to the practice of the pulmonologist. A classical example is the critical care which forms an integral component of pulmonary medicine. It also incorporates tuberculosis, other pulmonary infections, environmental and occupational medicines, sleep disorders and general systemic diseases affecting the respiratory system in one or the other way. Although the critical care is relevant to most of the medical and surgical specialties, the pulmonologists have a more vested interest than other specialists. Assisted respiration which forms the core of most critical care lies in the primary domain of pulmonologists.

We have taken care not to forget the need to push forward and meet the goals of excellence in health care. The real test of merit of a book lies in its readership by the students and adoption of its recommendations in clinical practice. Hopefully, the material in the text will benefit a diverse category of people including internists, general physicians, pulmonologists, pediatricians, intensivists, anesthesiologists and others who need to handle patients with respiratory diseases and critical care.

SK Jindal

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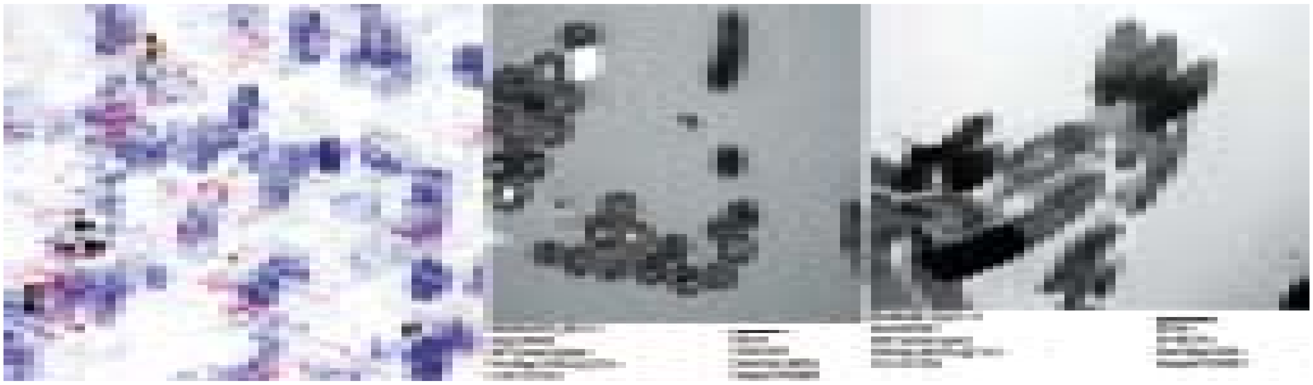

Fig. 1: Mycobacteria in the granuloma, engulfed by macrophages and its ultramicroscopic structure

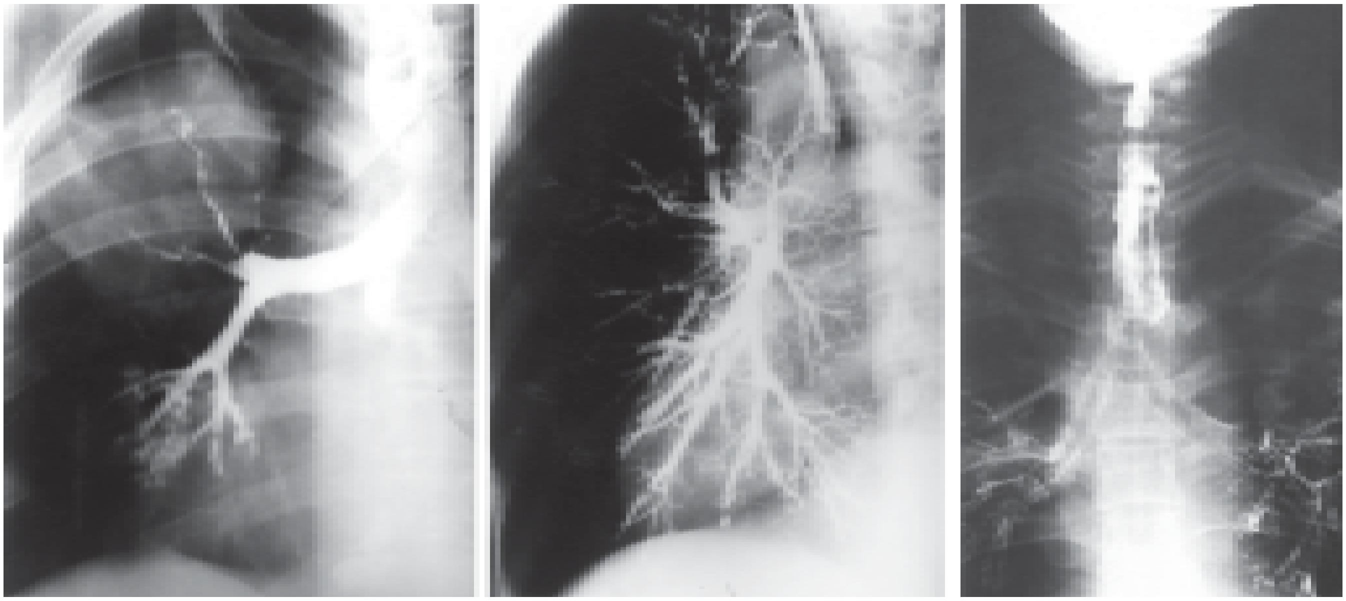

Fig. 2: Bronchography with instillation of a radiopaque dye (Dionosyl) with the help of a catheter was a common procedure to delineate the bronchial tree and diagnose lesions such as bronchial masses, bronchiectasis, fistulae and pouches. Endoscopic and scanning procedures have done away with old, gold-standard

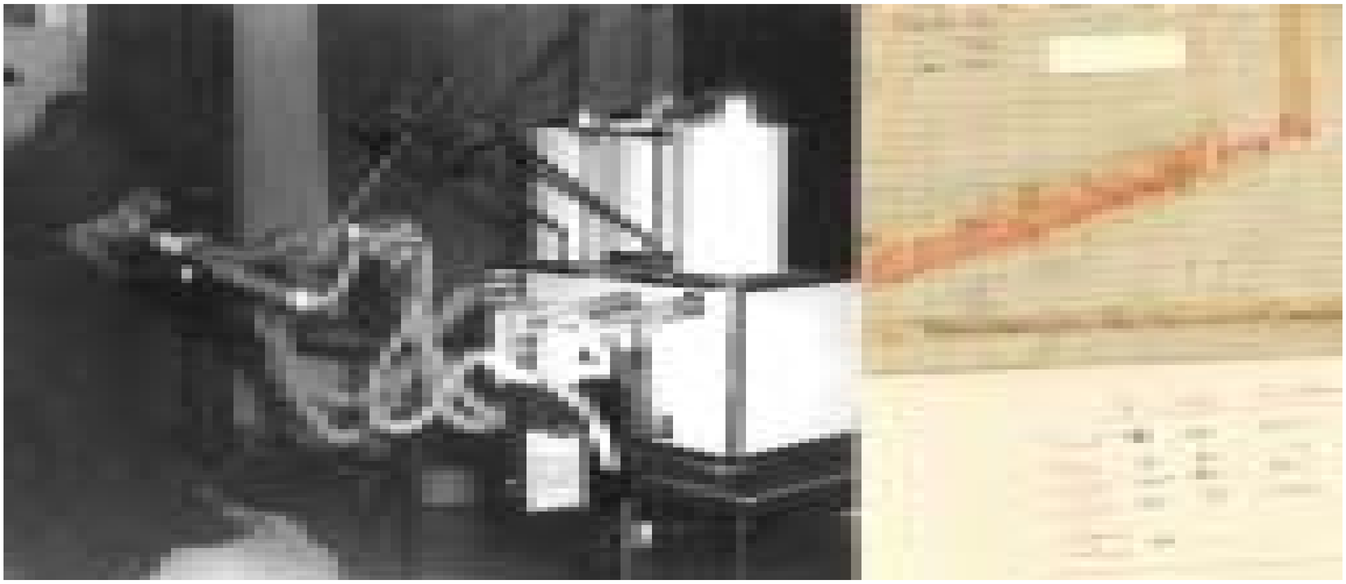

Fig. 3: Differential spirometry was used to assess the function of each lung separately. The figure demonstrates the nonfunctional left lung (Right). This was generally performed with the help of a double barrel, volume displacement spirometer (Left)

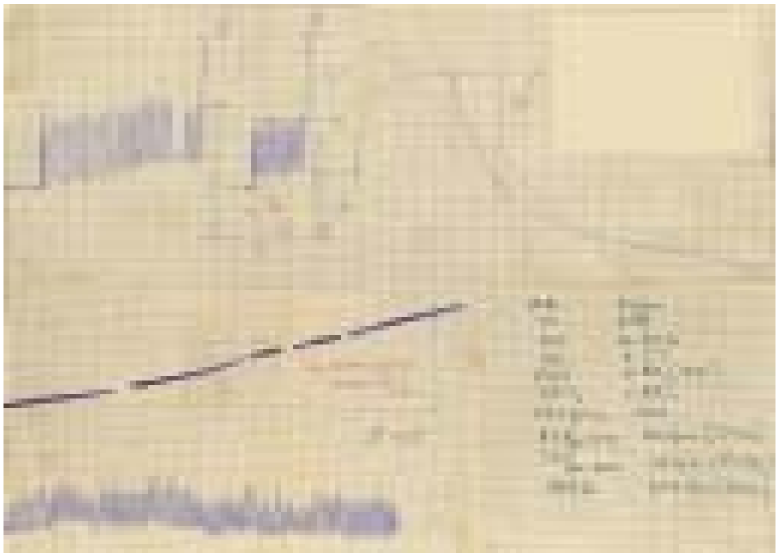

Fig. 4: Oxygen consumption obtained with the help of a spirometer by measuring the amount of oxygen required to replace the consumed volume, after absorption of CO_2 from the exhaled air using the formula:

$$\text{Oxygen consumption} = VC \times FiO_2 - FeO_2$$

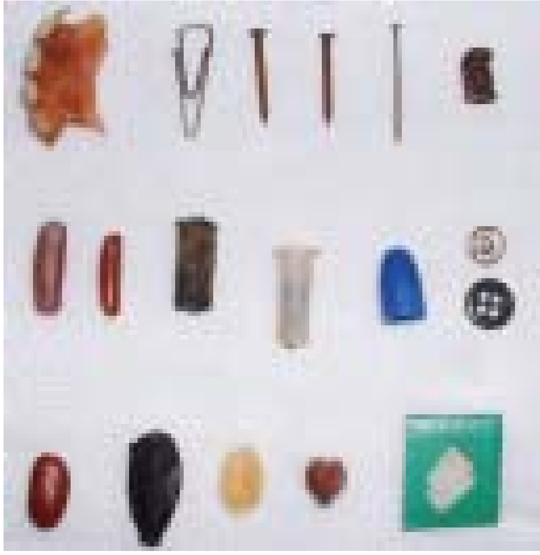

Fig. 5: Some of the foreign bodies recovered from the tracheobronchial tree (mostly, with the help of fiberoptic bronchoscopy)

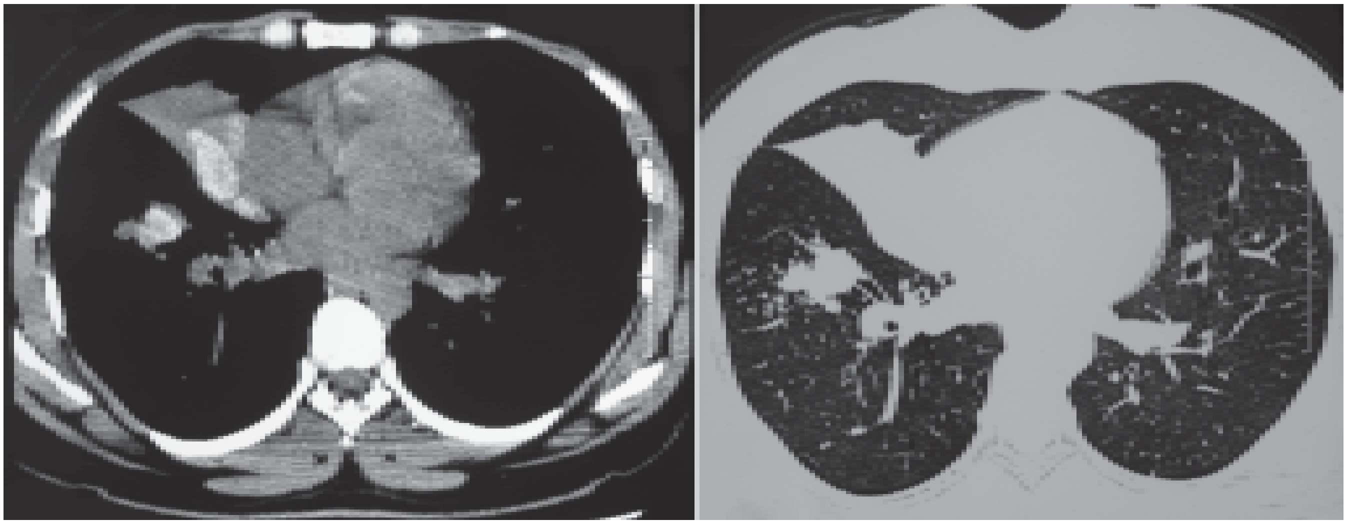

Fig. 6: Presence of high attenuation mucus in a patient with allergic bronchopulmonary aspergillosis. The mucus is denser than the paraspinal skeletal muscle

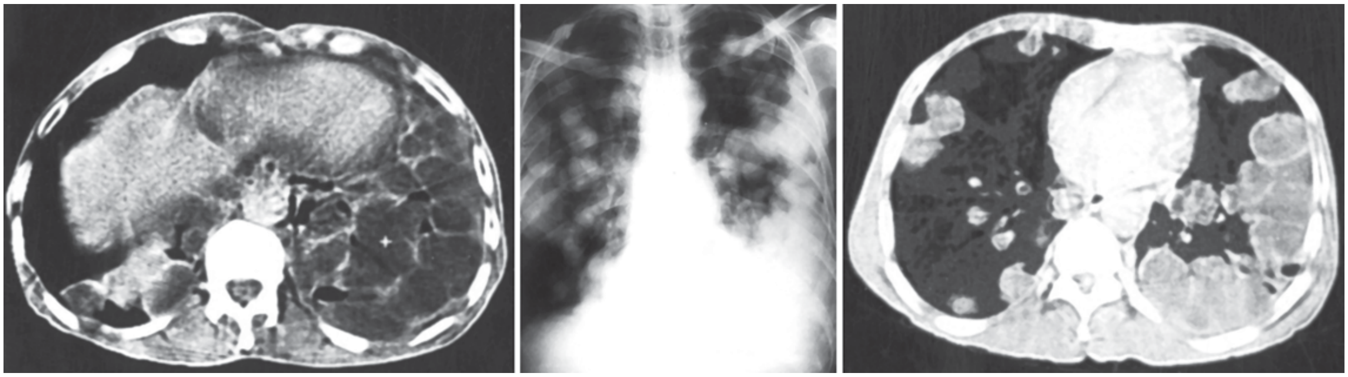

Fig. 7: Radiography in a patient with multiple hydatid cysts

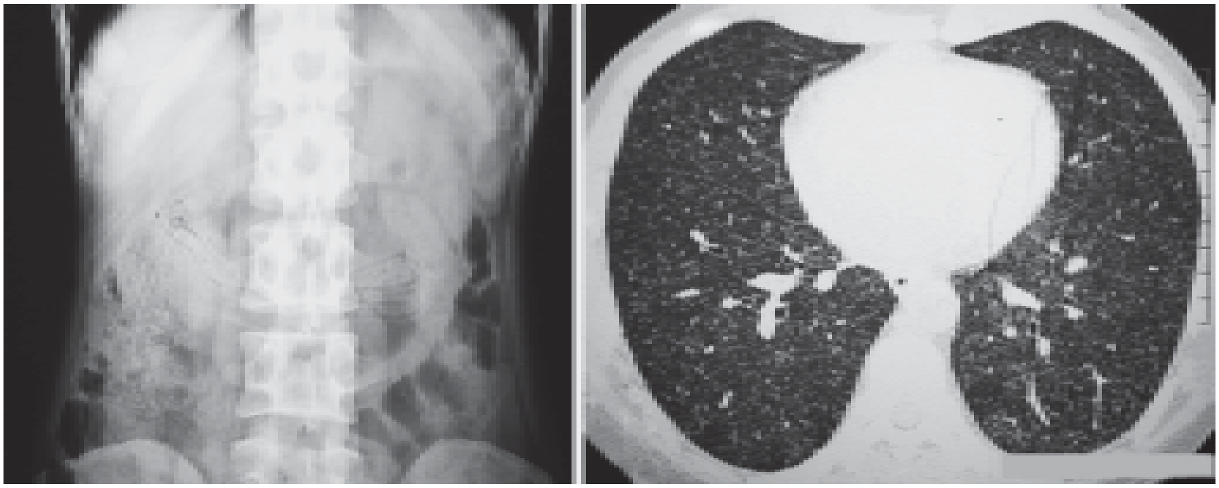

Fig. 8: A case of Loeffler's syndrome caused by intestinal round worms. Abdominal X-ray shows the presence of intra-abdominal worms. High-resolution CT of the chest demonstrates ground glass opacities and centrilobular nodules secondary to eosinophilic pneumonia

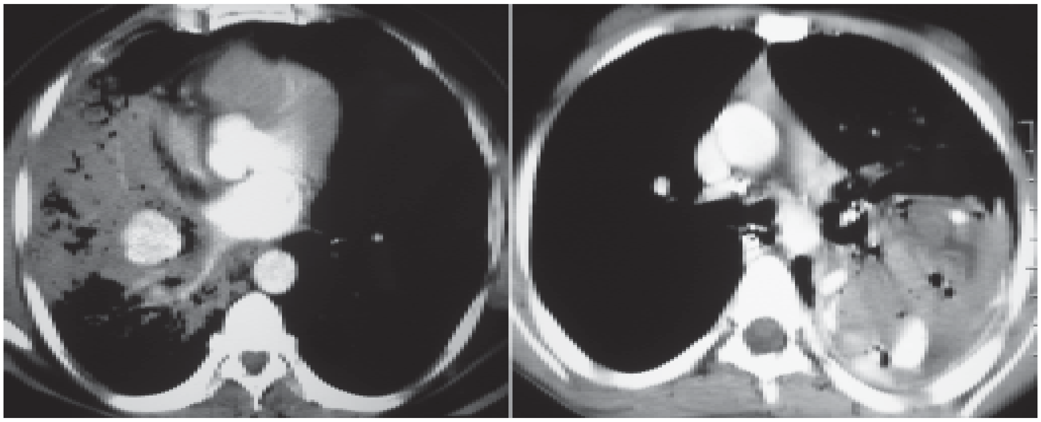

Fig. 9: Contrast-enhanced CTs of two different patients with community acquired necrotizing pneumonia demonstrating an uncommon but potentially life-threatening complication of infective pulmonary aneurysm. The CT films show the presence of contrast enhanced densities within the areas of consolidation consistent with the presence of vascular aneurysm

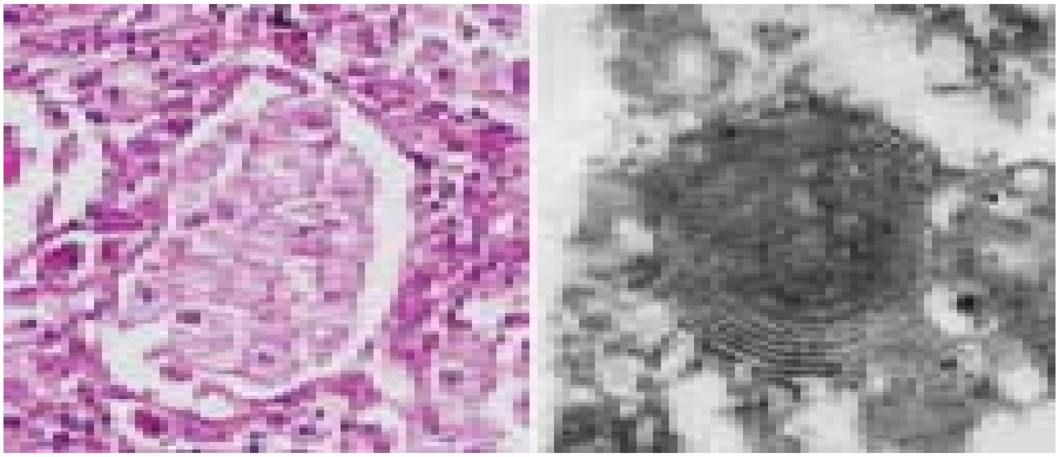

Fig. 10: Figure showing foamy macrophage with intracytoplasmic granular material in a case of pulmonary alveolar proteinosis (Hematoxylin and eosin, x200). Electron microscopic image of the same patient showing whorled lamellated surfactant bodies (x6450)

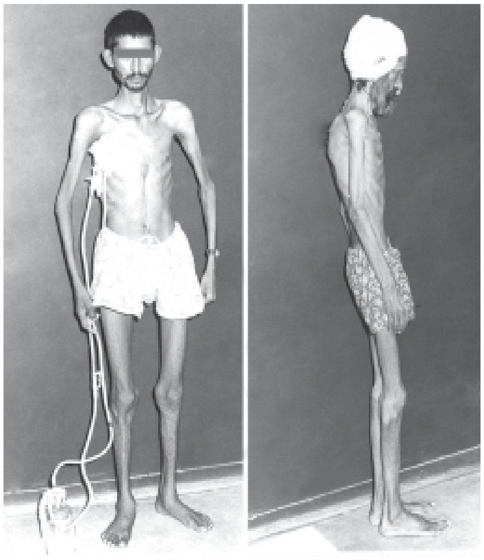

Fig. 11: Extreme wasting from tuberculosis (justifying the older terminology of consumption) was common to see in the TB-wards, even in the sixties and seventies. Fortunately, this degree of severity has become rare with the advent of effective chemotherapy and TB Control Programmes

Section

1

HISTORY AND DEVELOPMENT

SK Jindal

1

History of Respiratory Medicine

FE Udwadia

INTRODUCTION

The history of respiratory medicine cannot be separated from the overall history of medicine. The history of all medicine, including respiratory medicine begins with the history of man, for even primitive man realized that when a man ceases to breathe, he ceases to live. It needs also to be remembered that the history of medicine, like the history of the world is a chronicle of change. We in the present have built on triumphs and defeats of the past, just as those in the future will build on the successes and failures of the present.

> "Time present and time past
> Are both perhaps present in time future,
> And time future contained in time past."

Religion ruled medicine in the ancient past; then came empiricism and then came science. Even today, medicine, including respiratory medicine, is a mixture of science and empiricism. In ancient ayurveda "phlegm" (kapha), or secretions within the chest was one of the three "humors" that regulated the body, the other two being wind (vat) and choler (pitta). The Greeks paid the same importance to the humor "phlegm," but included a fourth humor "blood" and omitted "wind" from their concept of humors.

It was Hippocrates, the father of medicine (460–377 BC) teaching on the island of Kos, Greece, who divorced religion from medicine and who taught that disease was due to extraneous factors and influences. He introduced the importance of clinical bedside medicine, the important of history, physical examination, and the documentation of a patient's illness. His clinical description of diseases considering the meager facilities in that age remains unsurpassed to this day and still makes fascinating reading. Among the numerous descriptions of different diseases, one also finds a description of the clinical features of tuberculosis, a disease which still plagues the developing world. Tuberculosis is an ancient disease. The earliest evidence of this disease comes from a female skeleton unearthed from a cave in Liguria, Italy dating back to around 5300 BC. Besides a description of tuberculosis in Hippocratic writings, there was awareness of the clinical features of tuberculosis in the Rig Veda scriptures (around 1500 BC) and in texts of Ayurveda (second century AD). Ancient Chinese texts as early as in the third millennium BC, the famous Egyptian George Ebers Papyrus from Thebes (1550 BC) and the Edwin Smith Papyrus (1600 BC) also give descriptions of the disease.

After Hippocrates came many contributors to medicine. The most famous of these was Claudius Galen (AD 138–201). He indeed may be considered the most influential writer of all time, as his writings in medicine became fossilized as gospel truth for almost 1500 years. Though great for his era, Galen based his deductions and theories on observations following his dissection of animals, so that among some truths that he propounded, there lay buried numerous mistakes, which hindered the progress of medicine for well over a thousand years. One of his greatest mistakes was the propagation of his belief that the blood from the right ventricle reached the left ventricle through pores (invisible small openings) within the interventricular septum. His view on the circulation of blood in humans was really a figment of imagination, yet it stood for close to 1500 years after his demise. Why should this have been so? It is because dissection of the human body was considered taboo in that day and age so that many of his hypotheses lacked the fundamentals of scientific observation, and study.

After the decline and fall of the Roman empire (410 AD) the Western World was enveloped in the Dark Ages—war, disease and anarchy prevailed. The Dark Ages (470 AD to 1000 AD) slowly gave way to the Renaissance, a brilliant period in the history of Man.

Many medical historians are of the opinion that the history of modern medicine began with the publication in 1543 of "De Humanis Corporis Fabrica" by Andreas Vesalius, a 25 year old young man who was professor of anatomy in the University of Padua, Italy. Vesalius dissected the human body and through meticulous observation and description illustrated the musculoskeletal framework as also the internal structure of the body in the form of exquisitely detailed anatomical plates. These were designed and executed in the studio of the great Italian artist Titian. Vesalius exploded the numerous untruths in the teaching of Galen, which had dominated medicine for well over a thousand years. He proved above all that the ventricular septum had no pores and that blood from the right ventricle could not therefore enter the left ventricle through septal pores. Vesalius described the venous system of the thorax, discovered the azygos vein and noted its entry into the superior vena cava. His numerous contraindications of the many hypotheses put forth by Galen raised a furor of opposition from the medical fraternity who believed that the teachings of Galen were sacrosanct and could not be contradicted. Vesalius disappointed, frustrated, and almost hounded by the opposition, tore up his many manuscripts and fled Padua to become physician to Charles V and then to Philip III of Spain. He never researched on anatomy again and thus was destroyed a great man in his prime—destroyed by the bigotry, jealousy and hate of lesser mortals.

The next individual who like Vesalius contradicted Galen was Michael Servetus. How was blood to reach the left ventricle from the right ventricle if not through the pores within the septum as enunciated by Galen? Servetus had worked with Vesalius in Paris. He was Spanish, an unusual figure of the Renaissance—a humanist, a theologian and a man of medicine. In a theological treatise, Christianismi Restitutio, he briefly described the pulmonary circulation. He stated that the blood from the right ventricle had to flow thorough the pulmonary artery via its branches into the lungs. His theological treatise was judged to be heretical by the church and this brave man who thought differently from the general herd of humanity was burnt at the stale for his heresy. We however now know that Nafis, a physician from Damascus had already described the flow of blood from the right ventricle through the lungs as early as the 13th century, 400 years ahead of Servetus. The credit for the first discovery of the pulmonary circulation should therefore go to him.

The discovery of the overall circulation of blood in man, based on meticulous observation, experimentation, and for the first time on scientific principles (akin to the principles followed by Newton and Kepler who also belonged to this Baroque age—the 17th century) is one of the greatest medical discoveries of the world. Future generations could never have contributed to cardiorespiratory medicine without this monumental discovery. The credit for this discovery goes to William Harvey. He was a physician on the staff of St. Bartholomew's Hospital in London. He announced the discovery of his work in 1616. His classic work "Exercitatio anatomica de Motu Cordis et Sanguinis in Animalibus" was published rather shoddily, 12 years later in Frankfurt, in which he described circulation as we know it today. It immediately divided the world into two hostile camps—one for and one against Harvey. Truth ultimately prevailed and Harvey has the distinction of being one of the all time greats in the field of medicine.

Though Harvey published his discovery of circulation in the 17th century, knowledge in the physiology of respiration came a century and a half later. Priestley discovered oxygen, but did not realize its importance in respiration and respiratory physiology. It was Antoine Lavoisier who named Priestley's gas oxygen and noted its characteristics and its importance in respiration. He was probably France's greatest chemist, an aristocrat by birth, who unfortunately was guillotined during the turbulent times of the French revolution.

Bernardino Ramazzini (1633–1714) pioneered the science of occupational diseases. He wrote on silicosis in stone masons and in miners working in mines. Over the next 300 years, occupational lung diseases have graduated into an important subspecialty of pulmonary medicine.

1800–2000

I shall introduce this period with none other than the great French physician René-Théophile-Hyacinthe Laennec (1781–1836) who is an immortal in the history of medicine. A pupil of Nicolas Corvisart, the first cardiologist in the Western world and also the personal physician of Napoleon Bonaparte, Laennec was a physician at Salpétrière Hospital and the chief at the

Necker Hospital in Paris in 1814. Corvisart, Laennec and others would place their ears directly to the chest to hear heart sounds. Laennec for years has been obsessed to hear sounds within the chest with greater clarity. It is said that one day when crossing the Louvre (the residential palace of the Bourbon Kings of France), he saw a boy listening with his ear to one end of a beam to scratches made by another boy with a nail at the other end of the beam. He was struck by the ease with which sound was conducted in this manner. In 1816, a young stout woman consulted him for symptoms of heart disease. Her young age and obesity did not permit him to put his ear directly to her chest (direct auscultation). He lightly rolled up a thick sheaf of paper, placing one end over the precordium and the other end over his ear. To his surprise, he could hear the heart sounds with far greater clarity than ever before, when he used to place his ear directly to the chest. He grasped the significance of this discovery and noted that the method of indirect auscultation would enable one to hear not only the beating of the heart, but likewise all movement capable of producing sound in the thoracic cavity.

Laennec in his treatise on "Mediate Auscultation" described his first monaural stethoscope, a wooden piece 9" long, 1½ inches in diameter. It was made in two pieces, the detachable earpiece and the chest piece, which could be screwed together. Following minor modifications, by the 19th century, rubber tubing was introduced to create a flexible monaural stethoscope. Finally, the familiar two ear instrument with rubber tubings was devised by the American physician George P Cammann in 1852. Laennec made excellent use of his invention, studied both normal and abnormal breath sounds, described them in detail and drew conclusions from what he heard as to the nature and extent of the disease in the chest. Above all, he verified his findings with what was revealed at autopsy. He was the first man to create a diagnostic system of auscultatory findings in the diagnosis of pulmonary and cardiac disease. He described and gave the correct significance to adventitious sounds—rhonchi, râles, and through his system of mediate auscultation diagnosed pulmonary ailments such as bronchitis, pneumonia and tuberculosis.

Laennec's treatise on "Mediate Auscultation" focused particularly on pulmonary tuberculosis, which was prevalent all over the world in the 19th century. He described the early diagnosis of tuberculosis. He noted the presence of the tuberculous nodule, which was ubiquitous in every organ affected by the disease. On this basis he postulated that tuberculosis was a single disease, which could affect many organ systems. This was indeed a remarkable observation considering that the tubercle bacillus causing the disease had not been discovered in Laennec's time. Laennec unfortunately himself suffered from and succumbed to tuberculosis—as did many of his contemporaries, including the surgical student and poet John Keats. Laennec, brilliant though he was, did arrive at some erroneous conclusions. He denied that tuberculosis was contagious when it was strongly so; he believed that it was often hereditary when it was not so. He felt that psychological factors such as grief, sorrow, and unrequited love played a role in its causation and perpetuation. Laennec's superb writings prompted Thomas Addison, the English physician to remark that Laennec contributed more to the advancement of medical art than any other single individual.

There were many great individuals during and after Laennec's time. Mention must be made of the German School of Medicine and of Rudolf Ludwig Karl Virchow who dominated medicine for more than half of the 19th century. He was unquestionably one of the greatest pathologists who ever lived and was a worthy successor to the great pathologists, Morgagni and Rokitansky. He noted that the cell was the seat of disease and described the macroscopic and microscopic changes of several diseases, including those of the lung. He was the first to show that pulmonary emboli arose from venous thrombi chiefly present in veins of the lower extremities. His work was embodied in his opus – Di cellular – pathologie. It is worth noting that none of this work would have been possible had it not been for the discovery of the microscope by the Dutch draper Anton-van Leeuwenhoek, illustrating what has been stated at the beginning of this chapter, that the history of respiratory medicine is inseparable from medicine as a whole.

We now go on to briefly mention just two of the many great microbe hunters in the history of medicine. Till the early part of the 19th century, disease was thought to be caused by miasmas, humors or vapors. The miasmic theory of disease was challenged by many, but ultimately shattered by Louis Pasteur, a French chemist who was born in December 1822 and who went on to study chemistry at the École Nationale in Paris. He contended through meticulous experimentation and observation that all infectious diseases were caused by microorganisms and that a specific microorganism was responsible for a specific disease. He postulated that if these microorganisms could be identified, specific vaccines could be prepared and could well prevent specific disease. This was a principle enunciated in relation to all infectious diseases, including those involving the respiratory system. It behooves the world to remember that it was a chemist and not a man trained in medicine who became one of the greatest benefactors of mankind.

Pasteur's counterpart in Germany was Robert Koch, a great microbiologist. Koch's greatest triumphs was his discovery that tuberculosis was caused by a specific organism—*Mycobacterium tuberculosis*. In 1882, Koch cultured the tubercle bacillus presenting his results in 1884 to the Berlin Physiological Society. He also presented in his paper, Koch's postulates, enunciating a specific discipline, which needs to be fulfilled if a specific organism is to be considered responsible for a specific disease.

The history of tuberculosis now became increasingly complete. The disease could be diagnosed clinically ever since the brilliant clinical description of Laennec. The morbid anatomy had been determined by Morgagni, Rokitansky and Virchow. The possibility that tuberculosis was a communicable disease was entertained by a few prominent clinicians and pathologists. And at last came the cause of the disease, which till the discovery of the tubercle bacillus was deemed a mystery. Yet even great minds make mistakes. In 1890, Koch announced at the Berlin International Congress that he had discovered a substance that could cure tuberculosis; a substance that could inhibit the growth of the tubercle bacillus in the test tube as also in human beings. This substance (which he kept secret for a while) was none other than a glycerin extract of the tubercle bacillus termed tuberculin. Tuberculin was administered to thousands of individuals over the next year. The treatment proved a fiasco to the embarrassment of the great Robert Koch. Yet in years to come the preparation of tuberculin did have diagnostic use; an intradermal injection of tuberculin would often produce a strong reaction if the patient in the past or present had been infected by tuberculosis. Even today, the tuberculin test is a worthy diagnostic aid to infection caused by the tubercle bacillus.

We must now add a post-script to the story of tuberculosis. The search of a vaccine or other means of immunization against this disease continued and continues to this day. Albert Calmette of the Pasteur Institute and Jean Marie Guérin developed a new method of preparing a vaccine. They used the live bovine strain of the tubercle bacillus and on repeated subcultures of this strain noted that the bacillus lost its virulence, but retained its protective action. The vaccine was named BCG (Bacillus Calmette-Guérin) and from 1924 was tried out on humans. Thousands of children were vaccinated. Its efficacy was controversial. Recent work bears out its usefulness, particularly in the prevention of tuberculous meningitis, one of the worst forms of tuberculosis, which invariably caused death before the advent of anti-tuberculosis drugs.

Mention must be made at this point of one of the unfortunate disasters in respiratory medicine. The disaster occurred in Lubeck, Germany, in 1930, when 249 babies who were supposed to be injected with BCG vaccine were inadvertently injected with a living virulent strain of *Mycobacterium tuberculosis*. Seventy-six babies died of progressive tuberculosis. The remaining developed mild tuberculosis, but were alive at the end of 12 years, pointing perhaps to the remarkable immunological defenses the human body is endowed with.

One of the greatest discoveries of the late 19th century was William Roentgen's discovery of X-rays in 1895 — again a discovery of a physicist and not by a man trained in medicine. Radiographic examination of the chest with increasing refinements proved an invaluable asset not only in the diagnosis of pulmonary tuberculosis, but of numerous other pulmonary diseases—both infectious and noninfectious in etiology.

In 1898, Gustav Killian reported his experience with the first bronchoscopy. Technical developments over several years established bronchoscopy through a rigid bronchoscope as an important diagnostic and therapeutic modality in respiratory medicine. In 1967, Ikeda in Japan devised the flexible fiberoptic bronchoscope and this opened up new horizons following the widespread use of fiberoptic bronchoscopy in pulmonary medicine.

THE DISCOVERY OF CHEMOTHERAPY AND ANTIBIOTICS

The diagnosis of respiratory diseases using clinical methods, microbiology and a radiographic examination of the chest, was increasingly possible. But how was one to treat respiratory and other diseases? It was Paul Ehrlich, a disciple of Robert Koch who invented the concept of chemotherapy—the administration of a chemical substance to treat disease. In 1905, after several experiments, Paul Ehrlich discovered the first antimicrobial agent to treat syphilis. In 1925 Gerhard Dogmak invented Prontosil, the first of the sulfa drugs to be used against several microorganisms. More refined and less toxic sulfa drugs continue to be used in modern medicine. Finally, in 1929 came the great discovery of the antibiotic penicillin (a substance produced by the fungus *Penicillium notatum*), by Alexander Fleming which was available for clinical use in 1944 through the brilliant work of Chain and Florey. This discovery revolutionized the treatment of a number of incurable acute infections. Research on antibacterial effects of several fungi and moulds continued unabated. In 1942, Selman Waksman, a Russian Jew who had migrated to the USA and had become a microbiologist, discovered streptomycin from the fungus *Streptomyces griseus*. This drug was the first effective drug against the tubercle bacillus. Unfortunately, the use of this drug alone led to the multiplication of resistant strains. After that followed a quick discovery of other drugs against tuberculosis and other microorganisms. The impetus to the discovery of other drugs against tuberculosis was partly due to the fact that the tubercle bacillus quickly became resistant to the use of a single drug regime. The discovery of Para-aminosalicylic Acid (PAS) was followed in 1950 by the discovery of isoniazid. Excellent clinical trials in Edinburgh by Professor John Crofton and his team showed that the combined use of streptomycin, PAS and isoniazid almost always resulted in a cure if taken meticulously and regularly for the prescribed period of time. Poor compliance invariably resulted in resistant strains. The next few decades saw tremendous research on other drugs to counter the growing menace of tuberculosis. Numerous drugs have come into use, but other than rifampicin, none of these drugs in use can match the efficacy of streptomycin and isoniazid. The introduction of isoniazid in 1950 and rifampicin in 1965 paved the way for modern short-course chemotherapy, which was first introduced in the 1970s.

In India initial efforts to combat tuberculosis were spearheaded by voluntary organizations and by the setting up of sanatoria in temperate hill stations. After India's independence in 1947 two pioneering institutions were established—The Tuberculosis Chemotherapy Centre in Chennai and the National Tuberculosis Institute in Bengaluru under the Indian Council of Medical Research and the Government of India respectively. These two institutes did pioneering research to help shape tuberculosis control in India and to an extent in other countries. The famous Madras chemotherapeutic trial showed that domiciliary treatment of patients with tuberculosis was successful notwithstanding poor living conditions and a poor diet, provided there was compliance to therapy. This led to a closure of sanatoria all over world. Several intermittent chemotherapy regimes were also devised by the Madras and Bangalore centers in collaboration with the British Research Medical Council. This indeed was excellent research in respiratory medicine the like of which has not been equalled in subsequent years in our country.

Numerous other antibiotics to counter other infections have been discovered. However indiscriminate use of antibiotics has led to the dangerous emergence of many antibiotic-resistant bacteria. These indeed pose a great health hazard particularly in critical care units and in patients who are immunocompromised.

Respiratory Physiology

The exchange of oxygen and carbon dioxide within the lungs was known since the beginning of the 12th century. There however was debate whether oxygen was transferred from the alveoli to the capillary blood by active secretion or simple diffusion. August and Marie Krogh in a series of publications proved that the transfer of oxygen and carbon dioxide across the alveolar capillary membrane was a simple physical process of diffusion. Work on pulmonary function was carried out in several laboratories in Europe and America. Outstanding among these was the application of pulmonary function and pulmonary physiology to clinical respiratory medicine through the work of Comroe in San Francisco, America.

The knowledge on pulmonary physiology, gas exchange and pulmonary mechanics was put to clinical use in 1953 by Bjorn Ibsen who founded the first Intensive Care Unit in the world in Copenhagen to treat patients with poliomyelitis that had caused respiratory paralysis. This was an effective counter to the epidemic of poliomyelitis that raged in that year. Ibsen's approach incorporated the use of an endotracheal tube or a tracheostomy through which, to start with, teams of medical students working in relays pumped oxygen enriched air into the lungs of paralyzed patients till such time as they could breathe spontaneously. Soon ventilators were devised first in the form of the iron lung—a contraption in which the patient was inserted (with only the head sticking out). Negative pressure induced within the machine allowed the chest to expand and the lung to inflate. Release of the negative pressure allowed the lungs to passively deflate. An improvement over the cumbersome iron lung was the invention of the ventilator, a device which could provide positive pressure ventilatory support through an endotracheal tube or a tracheostomy to a patient in respiratory failure. Over the years, the ventilator has evolved into a superb sophisticated machine that renders mechanical ventilator support with ease and efficiency.

There is one other aspect of pulmonary medicine, which deserves an important mention. It is the epidemiological proof of the strong positive relation between cigarette and bidi smoking and cancer of the lung, and of cigarette or bidi smoking to Chronic Obstructive

TABLE 1.1: Advances in the last half century

1. A vast array of imaging techniques—in particular High Resolution Computed Tomography (HRCT). CT guided transthoracic biopsies for the evaluation of localized or peripheral lung pathologies. The discovery of Positron Emission Tomography (PET) is chiefly used in staging lung cancer.
2. The study of bronchoalveolar lavage (BAL) fluid obtained through a fiberoptic bronchoscope; the widespread use of transbronchial lung biopsy and biopsy of mediastinal glands through a flexible bronchoscope.
3. Advanced microbiological techniques; techniques for quicker cultures of *Mycobacterium tuberculosis* with quick drug sensitivity reports.
4. A thorough physiological evaluation of lung function.
5. Advanced biochemical, genetic and molecular studies; unraveling of the genome of the tubercle bacillius.
6. Improved pathological studies.
7. Powerful antibacterial drugs.
8. Antiviral drugs.
9. The development of vaccines to fight respiratory disease.
10. The development of intensive care.
11. Advanced anesthesiology and surgery, including surgery for lung transplant.

Pulmonary Disease (COPD). It was Doll and Hill who in an excellent epidemiological study in the early fifties established that the incidence of lung cancer was about 10 to 20 times greater in those who were heavy cigarette smokers compared to those who did not smoke. This was proven again and again by numerous other epidemiological studies. The incidence of lung cancer is shown to be reduced following the stoppage of smoking. The incidence of cancer in poor developing countries is on the rise mainly because of the increase in smoking habits in South and South-east Asian countries.

Advances in the last half century are too numerous to be dealt with. A few of these are briefly tabled in Table 1.1.

It is impossible to discuss each of these at length in a short chapter on the History of Respiratory Medicine, but a brief mention of the history of thoracic surgery is warranted. Carlo Forlanini (1847–1918) of Pavia attempted the first artificially induced pneumothorax in a patient with cavitative tuberculosis in 1888. The Carlo Forlanini Institute in Rome is a tribute to his memory. The rationale was to “relax” the cavity by partially collapsing the diseased lung. A more radical approach was the performance of thoracoplasty in 1930s, the posterior portions of the second to seventh ribs being removed enabling partial collapse of the lung on the affected side. This prompted healing of cavities in tuberculosis. The next advance in thoracic surgery was the resection of part or whole of the lung. The pioneer in this field was Evarts Graham (1883–1957) in Washington who first performed resection for lung cancer. Increasing skill and practice allowed for lobectomies, pneumonectomies and segmental resections. Thoracic surgery came in use not only in lung cancer, but also in other lung diseases, notably tuberculosis and suppurative lung disease. However neither tuberculosis nor cancer would allow an easy conquest.

The first lung transplantation (single lung transplant) was performed in 1963 by Hardy for a patient with a left lung cancer. The patient died after 18 days. Refinements in technique and postoperative care led finally to an improvement in the horrendous mortality experienced in the initial 20 years. Today double lung transplant and heart-lung transplant are successfully performed with a fairly good three and five years survival rate in a number of transplant centers in the world. Unfortunately lung transplant surgery has not taken off in India.

Just as old problems are solved, new problems arise. The ancient problem of tuberculosis is still a menace, particularly in developing countries. The problem is confounded by the pandemic of Human Immunodeficiency Syndrome (HIV) infection, which contributed strongly to multiple drug resistant tuberculosis and extensive drug resistant tuberculosis. Both tuberculosis and HIV infection literally fuel each other.

The introduction of Directly Observed Short-term Therapy (DOTS) in India has made an appreciable dent both in the detection rate and success rates of the treatment of tuberculosis. But much more needs to be done before India and other developing countries can claim success in the control of the disease.

One can conclude by stating that though respiratory medicine has come a long way, it still has a longer way to go. It will continue to follow a trail beset with trials and tribulations, defeats and victories, interspersed with periods of great discovery and scintillating glory.

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2

Anatomy and Architecture: A Clinical Perspective

SK Jindal

The respiratory systems essentially comprises of three different structural and functional units:

1. Respiratory tract (from the nose and the mouth to the alveoli), meant for air conduction.
2. Lung parenchyma (the alveoli and the surrounding interstitium, which includes the blood capillaries, lymphatics and interstitial matrix with several different kinds of cells).
3. Respiratory regulatory system.

In addition, the pleura, the thoracic cage and the mediastinum, which are also important in the overall respiratory function, are considered as important constituents of the respiratory system.

LUNG ANATOMY AND MORPHOLOGY[1-5]

Respiratory Tract or Airways

Upper Respiratory Tract

The components of the upper respiratory tract include the nose, the mouth, the pharynx and the larynx upto the level of the vocal cords. The upper respiratory tract largely lies in the domain of the otorhinolaryngologists and the oral physicians, but the diseases of different parts of the upper respiratory tract may frequently pose problems in the differential diagnosis of respiratory diseases. Several different diseases may also involve both the upper and the lower respiratory tracts. Sometimes, the diseases of the upper respiratory tract, particularly of the sinuses and the larynx, may precede or predispose to the development of diseases of the lower respiratory tract. The upper respiratory tract also performs the function of filtering, warming and humidifying the inspired air, thereby playing an important role in the pulmonary defense mechanisms.

The nasal cavity is divided into two separate parts by a median septum. The floor of the nose constitutes the hard palate and the roof of the base of the skull—maxillary, ethmoid and sphenoid bones. There are three bony projections from the lateral wall of each cavity, called superior, middle and inferior turbinates and the space between the two turbinates is the meatus. Sphenoethmoidal recess is the space above the superior turbinate. The nasal cavity is surrounded by the paranasal sinuses, which are the air containing cavities in the maxillary, frontal, ethmoid and sphenoid bones and are respectively known as the maxillary, frontal, ethmoidal and sphenoidal sinuses. The sinuses, being in continuity with the respiratory tract, bear an important clinical relationship with respiratory tract diseases.

Posteriorly, the nasal cavity continues with the nasopharynx, i.e. the part of the pharynx behind the nose. The nasopharynx contains adenoids, the lymphatic tissue, which when hypertrophied may pose important challenge in the differential diagnosis of diseases, especially in the children. The openings of the Eustachian tubes, which connect with the middle-ear are also located in the nasopharynx. It is through this tube that the problems of nasopharynx may directly spread to the otherwise closed, middle-ear cavity.

Nasopharynx continues inferiorly into the oropharynx—the space behind the oral cavity, upto the hyoid bone and thereafter into the hypopharynx, which extends from the hyoid bone upto the upper end of the esophagus and the larynx.

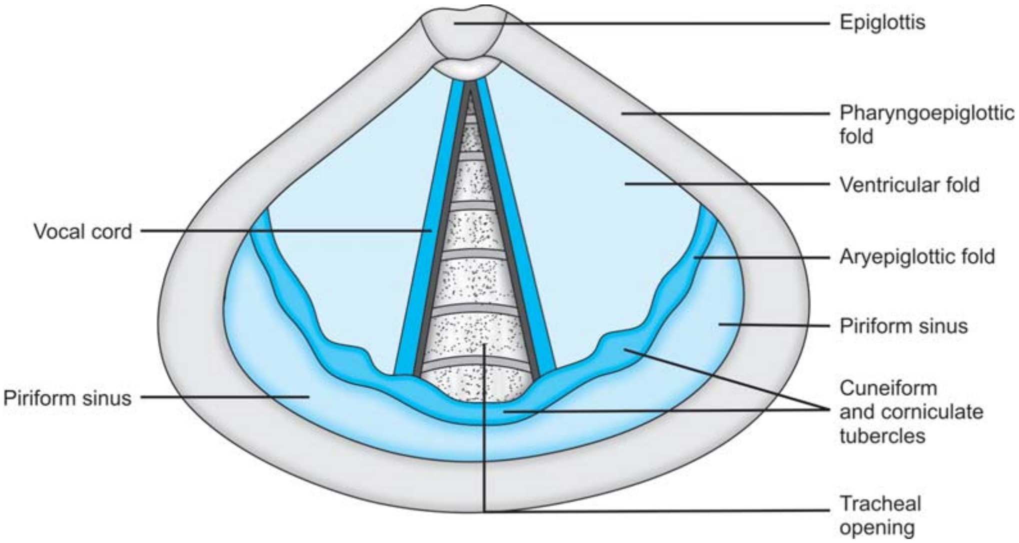
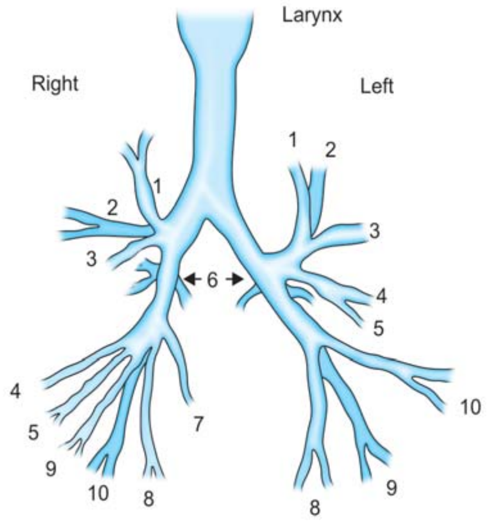


Fig. 2.1: Laryngeal opening as seen from above at the level of vocal cords

Larynx constitutes an important component of the upper respiratory tract. It is the seat of phonation and acts as sentry for the lower respiratory tract by preventing the aspiration of secretions and by regulating the flow of air. The larynx consists of several cartilages, ligaments and muscles. The laryngeal opening (Fig. 2.1) is guarded by the two vocal cords, which open with each cycle of inspiration and expiration to allow the movement of air in and out of the lungs. The vocal cords constitute both an anatomical and a functional landmark between the upper and the lower respiratory tracts. The respiratory tract below the vocal cords is normally protected from routine environmental onslaughts and is microbiologically sterile. Impaired movement or paralysis of a vocal cord compromises the respiratory defenses and is also responsible for a change in the character of the voice.

Lower Respiratory Tract

Starting with the trachea at the opening of the vocal cords, the lower respiratory tract consists of a branching system like that of a tree. The trachea divides into the two main bronchi (right and the left) which further divide into lobar, sublobar, segmental, subsegmental bronchi and the terminal bronchioles (Fig. 2.2). A single lung unit supplied by a terminal bronchiole is labeled as an acinus, which is also supplied by an independent branch of the pulmonary blood vessels and lymphatics. Acinus is an independent functional unit of the lung.



Bronchial divisions

Upper lobes : 1. Apical, 2. Posterior, 3. Anterior
Left side 4 and 5. Superior and inferior lingular
Right side (middle lobe),
4.Lateral, 5. Medial

Lower lobes : 6. Apical lower, 7. Medial (Rt. only),
8. Anterior, 9. Lateral, 10. Posterior

Fig. 2.2: Divisions of the tracheobronchial tree

The bronchial divisions up to the terminal bronchioles, primarily meant to conduct the air to the alveoli are called the "conducting airways." They do not play any role in air exchange during health. The respiratory tract beyond the terminal airways, which

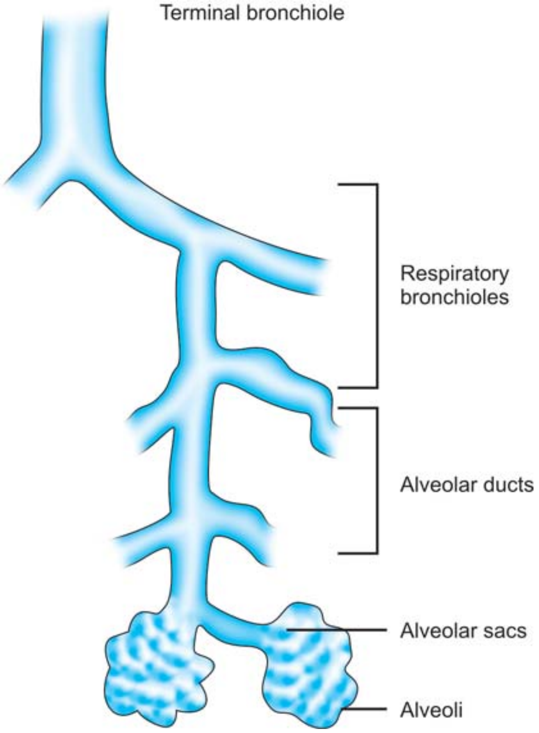


Fig. 2.3: Schematic structure of the terminal respiratory unit

plays an important role in gas-exchange, includes the respiratory bronchioles, alveolar ducts and the clusters of alveoli (Fig. 2.3). This part of the respiratory tract is therefore labeled as the "gas-exchange unit" of the lung.

The Trachea

The trachea extends from the level of the vocal cords above to the carina below. The extrathoracic part of the trachea begins at the level of the sixth cervical vertebra just below the cricoid cartilage and is covered anteriorly and laterally by the thyroid gland in the upper part of the neck. The lower part lies subcutaneously and enters the thoracic inlet, along with the esophagus situated behind the trachea. The intrathoracic part extends up to the fifth thoracic vertebra, corresponding anteriorly to the manubriosternal joint (Louis angle) and bifurcates at the carina into the right and left main bronchi.

The tracheal wall is composed of cartilaginous rings, which do not allow the tracheal tube to collapse. The cartilaginous rings are partially incomplete posteriorly and the two posterior ends are jointed together by fibrous and elastic tissue. The tracheal lumen is somewhat oval in cross-section and remains patent throughout.

Bronchial Tree and Alveoli

The right and the left main bronchi enter the right and the left lung, respectively at the lung hila. Normally, the right main bronchus, which is in direct continuity with the trachea, is broader and shorter in length while the left main bronchus is more angulated, narrower and longer. The right bronchus is therefore the preferential site for aspiration of foreign bodies and secretions, especially in the erect position.

The right main bronchus branches into the right upper lobe bronchus, which divides into apical, anterior and posterior branches and the intermediate bronchus, which further divides into middle lobe and lower lobe branches. Similarly, the left main bronchus at about 4 to 5 cm length, divides into upper and lower lobe divisions, which divides further into segmental and subsegmental branches. There are 10 segmental branches on the right and 8 segmental branches on the left side. Each generation of bronchial tree is numerically labeled with the main bronchi as the first generation bronchi (Table 2.1). There are about 8 to 10 generations of bronchial divisions, which end as terminal bronchioles, followed by three to five generations of respiratory bronchioles. The last generation of respiratory bronchioles gives rise to two to three generations of alveolar ducts, which after further branching lead to alveolar sacs, constituted by a variable number of alveoli. The alveolar ducts together with the alveolar sacs, which stem from the most proximal respiratory bronchiole constitute the terminal respiratory unit (see Fig. 2.3), which is both the structural and the functional unit of the lung. In the two adult lungs, there are about 1,50,000 units, with about 2,000 alveoli in each unit.

The alveoli actually start appearing directly from the walls of the terminal generation of respiratory bronchioles. An alveolus is generally a polyhedral air sac with a thin and flat, single cell-layered wall.

Morphological Divisions of the Lungs

The two lungs are divided into five lobes by the presence of fissures—the right lung into three and the left into two lobes. The oblique fissure on both the sides separate the upper and the lower lobes, while the horizontal fissure on the right side divides the upper lobe into the upper and the middle lobes. The oblique fissure can be drawn on the chest wall by a line from the third dorsal vertebra opposite to the spine of scapula, sloping downwards, laterally and anteriorly along the fifth rib upto the sixth costochondral junction anteriorly. The horizontal fissure on the right side may be drawn horizontally along with

TABLE 2.1: Bronchial and bronchiolar division

Structures	*Generation from*				
	Trachea	*Bronchus*	*Segmental bronchiole*	*Terminal number*	*Diameter (mm)*
Trachea	0			1	2.5
Main bronchi	1			2	11-19
Lobar bronchi	2-3			5	4.5-13.5
Segmental bronchi	3-6	0		19	4.5-6.5
Subsegmental bronchi	4-7	1		38	3 - 6
Bronchi		2-6		Variable	
Terminal bronchi		3-7		1000	1.0
Bronchioles		5-14		Variable	Variable
Terminal bronchioles		6-15	0	35000	0.65
Respiratory bronchioles			1-8	Variable	Variable
Terminal respiratory bronchioles			2-9	630,000	0.45
Alveolar ducts and sacs			4-12	14 million	0.40
Alveoli				300 million	0.25-0.3

4th costal cartilage to meet the oblique fissure in the mid axillary line. On the left side, the lingua, not separated by any fissure, is a part of the left upper lobe.

Each lobe is divided into segments by the presence of the septae. On the right side, the upper lobe is divided into apical, anterior and posterior segments; the middle lobe into the medial and the lateral segments; and the lower lobe into the lower apical (or superior) medial basal, lateral basal, anterior basal and posterior basal segments. On the left side, the upper lobe is divided into two, i.e. apicoposterior and anterior segments; the lingual into the superior and the inferior segments; and the lower lobe into the superior, anterior basal, posterior basal and the lateral basal segments. There is no medial basal segment on the left side. Therefore, the left lung contains 8 segments in comparison to 10 segments of the right lung.

Each segment is further divided into subsegments and sequentially into the lobules and the acini.

ARCHITECTURE OF LUNG PARENCHYMA[5-9]

The parenchyma of all the five lung lobes together consist of about 300 million alveoli, which when spread over, equal the surface area of a tennis court. The alveoli are surrounded by the lung interstitium comprising of loose-binding (extra-alveolar) connective tissue fibrils. The matrix of lung parenchyma consists of different materials, such as the collagen, elastin, glycosaminoglycan and fibronectin, which provide a framework of support of the alveolocapillary membrane that constitutes the bulk of the interstitium of the lung parenchyma. The major bulk is contributed by the collagen and the elastin, which together constitutes most of the interstitium—the glycosaminoglycan and fibronectin comprise only about 2% of the interstitium.

The basket-like arrangement of the matrix also allows the alveolar expansion in all directions. Within the lung interstitium, along the millions of alveoli, lie the divisions of the respiratory tract, i.e. the airways which supply air to the alveoli and the neurovascular bundles, which include the smaller branches of the pulmonary arteries, veins, the nerves and the lymphatics. The patency and the function of the airways, the alveoli and the vessels are maintained by the lung matrix. Any alternation in the structure and the function of the lung matrix affects the alveolar structure and function. Similarly, the pulmonary vasculature is also affected by the interstitial structure and disease.

An alveolar duct along with its peripheral structures is called a primary lobule. The smallest division of the lung parenchyma bounded by the connective tissue septae is the secondary lobule. A secondary lobule generally consists of two to five acini, i.e. two to five terminal bronchiole along with their peripheral structures.

These are small holes in the walls of the adjacent alveoli which are known as the pores of Kuhn. Communications may also exist between the terminal respiratory bronchioles and the alveoli through the canals of Lambert. These communications allow collateral ventilation, as well as the passage of alveolar cells and the microorganisms in a disease state.

Mucosal Lining and Lung Cells of the Respiratory Tract

Besides the gas exchange, respiratory tract mucosa performs numerous secretory, absorptive and excretory functions. There is a change of the mucosal epithelium from the nose to the alveoli. The nose, nasopharynx and the paranasal sinuses are lined by the ciliated columnar and the ciliated, stratified columnar epithelium. While the larynx is also lined by ciliated columnar epithelium, the vocal cords possess a squamous epithelium with no secretory functions. The entire lower respiratory tract up to the terminal bronchioles is lined by ciliated epithelium with the gradual transition of the columnar cells to the cuboidal and finally the squamous cells in the alveoli.

There are at least two epithelial cell types in the airway surface, of which nearly half are ciliated in nature. The cilia move the superficial liquid lining layer with their continuous beating. The glands in the submucosa of the airways are responsible for the production of airway secretions, which play an important role in the airway defense as well as the neurotransmission and endocrinal function.

The cell population of the gas exchange lung parenchyma consists of four subpopulations:

A. Epithelial
B. Endothelial
C. Interstitial
D. Alveolar macrophages.

The epithelium is essentially composed of a mosaic of lining cells, the squamous pneumocytes (Type I) and the secretory granular pneumocytes (Type II). The Type II cells are more numerous, but cover only 3% of the alveolar surface. They perform the important synthesizing and secretory functions and produce a large number of proteins including the surfactant-associated proteins and help in resorption and transepithelial exchange of fluids.

On the other hand, the Type I cells are fewer, but larger in size and cover most of the alveolar surfaces. Type I cells also express a few proteins and play some role in fluid flux. The Type I cells are complex branched cells.

There are other interspersed cells such as the brush cells (Type III), mesenchymal and the endothelial cells. The brush cells have brush borders like that of the intestinal cells with possibly an absorptive function.

The alveolar macrophages are the free cells lying within the surface layers, submerged beneath the surfactant. The alveolar macrophages are capable of self renewal by mitosis. There are also Clara cells at the level of terminal bronchioles, which produce a surfactant like material. They also secrete the aqueous (or sol) layer lining of the bronchial mucosa.

Kulchitsky or Amine Precursor Uptake and Decarboxylation (APUD) cells are the other important cells in the surface epithelium. They possess an endocrine function of producing serotonin. They also constitute the origin of the carcinoid tumors of lungs.

BLOOD SUPPLY OF LUNGS[6-12]

The lungs receive a dual blood supply from the pulmonary and the bronchial (i.e. the systemic) circulation.

Bronchial Circulation

The bronchial circulation from the left ventricle is supplied via the bronchial arteries, which arise from the aorta or its intercostals branches. Normally, there are two main divisions (right and the left) of the bronchial artery, which follow the further bronchial divisions, but both the number and the origin of the bronchial arteries are variable and inconsistent. Terminally, the bronchial arteries are divided into bronchial arterioles and capillaries to finally anastomose with the pulmonary capillaries and constitute an extensive bronchial pulmonary vascular anastomotic bed around the terminal bronchioles and the alveoli.

In healthy individuals, the bronchial circulation is small and constitutes less than 3% of the total blood supply of the lungs. It differs from the pulmonary circulation since it contains oxygenated blood from the left ventricle at systemic blood pressure levels (Table 2.2). It is primarily nutritive in its function for the tracheobronchial tree. The bronchial blood supply may enormously expand in congenital pulmonary vascular

TABLE 2.2: Differences between pulmonary and bronchial circulation of the lungs

	Pulmonary	*Bronchial*
1. Blood supply	Right ventricle	Left ventricle
2. Fraction of lung circulation	Most (> 97%)	Less than 3%
3. Arterial pressure	Pulmonary	Systemic
4. Resistance	Low	High
5. Main vessels	Large sized, elastic	Small sized, muscular
6. Function	Gas exchange	Nutritive for the bronchial tree

or right ventricular anomalies. Extensive increases may also occur following pulmonary thromboembolism, in bronchiectasis and other fibrocavitary diseases of the lungs.

Pulmonary Circulation

Pulmonary circulation constitutes the primary or the bulk of the blood supply of the lungs. The pulmonary artery arises from the right ventricle and divides into right and left main branches, which enter the hila of the lungs along with the right and left main bronchus, respectively and follow the airway divisions. They are further divided into medium-sized muscular arteries, arterioles and finally capillaries. The pulmonary venous system similarly consists of pulmonary vessels and veins, which follow a centripetal course and terminate into superior and inferior pulmonary veins, which drain into the left atrium, either independently or after joining together and forming a common trunk.

The pulmonary vessels lying in the alveolar walls are called alveolar vessels, while those lying in the loose binding connective tissue are called the extra-alveolar vessels. The alveolar vessels are directly affected by the changes in the alveolar pressure.

The pulmonary circulation is primarily concerned with the gas-exchange function of the lung. The extensive pulmonary capillary network around the alveoli provides a direct interface between the air in the alveoli and the blood in the capillaries, separated by a thin layer of alveolar epithelium, vascular endothelium and the lung interstitium. The pulmonary endothelial cells produce a large number of hormones and chemical mediators responsible for metabolic and endocrinal functions. The pulmonary circulation through an extensive capillary network around the alveoli has been conceptually equated to the presence of a sheet of blood all around the alveolus contained in a thin layer of capillary endothelium (Fig. 2.4). The capillary network crosses several alveoli before coalescing into venules, thus providing a sufficient transit time for the blood to pass from the arterial to the venous end. This allows a free exchange of gases (oxygen and carbon dioxide) through the alveolocapillary membrane. A minor fraction of pulmonary blood flow (1% to 3% of total) may pass directly from the arterial to the venous side, bypassing the alveolocapillary network. This amount of nonoxygenated blood represents the shunt fraction which is present in a normal human lung.

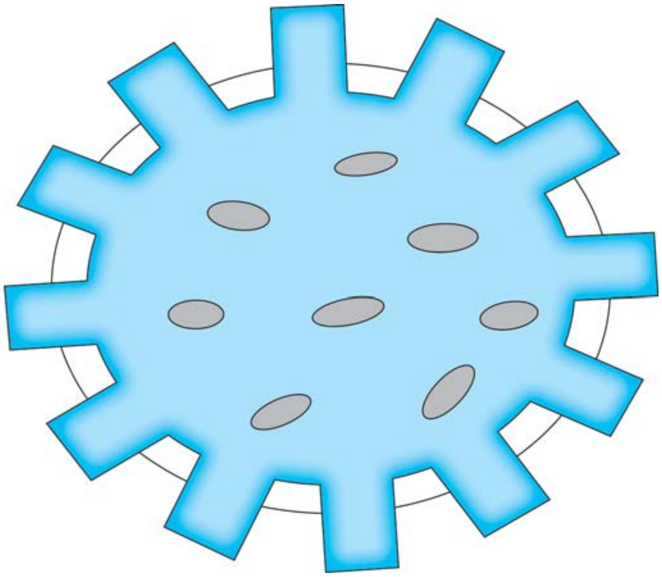


Fig. 2.4: Conceptual surface view of an alveolar wall. The capillary network when engorged, covers the whole alveolus like a sheet of blood

LYMPHATIC DRAINAGE

There are considerable variations in the lymphatic drainage of the two lungs. The lymphatics of the lungs form extensive intercommunicating networks around the bronchial and the vascular divisions in the peribronchial and the perivascular spaces. These lymphatics drain into the several groups called "stations of lymph nodes," located along the bronchial tree and ultimately into the hila (right and the left along the main bronchi) and the tracheobronchial lymph nodes. The various tracheobronchial lymph nodes groups include the superior group (between the trachea and the right or the left main bronchus) para-aortic and an inferior or infracarinal (below the carina) group. The further drainage occurs into the paratracheal glands (along both sides of trachea) and the supraclavicular glands in the neck. The paratracheal lymphatics also communicate with the paraesophageal glands in the mediastinum and the retroperitoneal abdominal nodes.

The lymphatics from all the groups of tracheobronchial nodes lead into the thoracic duct on the left side and the lymphatic duct on the right side, which finally drain into the venous system, i.e. the innominate veins of the two sides. The right lung drains into the right tracheobronchial, paratracheal and supraclavicular glands and the left lung drains into the left side glands, but there is a great degree of intercommunication between the two sides, especially of the paratracheal glands. An important exception to the same side drainage is seen for the left lower lobe lymphatics, which drain into the right-sided glands. There are also communications between the superficial and the deep lymphatic plexuses via the interlobular septal lymphatics. Thus, there is a potential for bidirectional flow of lymph.

The lymphatic drainage serves several important functions such as the removal of dust particles, toxins and microorganisms from the lungs. They also play an important role in the maintenance of lung-fluid balance. The lymph node enlargement, which occurs in several inflammatory, infective and neoplastic diseases of the lungs may therefore provide an important clue to the differential diagnosis of these diseases. Particularly in the cases of lung cancer, the site of lymph node is important in deciding the disease-stage and treatment modality.

NERVE SUPPLY[13]

The lungs are innervated by both the sympathetic and the parasympathetic autonomic nerve supply from the upper six thoracic sympathetic ganglia and the vagus, respectively. The innervation consists of afferent (i.e. the sensory) and the efferent (i.e. the motor pathways).

Parasympathetic (Cholinergic) Nerve Supply

The efferent fibers arise from the stretch receptors in the alveolar walls and lung interstitium and from epithelial irritant receptors of the airways. The afferents also arise from the irritant receptors of the laryngotracheal mucosa. They form a plexus around the carina and join the vagus nerve. The vagus nerves also contain the efferent fibers for the bronchial smooth muscles and the mucous glands. The efferent activation from irritant and stretch receptor stimulation causes the reflex efferent reaction causing bronchoconstriction and mucous hypersecretion.

Sympathetic (Adrenergic) Nerve Supply

The sympathetic efferent fibers from the upper thoracic sympathetic ganglia supply the pulmonary plexus around the carina and the sympathetic nerve, which innervate the bronchial smooth muscles, glands and the blood vessels. Sympathetic, efferent stimulation results in bronchodilatation, vasoconstriction and diminished bronchial mucous secretion. Of the various sympathetic receptor subtypes, only the β_2 and the α adrenergic receptors are present in the lungs.

The lungs are also supplied by fibers, which are neither adrenergic nor cholinergic in action. These fibers, which are carried by the vagal nerves, may play an important role in maintaining the bronchomotor tone and in the pathogenesis of bronchospastic disorders, as in asthma.

Lung Receptors

Receptors are the nerve endings, which are sensitive to specific, sensory stimuli. As stated above, the lungs are extensively supplied by stretch and irritant receptors in the alveolar and the bronchial walls, respectively. They are present in the airway epithelium, submucous region, interalveolar septa and smooth muscles. They are also present to some extent on the pleural surface. There are no pain or thermal nerve endings. The lung interstitium also contains a large number of juxtacapillary (J) receptors around the capillary walls. These receptors, also known as Paintal's J receptors, are stimulated by the parenchymal connective tissue distortion in the presence of vascular congestion and interstitial edema. The peptidergic nerve endings present around tracheal glands have species-specific excitatory or inhibitory effect on secretary function. There is also a diffuse, neuroendocrinal system (amine uptake and decarboxylation-APUD) distributed along the airway epithelium. The exact role of the APUD system is not known; it might affect the smooth muscle function.

The Pleura

The membranous covering of the lung and the pleura is an important constituent of the respiratory system, both structurally and functionally. The pleura consist of a visceral layer, which lines the outer lung surface and a parietal layer, which lines the inner surface of the thoracic cage. The two pleurae together form a continuous layer joined at the hilum to constitute a potential space, the pleural cavity, which is closed on all sides and contains a small quantity of fluid to prevent friction between the two pleural layers. There occurs an excessive fluid collection in this cavity in several inflammatory, neoplastic and other diseases involving the pleura.

The visceral lining of the pleurae also extends into the oblique and the transverse fissures to form the potential pleural space between the lung lobes in the fissures. The parts of the pleurae lining the mediastinal and the diaphragmatic surfaces, also respectively known as the mediastinal and the diaphragmatic pleura, constitute the mediastinal and the diaphragmatic pleural spaces respectively. Loculated collection of fluid may occasionally occur inside these pleural spaces in various pathological conditions.

Histologically, the pleura consists of the squamous epithelial cell lining over a connective tissue layer. The blood supply, lymphatics and nerve supply of the visceral pleura is similar to that of the lung, which it overlies. The parietal pleura is a part of the thoracic cage and derives its blood supply from the systemic circulation through the intercostals and the branches of the internal mammary arteries. Lymphatic drainage of the parietal pleura occurs to the nodes along with internal mammary artery and to the posterior mediastinal glands near the heads of the ribs. Similarly, the nerve supply of the parietal pleura is through the spinal nerves for the costal and the mediastinal pleurae and through the phrenic nerve for the diaphragmatic pleura. On the other hand, the visceral pleura is innervated by the autonomic nerves.

Thoracic Cage

The thoracic cage, which constitutes the walls of the thoracic cavity provides a protective house for the lungs, the heart, the great vessels, the esophagus and the other mediastinal structures. It is constituted by the sternum anteriorly, the thoracic spine posteriorly and the ribs and the intercostal muscles laterally. Inferiorly, the two diaphragms on each site separate the thoracic cavity from the abdominal cavity. The contents of the neck, such as the trachea, the esophagus, the neck-vessels and the nerves enter the thorax through the thoracic inlet at the upper end of the thoracic cavity. The thoracic inlet is constituted by the upper border of the manubrium sterni, the first rib and the first dorsal vertebra.

The thoracic cage not only contains the lungs and other thoracic structures, but also plays an important role in the process of respiration. The contraction of the inspiratory intercostals muscles, causing upward and forward movement of the ribs and the downward movement of diaphragms, results in the expansion of the thoracic cage and a fall in the intrapleural pressure, which causes the air to move into the tracheobronchial tree allowing the inspiration to occur. Expiration occurs after inspiratory muscle contraction ends and the thoracic cage returns to its original position. Expiration occurs as a passive phenomenon except in condition of respiratory distress when the expiratory muscles help the expiratory process through their active contraction.

The two lungs also provide a soft bed, the cardiac fossa for the heart. The inspiratory inflation and expiratory deflation of the lungs have an important bearing on the cardiac function.[14] The overall mechanical cardiopulmonary interaction provides a conducive environment for an efficient circulatory function.

Respiratory Muscles

There are three groups of muscles involved in respiration:

- The diaphragm,
- The intercostals, and
- The accessory muscles of respiration.

Diaphragm: It consists of a fan-like musculotendinous structure, which consists of muscle fibers attached to the inside of the thoracic cage at the thoracic outlet, inserted into a central tendon. Based on their attachment, the muscle fibers are grouped into three parts—the sternal part attached to the xiphoid process; the costal part attached to the inner surface of the costal cartilages and anterior ends of ribs; and the lumbar part, which is attached to the medial and the lateral lumbocostal arches. Similarly, the central tendon has got the right middle and left leaflets. The diaphragm is innervated by the phrenic nerve, which arises from the cervical plexus, with fibers from third, fourth and fifth cervical segments of the spinal cord. Phrenic nerve stimulation causes the contraction of the diaphragm, which as a result of contraction, moves down and causes lung inflation due to an increase in the volume of thorax. Weakness or paralysis of the phrenic nerves will therefore result in the elevation of the diaphragm, which will also not move with the inspiratory effort.

The thoracic mediastinal structures, such as the aorta, the esophagus, the inferior vena cava, other small vessels and nerves pass across the diaphragm to enter the abdominal cavity. There are other small recesses in the diaphragm such as the foramen of Morgagni anteriorly and the Bochdalek foramen posteriorly. Sometimes, the abdominal contents may protrude through the spaces into the thoracic cavity, i.e. the diaphragmatic or hiatus hernias. The point of esophageal entry into the abdomen serves the role of a sphincter, which allows the food to pass down into the stomach, but prevents the regurgitation of the contents into the thoracic part of esophagus. Gastroesophageal reflux, which occurs as a result of the loosening of this sphincter, plays an important role in the clinical symptomatology and etiologies of several respiratory problems.

Intercostal respiratory muscles: The intercostal muscles spread obliquely between the intercostals spaces of the ribs. The intercostals muscles directly inserted to the ribs, have no tendons. There are two groups of the intercostals muscles—the internal and the external intercostals. The external intercostal muscles arise from the lower border of the upper rib and get inserted into the upper border of the lower rib of an intercostals space. They are also called the inspiratory muscles since they actively take part in the inspiratory effort by their contraction, which by raising the ribs results in the expansion of the thoracic cavity and therefore creating a rise in the negative pressure in the pleural cavity. The internal intercostals, also called the expiratory muscles are passive during normal expiration, but assume an important role during the labored breathing in conditions causing respiratory distress when the expiration becomes an active process. The same may happen during hyperventilation, deep coughing and other similar conditions requiring a strong and active expiratory effort.

Intercostal muscles are supplied by systemic circulation through the intercostals vessels (an artery and a vein) which arise from the aorta. They are innervated by the intercostal nerves, which are derived from the inferior part of brachial plexus. The intercostal nerves along with the intercostals vessels run along the inferior borders of the ribs to supply the intercostal muscles of the respective space.

Accessory muscles of respiration: The scaleni, sternocleidomastoids, muscles of the alae nasi and of anterior abdominal wall (rectus abdominis, the external oblique, the internal oblique and the transverses abdominus) constitute the group of the accessory muscles of respiration since they assist respiration whenever an increased demand for augmented ventilation arises. Their role is rather limited in their overall contribution to the respiratory process. However, the presence of hyperactivity of accessory muscles is an important clinical indication of the underlying respiratory distress and/or failure.

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3

Lung Development

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INTRODUCTION

Unlike the heart, kidneys, liver and other viscera that begin their function early in the fetal life, the lungs are nonfunctional because of the aquatic environment *in utero*. The lungs start function with the first breath at birth. The process of lung development involves complex morphogenesis by means of which epithelial tubules and blood vessels are formed that ultimately give rise to airways and alveoli. Lung development primarily involves two phases, i.e. prenatal and postnatal (Table 3.1). The human lung arises from the laryngotracheal groove, which occurs approximately four to six weeks gestation.[1-3] During this time, the respiratory diverticulum (lung bud) appears ventrally to the caudal portion of the foregut. Location of the lung bud, along the gut tube is directed by various signals from the surrounding mesenchyme, including growth factors.[4,5] The proximal portion of this bud gives rise to larynx and trachea, separated by esophagus. The distal part of primitive bud gives rise to left and right main stem bronchi.

TABLE 3.1: Different phases of lung development

A. Prenatal development: Phases
  1. Embryonic stage: Day 26 to the next 7 weeks
  2. Lung development

i. Pseudoglandular	5 to 17 week
ii. Canalicular	16 to 26 week
iii. Terminal saccular	24 week to until term
iv. Alveolar	36 week to until birth and postnatally

B. Postnatal
  Alveolar stage continues up to about 18 months of age

The lung development in humans follows four distinct phases, i.e. pseudoglandular stage, which lasts from 6 to 16 weeks, during this period all major lung elements except alveoli, appear. This is followed by the canalicular stage (16 to 26 weeks) during which lumens of bronchi enlarge and become highly vascularized, by the 24 week respiratory bronchioles and alveolar buds develop. During the next phase, also known as the terminal saccular period, the blood air barrier gets established with the appearance of specialized cells of the respiratory epithelium, including the type I alveolar cells (responsible for gas exchange), and type II alveolar cells, which secrete pulmonary surfactant.[6,7] Alveolarization in humans begins after week 20 and continues up to 7 years of age, giving rise to an alveolar gas diffusion surface of 70 m^2 area and 1 μm thickness.

Development of Airway Epithelium

The development of airway epithelium occurs during the embryonic stage as previously described, it relies on the epithelial-mesenchymal interactions between the components of the airway wall including surface lining fluid, submucosal gland and the basement membrane, including the basal lamina and fibroblasts.[8-10] There occurs differential growth of the epithelial tube into a mesenchymal derivative containing the cells and the matrix. This development moves from a proximal to distal pattern following the epithelial tube. Subsequent branching of the airway tree results in producing alveolar septum.[11,12]

After the bronchial tree is established, growth occurs in two directions either longitudinally to extend the length or circumferentially to increase its diameter. In mammals, the majority of growth occurs postnatally, thereby making the perturbations by environmental contaminats crucial.[13-16] The distal airways, located at the junction between the gas exchange area and tracheobronchial tree form the extensive transition zone of the human lung. The development of submucosal glands occurs in four phases (a) formation of buds by projections of undifferentiated cells, (b) outgrowth and branching of the buds into cylinders, (c) differentiation of mucous cells in proximal tubules, (d) differentiation of serous cells in peripheral tubules and acini along with continuous proliferation of most distal areas.

Alveolar formation starts late, it is primarily a postnatal event. Besides the growth of the septae into the terminal saccules, there is formation of smooth muscles, elastin and other matrix cells.

Pulmonary Vasculature

Primitive right and left pulmonary arteries grow caudally from the aortic sac when the lung bud is also forming. They become associated with the developing respiratory primordium. The growing pulmonary arterial system maintains this association with the development of the airway system throughout thereafter. The blood supply to the respiratory primordium drains into a venous plexus that empties into the heart through a single pulmonary vein. The venous drainage system is complete around midway through gestation and corresponds to the conducting airways and arterial system.

There is only a small proportion of blood of the total cardiac output, which flows to the lungs during fetal development. The resistance to flow in the pulmonary arteries is high. After birth, there is a sudden drop in pulmonary arterial pressure and a rise in the blood flow. This is attributed partly to the anatomical alterations and partly to local vasomotor responses.

The blood circulation during fetal life takes a somewhat different route (Fig. 3.1). The oxygenated blood from the placenta is returned to the fetus through the umbilical vein and flows through the ductus venosus and inferior vena cava into the right atrium, shunted through the foramen ovale into the left atrium from where it goes to the left ventricle, aorta and gets distributed preferentially to the upper part of the body, the heart and the brain, through the brachiocephalic vessels. On the other hand, the venous blood returning to the right atrium from the superior vena cava, which is poorly oxygenated passes into the pulmonary artery through the right ventricles, gets shunted into the descending aorta (through the ductus arteriosus) from where it is distributed to the lower part of the body, the placenta. The pulmonary artery blood also flows to the lungs.

The intrauterine lung performs only the nonrespiratory functions. It does not participate in gas exchange. Importantly, it is one of the important sources of amniotic fluid and surfactant formation. It also serves as a blood reservoir, provides host defenses and participates in the activation and inactivation of biological substances.

Beginning of Postnatal Life

The lungs take over the gas exchange function immediately after delivery, which marks the end of the fetal life. With the very first breath—the cry, the ventilatory system is “turned on.” Immediately, the liquid in the lungs gets replaced with air. There occur significant changes in the pulmonary and cardiac circulation, the “normal circulation” is miraculously established with the first breath. Lung expansion gets complete during the first few breaths along with circulatory adjustments.

Regulatory Factors

A number of regulatory molecules are required for lung development. Lungs are formed from anterior endodermal cells that also generate the ventral foregut. Therefore, the genes (e.g. GATA-6, HNF-3B and Thyroid Transcription Factor-1) involved in ventral foregut development are important for the early lung development. Vitamin A (retinoic acid) is also essential for growth. There exists a molecular cascade that regulates and determines the growth. The knowledge of this cascade is an important area of interest to determine not only the development anomalies, but also the development of diseases, later in life.

Role of Growth Factors in Lung Development

Growth factors are known to play an important role in the development of lungs, including Platelet-Derived Growth Factor (PDGF-A and B) and their receptors PDGFR α and β are involved in the early mid stage of lung development. PGDGE-A and B mRNA level increase[17,18] in parallel with all proliferation rates during the pseudoglandular stage of lung development; cell proliferation within lung explants is inhibited by PDGF A and B antisense oligonucleotides, as well as PDGF neutralizing antibodies.[19,20]

- PDGF-A exhibits a complete failure of alveolar septation,[18] whereas the over expressions of PDGFA cause marked mesenchymal cell proliferation with in the lungs.

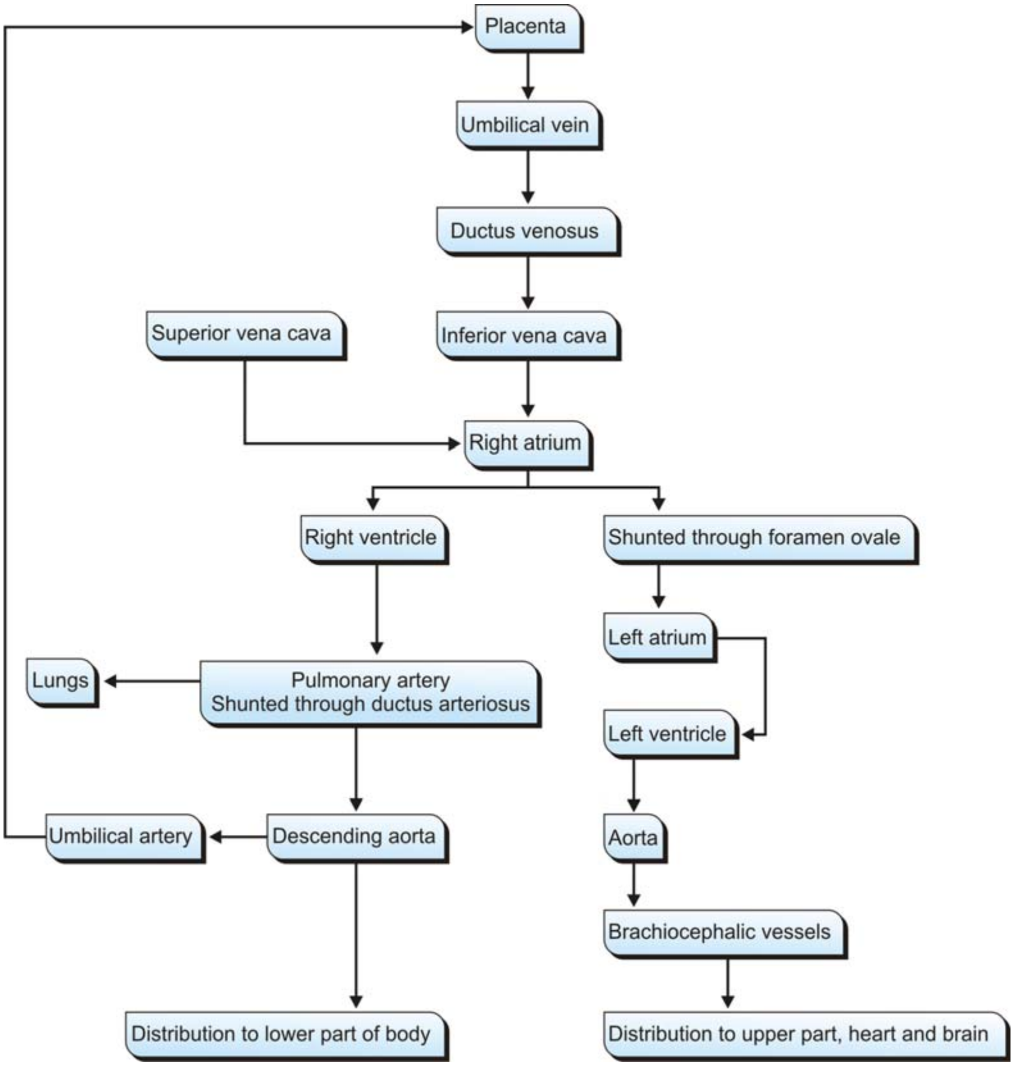
Placenta
Umbilical vein
Ductus venosus
Superior vena cava
Inferior vena cava
Right atrium
Right ventricle
Shunted through foramen ovale
Left atrium
Lungs
Pulmonary artery
Shunted through ductus arteriosus
Left ventricle
Umbilical artery
Descending aorta
Aorta
Brachiocephalic vessels
Distribution to lower part of body
Distribution to upper part, heart and brain

Fig. 3.1: Schema of human fetal circulation

- PDGF-A and B have Shear Stress Responsive Elements (SSRE) in their promoter regions suggesting their expressions levels can be influenced by the exposures of cells to physical forces. This stretch-induced cell proliferation is abolished by PDFG-B and PDGF-β antisense oligonucleotides, PDGF-BB neutralizing antibodies and a PDGFR inhibitor.[21]

Vascular Endothelial Growth Factor (VEGF) exerts potent mitogenic effects on endothelial cells via the VEGF receptors (VEGFR2).[22] VEGF and VEGFR2 mRNA increase as the lung matures.[23,24] VEGF proteins plays a role in directing vascular growth in regions destined for gas exchange.

- VEGF was responsible for the endothelial cell proliferation induced by increase in lung expansion.

Insulin-Like Growth Factors (IGFs) I and II act via the type I IGF receptor.[25]

- IGF I and II mRNA levels are increased and decreased following increase and decrease in lung expansions.[26-28]
- IGF may mediate changes in lung growth induced by alterting lung expansion.

TGF-β-Transforming Growth Factor (TGF-β) inhibits fetal newborn and adult type II cell proliferation, surfactant synthesis and surfactant protein gene expression.[29-31]

- TGF-β, EGF (Epidermal growth factor) and gene deletion of this receptor prevents the attenuation of mesenchymal tissue between adjacent airways and reduces surfactant protein levels.

Fibroblast Growth Factor Family (FGF) consists of over 20 growth factors.[32]

FGF 1 and FGF 2 differ at different stages of lung development and FGF 7 (keratino growth factor KFG) proposed that KGF both enhances[33-35] and inhibits growth of the developing lung.

Parathyroid Hormone-Related Protein (PTHrP) induces surfactant protein and surfactant phospholipids biosynthesis, increases PTHrP expressions and receptor binding and enhances its effects on surfactant phospholipid synthesis.[36]

Role of Environmental Factors during Lung Development

The various regulatory mechanisms are influenced by several environmental factors and results. They significantly influence the occurrence of diseases. Hypersensitivity diseases in particular, may have their roots in *in utero* sensitization to allergens. Similarly, exposure of the fetus to tobacco smoke from a smoking mother (passive smoking) or even from other smokers in company of the pregnant mother (tertiary smoking) have been implicated in the development of allergic disorders and lung function impairment after birth.

a. *Influence of in utero exposure to allergens on development:* Exposure of the fetus to allergens inhaled by the mother during pregnancy can result in its sensitization to those allergens. In one study, neonatal peripheral blood T-cells were obtained from whole blood and stimulated with several antigens or common inhaled allergens. It is well known that maternally derived T-cell would respond to commonly encountered antigens and fetal cells would respond only to the inhaled allergens.

Maternal avoidance of allergen could influence the development of allergic reactivity in the fetus. Levels of IL-4, IL-5, IL-10 and γ-interferon were determined and compared with allergen data. They observed that the cytokine levels did not correlate with allergens.

It has been hypothesized that Th-cell cytokine patterns are determined during infancy. Although the stimulation of neonatal T-cells occurs with allergen-produced cytokine profiles. It is suggested that exposure to allergens during development may be a critical factor for the development of allergenic phenotype infants and children who are genetically predisposed to allergy.

Maternal exposure to allergens can result in a protective IgG response that may decrease the fetal sensitization. The degree of the production of gamma interferon by stimulated T-cells have a stronger likelihood of predicting the future development of atopic disease. Th-2 phenotype during pregnancy is known to favor the prenatal development of allergy, thus the interaction between environment and genetic background during *in utero* life of a human infant determines the future allergic status of the child and adult.

b. *Neonatal exposure to allergens:* Several infectious diseases are thought to have a role in either facilitating the development of allergic sensitization to inhaled allergens during the neonatal period or subverting the allergic response. The "hygiene hypothesis" (discussed later in this chapter) focuses on early exposure to bacterial products that appear to have an allergy-sparing effect. In contrast, certain viral respiratory infections have been implicated in the promotion of allergen sensitization and development of asthma. Viral infections are frequently associated with wheezing in small children. The fact that many of these children progress to become asthmatic has led to the supposition that the early viral infection may either facilitate sensitization or damage airways hyperactivity.[37] One of the major respiratory viruses that appears to have a link to asthma is Respiratory Syncytial Virus (RSV). In the severe form, RSV causes wheezing and severe bronchiolitis and often interstitial pneumonia. It was recognized in the 1980s that children with most severe RSV, accompanied by wheezing, were often subsequently diagnosed with childhood asthma. Indeed, IgE specific for viral proteins, as well as elevated histamine concentrations in respiratory fluids, were found in severely affected children.[38]

More recently, it has been found that RSV preferentially induces a Th2 cytokine environment in atopic children and in some animal models. Studies have shown that infection of Balb/c mice with human RSV induces a T-helper cell type 2 response.[39] A previous study demonstrated that some calves infected with bovine respiratory syncytial virus[40] (a closely related bovine pathogen) develop a Th2 cytokine response when infected with the virus. Indeed, infection of IgE is also associated with this model. Further work with the bovine model has demonstrated that the disease is exacerbated when allergen is inhaled during the virus infection[41] and that sensitization can be enhanced by exposure to allergen during the viral infection.[42]

In contrast to these observations, a recent study has demonstrated that in the severe cases of respiratory disease with wheezing, γ-interferon is present in elevated amount. However, in this study, the identity of the virus causing the infection and wheezing was not elucidated.[43] Following up on these observations, Garofalo et al.[44] examined the role of Th1 and Th2 cytokines, as well as several chemokines in RSV disease. They found that macrophage inflammatory protein-1α was associated with severe RSV bronchiolitis. Thus, the role of cytokines in induction of clinical disease may be different to that previously thought to stimulate the subsequent development of asthma.

SUMMARY

The respiratory system in the fetus is elegantly designed to develop from an undifferentiated epithelial tube to a complex air conducting branching system and an enormous gas-exchanging surface with a large number of differentiated cells engaged in several different functions. The immediate functional transformation and adaptation of the respiratory and circulatory systems, to the “foreign” strenuous environments after the birth is both dramatic and miraculous. Although the alveolar formation and lung development continues postnatally for some period, most of the somatic growth is complete at birth.

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4

Genomics of Lung Diseases

L Keith Scott

INTRODUCTION

Since the discovery of Mendel's work, there have been exhaustive attempts to apply inheritance patterns to most of the diseases. However, if a disease did not satisfy traditional mendelian patterns, genetic contributions were usually discounted. This led many to look at other contributors of a disease state such as environmental factors and infectious disease-related factors. This narrow and focused research has produced much of our present understanding of diseases and generated numerous therapies. However, in spite of many successes, there were always gaps in our understanding of many diseases. Traditional views did not always explain why certain diseases progressed the way they did or why there could be person to person variation of the same disease. Many felt that the variable that influenced disease individuality was exposure, timing, pathogen virulence, coexisting disease, etc. Although these certainly do influence how a disease presents itself and progresses, these traditional contributors do not always fill our gaps in understanding.

In 2001, a preliminary map of the human genome was published.[1] This provided investigators with a new look at diseases and a new way to perceive diseases. With advances in genomic technologies allowing high throughput analysis of a large number of genes at one time, investigators began to relook at genomics in a new light and away from the traditional genetic inheritance paradigm. New tools were introduced with heavy dependence on computation and the age of bioinformatics and computational biology were born. A few years later, the map of the human genome was deemed complete, augmenting bioinformatic investigations further. This revolution began the realization that genomics is a dynamic and complex process and the simplicity of mendelian patterns but a small piece of the genomics puzzle.

GENOMICS AND DISEASE

Some diseases, such as the heart disease can be easily associated with a genetic role, even though they might not adhere to strict mendelian rules. Other disease states were not as clear and the role of genetics was less obvious. Questions has risen and problems developed that did not make sense without some contribution of an individual's genome. For example, why would one person with an apparently normal immune system acquire pneumococcal pneumonia and barely get ill, while an equally matched person developed lethal septic shock? Was it a different bug? Was that person unlucky? Only after the push to better understand the genomics of the human in health and disease, not as a function of heredity, but as a dynamic process of cellular function, some of these questions were answered. The sequencing of the human genome, along with many new technologies, have been the basis of our discovery of how dynamic the genomic transcription-translation process really is. This understanding was further enhanced by additional understanding of protein function, binding and folding.

Lung diseases and all its contributors is an area of pathophysiology that encapsulates this process. Few organ systems are as impacted by environmental, infectious and perhaps genomic influences as the respiratory system. This chapter will discuss the genomics of lung diseases, concentrating on several major lung disease states: Acute

Lung Injury (ALI), Chronic Obstructive Pulmonary Disease (COPD)/Asthma, pulmonary hypertension and interstital lung diseases. There will also be a brief discussion on computational biology and complexity theory and how it relates to understand disease states.

GENOMIC NOMENCLATURE AND INVESTIGATIONAL TOOLS

To describe and present data on genomic studies, there needs to be consistent nomenclature and definitions. Few definitions are discussed below that will be used in this chapter.

Allele: Alleles are Deoxyribonucleic Acid (DNA) sequences at the same physical gene locus, which may or may not result in different phenotypic traits.

Bioinformatics: The science of applying computational tools to search databases, analyze DNA sequence information, and to predict protein sequence and structure from DNA sequence data.

Haplotype: A set of closely linked alleles inherited as a unit.

Homology: Genes derived from a common ancestor.

Locus (loci): Position on a chromosome of a gene or other chromosome marker (can also be the DNA at that position).

Microarrays: This is a technology that allows the high throughput analysis of multiple genes from a single sample. The technology is based on probes, which are immobilized in an ordered two-dimensional pattern. Probes are either spotted cDNAs or oligonucleotides and are designed to be specific for an organism, a gene or a genetic variant.

Polymerase chain reaction (PCR): It is a method for synthesizing millions of copies of a specific DNA sequence.

Single-nucleotide polymorphism (SNP) (Polymorphism): A SNP is a DNA sequence where a single nucleotide in the genome differs between members of a species.

Genomic Research

Since the beginning of high throughput genomics, there has been a tendency to single out small number of genes and make claims regarding the contribution of genes towards a particular disease state. This has been dubbed the reductionist approach and is more in line with the standard research paradigm.[2] It rapidly became clear that gene expression does not always translate to protein production or functionality. More recent research paradigms have focused on a system approach looking at the groups of genes and evaluating these groups as a part of a system involving single or multiple pathways. This approach has been enlightening and has generated a better understanding of host-gene-protein interactions and probably more of a "real world" picture.

Genomics and Acute Lung Injury

Acute lung injury is not a homogeneous disease as once thought. ALI can be related to a primary lung insult, such as aspiration or related to a process or distal to the lung such as pancreatitis. This has resulted in rethinking ALI, either as a primary process in which the injury is an epithelial-to-endothelial process, or a secondary process in which the insult is endothelial-to-epithelial. Both disease types are phenotypically similar, but may have very different morphologic response of the lung itself.[3] Although the etiology remains unclear, there does appear to be an imbalance between pro- and anti-inflammatory cytokines; oxidants and antioxidants; procoagulants and anticoagulants; neutrophil activation and neutrophil clearance; or proteases and protease inhibitors.[4] We will limit our discussion of what is felt to be the more significant proteins, involved in the development of ARDS.

Angiopoietin-2 (Ang-2) is a potent regulator of vascular permeability and inflammation in acute lung injury and acute respiratory distress syndrome.[5] This protein aids in promoting the cell to cell integrity and maintenance of gap junctions. Several studies have demonstrated that the high levels of Ang-2 are associated with ARDS related to primary lung injury and secondary lung injury,[6,7] VILI and hyperoxia related to ALI.[8]

Genomic studies have demonstrated differing gene expressions in animals with ALI induced by differing mechanisms. In one study, rats with ALI induced by LPS and others by high-volume ventilation were compared.[9] Microarray expression analysis revealed the different expressions of genes based on biological function between the groups. Genes that showed increased expression in the LPS group were metabolism, defense response, immune cell proliferation and cell death. Those with ALI induced by volutrauma were organogenesis, morphogenesis, cell cycle, and cell proliferation and differentiation. This supports the concept that ALI is really a downstream process, or phenotype, with many different genotypic avenues leading to the injury.

TABLE 4.1: Numerous genes, reported to be associated with ALI, listed by the gene symbol, gene name and the associated genetic variant

Gene symbol	*Gene name*	*Associated variant*
IL-6	Interleukin-6	Gene-wide haplotypes G/C-174
TNF	Tumor necrosis factor	G/A -308
VEGF	Vascular endothelial growth factor	C/T +938
IL-10	Interleukin-10	A/G - 1082
MIF	Macrophage inhibitory factor	Haplotypes
ACE	Angiotensin converting enzyme	I/D intron 16
NFkB	Nuclear factor kB	Ins/del ATTG -94
SFTPB	Surfactant associated protein B	T/C +1580 Intron 4TR
MLB2	Mannose-binding lectin	3 variant at multiple haplotypes Gly54Asp
CXCL2	Interferon-gamma-inducible protein	-665 TR

These studies, however, are greatly limited by phenotypic differences, incomplete gene penetrance and gene-environmental interactions.[10] All of that is further complicated by the different populations investigated and the degree of heterogeneity. Many genes have been associated with ALI (Table 4.1).

Polymorphism has also been demonstrated to be a variable in the development or response to ALI. In a study, the European descendents with ARDS were found to have an insertion/deletion polymorphism of the NF-κB promotor; those that were homozygous for the deletion of this promoter had higher lung injury scores, but no change in the outcome.[11] Similarly, the 4G/5G polymorphism of the plasminogen activator-1 gene has been shown to prolong ventilation in patients with pneumonia and ALI.[12]

Heme oxygenase-1 appears to offer cytoprotection to the development of ALI. The haplotype S-TAG of the heme oxygenase-1 gene is associated with an increased ARDS risk. In a somewhat different twist, the longer the repeats of the (GT) allele of the heme oxygenase gene, the higher were the heme oxygenase serum levels, which resulted in reduced risk of developing ALI.[13]

The list of genomic variables will expand over the next few years with each SNP or significant gene being promoted as a target of therapy or marker of disease. It is, however, a simplistic view that a “magic bullet” will be found using high throughput genomics. Genomics are extremely complex with gene-to-gene interaction, gene-to-environment interactions and varying penetrance, all confounding the data. Although bioinformatics has come a long way in accounting for these variables, the level of complexity is far beyond from our current understanding. Genetic studies that investigate disease states must account for population heterogeneity. Understanding this heterogeneity will be paramount, before any meaningful data can be conjectured or therapeutic interventions advanced.

Genomics and COPD/Asthma

Chronic obstructive pulmonary disease is a very complex disease state with both gene-environmental interactions and genetic susceptibilities. A recent study compared gene expression and SNPs in over 300 patients with COPD that had rapid decline in FEV$_1$ to those that had a lesser degree of decline.[14] Till date, these investigators have isolated over 50 genes that are differentially expressed (Table 4.2).

TABLE 4.2: Some of the major candidate genes that are differentially expressed in COPD

a1-AT Z2,
Arg139,
β2AR
Glu27 > Gln0.6,
Haplotype-IL1RN A1/IL1B ,
IL8 A,
IL6,
MMP-1,
IL4RA2
Glutathione Transferases (GSTP1 Ile105 > Val, GSTT1and GSTM1),
Heme oxygenase-1,
Catalase1Nicotine Receptor (CHRNA5)

Table key: a1-ATZ = heterozygosity for the Z allele of alpha one antitrypsin; mEH = microsomal epoxide hydrolase; β2AR = the beta 2 adrenergic receptor; IL1RN A = interleukin 1 receptor antagonist; IL8 = interleukin 8; IL6 = interleukin 6; MMP-1 = matrix metalloproteinase 1; IL4R = interleukin 4 receptor; glutathione transferases (GSTP1, GSTT1 and GSTM1); heme oxygenase-1; catalase; and the nicotine receptor (CHRNA5)

Genome wide analysis of patients with COPD was performed in 7,691 participants in the Framingham Heart Study.[15] Four SNPs on chromosome 4q were strongly associated with FEV1/FVC and one of these SNPs was also associated with FEV_1/FVC in the Family Heart Study and a similar Norwegian study.[16]

Recent studies identified 200 oxidative stress-related genes that were differentially expressed in the bronchial airways between smokers with and without COPD.[17,18] Looking at genome expression of the airway epithelium demonstrates that smoking exposure produces epithelial gene expressions that are specific for this exposure[19] and are associated with tobacco-related lung cancers.[20]

It is clear that the lung and epithelium of the lungs show differing genomic expressions in COPD progression and tobacco exposure. Even correlating some of these genes to eventual cancer development is an exciting advancement. However, like all genomic studies, there are limitations and cautions that must be observed when making broad conclusions. Even though genes may be expressed, this may not translate into protein synthesis or protein function. Therefore, proteomic studies are also needed to complement the genomic studies. With these tools in hand, investigators can shed new light in the understanding of the pathology of COPD especially on a molecular level.

A recent study by Lee et al,[21] preformed "shotgun" protein analysis of lung tissue and epithelium of patients without COPD, smokers without COPD and COPD that had ongoing tobacco exposure. They found twelve proteins that were differentially expressed. Of the twelve, matrix metalloproteinase (MMP-13) and thioredoxin-like 2 were significantly increased in the COPD patients. MP-13 was isolated mainly in the alveolar macrophages and type II pneumocytes with thioredoxin-like 2 was primarily seen in the bronchial epithelium.

There is far less data in asthma and genomic variability. Although there is obvious inheritance of allergic tendencies, less is clear about individual variation of patients with asthma; however, this is rapidly changing. One of the first steps has been the improved identification of the phenotypes of asthma. A recent study looking at hierarchal clustering analysis of 628 variables on 726 subjects found five subgroups (clusters) that were identified.[22] The clusters were:

***Cluster 1*:** Early onset atopic asthma with normal lung function treated with controller medications and minimal health care utilization.

Cluster 2: Early onset atopic asthma and preserved lung function, but increased medication requirements and health care utilization.

***Cluster 3*:** Older obese women with late onset nonatopic asthma, moderate reductions in FEV_1 and frequent oral corticosteroid use to manage exacerbations.

***Clusters 4*:** Severe airflow obstruction with bronchodilator responsiveness.

Clusters 5: Have severe airflow obstruction with bronchodilator responsiveness and use of oral corticosteroids.

This classification system may provide better categorization in order to apply genomic investigations.

Some genome comparisons have been performed, but usually have identified extreme differences in gene expression. As the sophistication of bioinformatics has developed, less robust gene expression changes can be found and may add to the ever increasing list of genetically determined phenotypes of asthma.[23]

In spite of the limitations to genomic studies in a disease process that affects different genetic pools, several genes have emerged consistently across diverse populations. The major genes are TNF alpha, IL4, FCERB, Adam 33 and $GSTP_1$.[24] Also, polymorphisms of the chemokine receptor-2 (CCR2) have been found to be present in asthma and may play a significant role in disease susceptibility.[25] A large cohort analysis identified a locus containing DENND1B on chromosome 1q31.3 that was associated with susceptibility to asthma.[26] This locus was found in children with both European and African descent.

More recent genomic investigations have begun to diverge from pathophysiologic variability and to look at therapeutic variability. Much of the attention has focused on the beta2-adenergic receptor (BDRB2). Although there are polymorphisms identified with this gene, there is also a question as how it may affect therapy with β-agonist.[27,28] It is likely that all therapies have potential for genetic variability in responsiveness[29] and this is why, pharmacogenomics is such an important field in the future of asthma therapy.

Genomics and Interstitial Lung Disease

Interstitial lung disease is a heterogeneous group of diseases that have eluted etiologies. Diagnostic classifications have been made, based on clinical course, high-resolution CT scan and pathologic tissue examination. There have been high hopes that genomics would hold promise as a diagnostic tool, particularly in early disease.[30]

Sarcoidosis

This is an inflammatory lung disease that has demonstrated altered BAL fluid with proteins that are not from leaked plasma.[31] Many of these proteins are not surprisingly related to inflammation. Many genomic studies have been able to narrow these proteins to the inhibitory nuclear factors kappa B-alpha (IκB) and nuclear factor kappa B (NFκB). Polymorphisms of the IkB promotor have been shown to be associated with sarcoidosis, with the -297T allele carriage. This was found to be more prevalent in patients in comparison to the control groups. Three common haplotypes were found, of which haplotype 2 (GTT) was most commonly associated with sarcoidosis. Subgroup analysis revealed that the -826T allelic carriage was most prevalent in stage II and III disease.[32] In high throughput genomic analysis, genes that were found to be associated with persistent disease included HLA-DRB1*1501, DQB1*0602, TNF-α, NFkB, cyclic AMP-responsive element modulator (CREM) and T-cell activation marker CD69. Those associated with self-limited disease included IL-1B, IL-8, growth related (GRO)-beta/-gamma and CCR 2,5,6.[33]

Usual Interstitial Pneumonia (UIP)

Usual interstitial pneumonia/idiopathic pulmonary fibrosis is the severest form of idiopathic interstitial pneumonia. The cellular make up is diverse and therefore the genomics of the disease is very descriptive of disease-related genomic complexity. In a study by Kelly et al,[34] genomic expression studies were performed on differing cellular matrix of UIP lung samples. They compared fibroblast, epithelial cells and type 2 pneumocytes. Using QT-PCR, they found that the tissue inhibitor of matrix metalloprotease-1 and matrix metalloprotease-2 gene expression was upregulated within the fibroblastic foci compared with the epithelium. Along with the previously mentioned mRNA, osteopontin was found to be upregulated in fibroblast, epithelial cells and type-2 pneumocytes. Also, levels of Bone Morphogenetic Protein (BMP)-4 antagonist gremlin were found upregulated in IPF/UIP, which seems to correlate with the severity of illness.[35]

UIP again is very complex, with differing states of fibrosis and repair expressing different genes and phenotypes. The phenotype of regenerative epithelium in UIP appears to be derived from bronchiolar basal cells and Clara Cells (CC). In severe fibrotic areas, CC-10 expressing cells were more prominent, while Surfactant Apoprotein (SP-A) positive cells were more prominent in less fibrotic areas.[36] In a case report of a child with UIP-like histology, mutations were found in the adenosine triphosphate-binding-cassette-A3 gene.[37] Its implications are yet to be investigated, but it further demonstrates the complexity of genomic studies, particularly of applying them to the diseased states and unfortunately, translating them into therapeutics.

As for diagnostics, genomic markers may offer diagnostic differentiation among the interstitial lung diseases. For example, the TH1 cells chemoattractant monokine, induced by interferon (IFN)-gamma (MIG) and IFN gamma-inducible protein of 10 kD expression, were significantly higher in NSIP compared with UIP.[38]

Genomics and Pulmonary Hypertension

Pulmonary artery hypertension (PAH) remains an idiopathic process, but there is an emerging data that the disease is multifactoral, multigenetic and environmental. The disease is often subgrouped into idiopathic, familial and assocated PAH. Heterozygous mutations in BMPR2 can be detected in 50% to 70% of patients with familial PAH and in 10% to 40% of patients with idiopathic PAH. Heterozygous or homozygous bone morphogenetic protein receptor type 2 (Bmpr2) deletion in pulmonary endothelial cells predisposes mice to develop PAH.[39] Although initially isolated in familial PAH, its presence without direct inheritance may represent a genetic milieu that promotes the development of PAH in the face of environmental factors and other inducers.[40] In children with PAH, the Activin Receptor-Like Kinase 1 gene (ALK1) has also been found in familial PAH.[41] However, its role and significance in the cases of idiopathic PAH is unknown.

Using a hypothesis generating approach to idiopathic PAH using microarray technology, have revealed a distinct expression profile in peripheral B-lymphocytes. This revealed 33 unique genes, which were differentially upregulated in idiopathic PAH.

The proteomic methods of investigation have shed more light on PAH. The PAH associated with sickle-cell disease cohort has been characterized by the high levels of apolipoproteins A-II and B and serum amyloid A, and low levels of haptoglobin dimers and plasminogen.[42] In a cohort of idiopathic PAH, the proteins Alpha-1-anti-trypsin and vitronectin were found to be down-regulated.[43]

Biocomplexity and Computational Biology

The age of genomics is upon us and has exponentially expanded our understanding of the molecular basis of many diseases, including the ones discussed above. Genomic expression studies often report a significant gene or a group of genes in a disease process. Many times this is based solely on mRNA expression and is not followed through protein translation and function. This

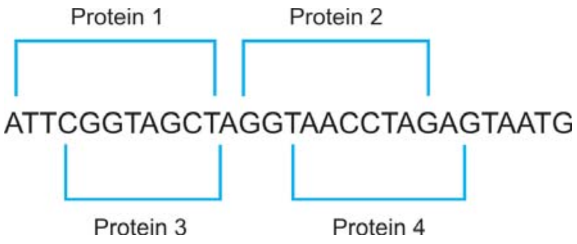

Fig. 4.1: Demonstrating that a specific DNA base pair sequence can represent many genes depending on the starting point and ending point of the transcription. Thus there is crossover among the sequence to produce many different proteins from a relatively small base pair sequence

is too simplicitic as the entire landscape of genomics is changing. We are just beginning to understand that gene-to-gene interactions and gene-to-protein interactions are far more complex than previous thought. Although the basic structure of DNA is eloquently beautiful and simple, that is where simplicity ends.

All of us were taught the genomic paradigm of one-gene one-protein and that a specific gene belongs to a specific chromosome. Now we know that this is not necessarily true. Many genes and DNA sequences can crossover to transcribe different proteins on the same gene. That is to say that a long DNA sequence may transcribe albumin, if started with a specific DNA sequence. If, however, the DNA transcription starts one base pair away, it may transcribe a protease, even though it is still within the albumin gene as shown in Figure 4.1. This means that all the DNA sequences that were once thought to be "junk" genes are a part of this shared-gene concept and is what makes us unique as a species. Only by using the bits and pieces of different genes to make a new gene so to speak, and understanding that the concept of one-gene one-protein is not true, can we explain our diversity. Added over this is the fact that genes seem to have the ability to change chromosomes; this is where we enter the world of complexity theory and the need to use complex computational tools to understand these complex interactions. It is likely that the only way that meaningful therapeutics will emerge from this age of genomics is through these tools.

A study, which identifies a gene that shows upregulation, in no way, translates to functional or phenotypic changes. Even confirming mRNA of the gene or the presence of the translated protein in no way assures that the protein has pathologic or physiologic function. This is one reason why there have been such disappointments in genetic therapeutics. Genomic studies need to be looked at in the context of the host, the environment and heredity to name a few confounders.[44]

This interaction has prompted the new science of biocomplexity and computational biology that evaluates the biologic pathways that generate disease.

New areas of investigations are emerging all the time. For example, looking at the spatial relationships of a nucleosome to the gene and how this relationship may influence function.[45] However, the biggest advance recently appears to be the study of epigenetics.

Epigenetics

Epigenetics is a new field that is shedding new light over many diseases. Epigenetics is the evaluation of phenotypes that are unique to a cell line or species that is not directly related to the base genome sequence.[46] These phenotypes result from non-genetic influences and can persist for several generations. How this affects lung diseases is presently unknown, but deserves considerable attention, particularly since most lung diseases have significant environmental influences. Each of these influences can affect phenotypic expression that cannot be explained by DNA sequences. This may greatly enhance our understanding of genetics and fill many questions about diseases and protein behaviors that are not easily explained by genetics alone.

SUMMARY

Genomics have come of age. Genetic contributions to disease states have moved beyond inheritance. New tools, such as microarrays have provided new insights into diseases, allowed new hypothesis to evolve and have thrust reductionist philosophy into the world of biocomplexity. Lung diseases have always been difficult to study due in part to the numerous influences that foster a disease or exacerbate a disease. Genomics and epigenomics are providing new insights into these diseases that will hopefully produce better diagnostics and therapies.

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Section

2

RESPIRATORY PHYSIOLOGY

SK Chhabra

5

Applied Respiratory Physics

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INTRODUCTION

Functioning of the respiratory system is largely governed by the physical principles and laws. Knowledge of simple, applied physics is important to understand the movement of air in and out of the lungs, the flow of blood across the pulmonary vessels, exchange of gases and maintenance of the fluid balance. This chapter provides a brief introduction to the general physics with reference to the respiratory functioning. More details are available in the respective chapters on individual subjects in the book.

STATE OF MATTER

Matter can exist in three classically different forms in nature—solid, liquid or gas; although plasma, a fourth state of matter has also been identified under the extremes of temperature and pressure. Matter is either an element made from similar atoms, e.g. iron or compound made from two or more types of atoms, e.g. water (H_2O) in nature. An element is a basic unit of matter, which retains the same properties on subdivisions by chemical or mechanical means. Oxygen and other gases, such as hydrogen, helium, chlorine and nitrogen are elements in nature.

Atom and Element

An atom is the smallest part of an element, which acts like its "building block". On the further subdivision of an atom, the elemental properties are lost and therefore, subatomic constituents of all atoms are identical. Atoms of certain elements (e.g. hydrogen, helium) can exist in free state (H, He) and there is no difference between the atoms and molecules of these elements. Atoms of many other elements (such as oxygen) do not exist free, but combine with other atoms of the same element to form molecules (e.g. O_2, i.e. O+O). Atoms of different elements may form molecules or compounds. Hydrogen can exist in atomic or molecular form, whereas nitrogen and oxygen occurs in molecular form (N_2 and O_2).

Molecule and Compound

All substances consist of exceedingly small particles called molecules. There are about 10^{19} molecules in 1 ml of air under the normal conditions of temperature (T) and pressure (P). A molecule possesses the distinctive properties of the parent element or compound. A molecule is found to consist of two or more atoms of same kind or of different kinds.

The number of molecules comprising a macroscopic quantity of a gas is enormous typically around 10^{23} molecules. The number of molecules and their velocity determine many properties of gases.

A compound is composed of two or more elements united chemically to form a substance different from the individual elements forming that compound. For example, carbon dioxide is a compound of carbon and oxygen. On subdivisions, the compound loses its properties and may resume those of the constituent elements. Both elements and compounds exist as molecules as the smallest component.

Molecular Movement

All the molecules of matter are in a state of incessant motion. This is known as Brownian movement and forms the basis of the kinetic theory of matter. This motion results from temperature—the higher the temperature, the larger the velocity of the molecules. At absolute zero temperature, the velocity of a classical molecule goes to zero. Molecules of a gas have great mobility and travel longer distances before colliding with other molecules. It is because of this mobility that a gas has no fixed shape and mixes readily with other gases.

Atomic and Molecular Weights

The mass of an atom is concentrated at its nucleus, which contains a definite number of neutrons and protons of identical masses. The neutrons or protons are also called nucleons. The mass of a nucleon is ≈ 1.6 x 10^{-24} gm (sometimes also called atomic mass unit, amu). Therefore, total number of nucleons of an atom determines the mass of an atom and is usually called atomic weight. This H´ atom has atomic weight equaling 1, whereas O´ atom has atomic weight equaling 16. Though their actual masses are around 1 x 1.6 x 10^{-24} gm and 16 x 1.6 x 10^{-24} gm, respectively. Similarly, molecular weight is determined by summing up atomic weights of the constituent atoms forming that molecule. As an example, H_2 molecule has a molecular weight = 2, and H_2O molecule has a molecular weight = 2 + 16 = 18. For obtaining their actual weights, we multiply those weights by amu (= 1.6 x 10^{-24} gm) to get the mass in gm.

If M is the molecular weight of given substance, then 1 molecule of that substance weighs M × 1.6 × 10^{-24} gm. This gives us that M gm of the substance will have 1/1.6 x 10^{-24} molecules, which is called Avogadro number, $N_o \approx 6.02 \times 10^{23}$. It is thus clear that M gm (also called 1 mole) of any substance will have N_o molecules.

Gaseous substance (which behave like an ideal gas) follow an equation PV = nRT

One can easily calculate the volume at NTP (normal temperature 0°C, and pressure ≡ 760 mm Hg) from η = 1 mole. It comes out to be 22.4 liters for any gas. Therefore, a quantity of any substance equaling molecular weight as gm has 6.02 × 10^{23} molecules and as a gas, occupies 22.4 liters at NTP.

Equal volumes of gases at the same temperature and pressure contain equal number of molecules **(Avogadro's Hypothesis)**.

PHYSICAL PROPERTIES OF GASES

The air we normally breathe is a mixture of gases of which oxygen and nitrogen constitute the main bulk. Breathing of additional or supplemental gases is required in abnormal situations. The physical properties of these gases influence the mechanics of normal breathing, as well as the therapeutic strategies.

Volume

Volume is the space occupied by a gas. The volume of a cuboid-shaped vessel is determined by the multiplication of internal length, width and height of the vessel. It is expressed in cubic centimeters (cc), cubic feet or liters (L), etc. (1 L ≡ 1000 cc or mL).

$$\text{Volume} = \text{Length} \times \text{Width} \times \text{Height}$$

A 10 cm cube has the volume equaling 1 L. Volume of a container of uniform cross-sectional area A and height is given by V = A h.

The gas shall occupy the available volume irrespective of the amount (mass) of gas. For example, if a small vessel containing oxygen is emptied in a larger vessel, the entire volume of the larger vessel will be occupied by the same amount of gas (Fig. 5.1).

Mass and Weight

Mass is the bulk or the total mass of number of molecules of the gas. In the above mentioned example, the mass of the gas in two cylinders shall remain the same, although the volume has changed. The number of molecules per

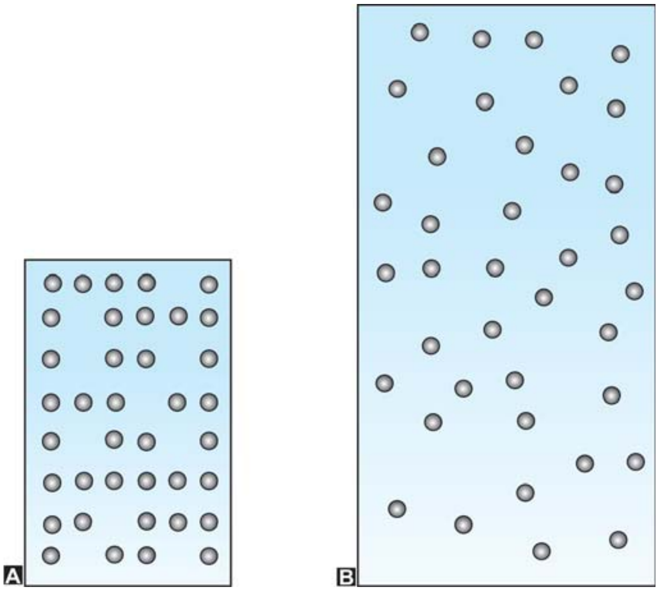


Fig. 5.1: Mass of a gas such as O_2 (i.e. number of molecules) in vessels A and B is unchanged, but the volumes are different therefore, the density of the gas in vessel A is greater than that in vessel B

unit of volume in the two vessels has changed, i.e. lesser number of molecules per unit volume in the larger vessel (Fig. 5.1).

Weight is often used synonymously with mass. Weight is determined by the pull of gravity on mass (i.e. m × g). Since the force of gravity on the earth is nearly constant, mass is equivalent to weight on the surface of the earth. In fact, weight is scaled to indicate mass and therefore both represent the same thing.

$$W \equiv \text{force} = mg$$

Density

Density is expressed as the weight in the grams of one liter of a gas. Since the weight of 22.4 liters of a gas is that of a gram molecule of that gas, one liter of gas shall weigh molecular weight/22.4 gm. When expressed this way, the density will be measured in gm/liter. It is also measured in gm/cc, which will equal 1/1000 in value to that in gm/liter.

Molecular weight of oxygen = 32
Density = 32/22.4
= 1.43 gm/liter

The density of a gas is also expressed as relative to the density of air. Density of air shall vary depending upon its composition. For all practical purposes, it comprises of 1 volume of oxygen (about 20%) and 4 volumes of nitrogen (about 80%). At NTP, the density of air is $(32 \times 1/5 + 28 \times 4/5) / 22.4 = 1.3$ gm/L. Therefore, the density of oxygen relative to that of air is 1.1. When expressed this way, it becomes unimportant, if the density of individual gases was calculated in gm/liter or gm/cc.

Pressure

The gas molecules are always in a state of motion and constantly bombard the walls of the container. The force applied to (or acting upon) a unit area of the wall is called the gas pressure. The closer the molecules, the greater the number, which strikes each unit area and therefore the greater the pressure applied. Also, larger the velocity (or temperature), larger is the impact on the walls, leading to greater pressure.

Gas pressure is generally considered as that of a stationary gas when the pressure exerted is the same at any point in a gas container. The pressure is usually expressed in the millimeters of mercury (mm Hg) or Centimeters of water (cm H_2O) or pounds per square inch (psi). One millimeters of mercury means force on a unit area (1 cm^2) on which 1 mm of height of Hg is placed. The volume of height h cm on unit area is $A \times h = h\ cm^3$ and in mass is hd where d is the density of the liquid. The force on unit area due to this is hdg, which is also the pressure p. Thus p due to a height h of a liquid of density d, p = hdg. The pressure due to 1 mm Hg can be calculated by putting h = 0.1 cm, d = 13.6 gm/cc and g = 980 cm/S^2.

1 mm Hg ≡ 1334 CGS units or dynes/cm^2
= 133.4 Pa (Pascal is another unit of pressure)

Atmospheric Pressure

Atmospheric air is pulled to the earth by gravity and generates a force upon the surface of the earth, resulting in atmospheric pressure. Atmospheric pressure is the sum of pressures of all gases (e.g. N_2, O_2 and CO_2) present in air). It is measured with the help of a glass tube filled with either mercury or water (manometer). The height of the column of mercury (or water) multiplied by its density is a measure of the atmospheric pressure. Standard pressure is measured at sea level and expressed in mm Hg (torr) or cm H_2O. One atmospheric pressure = 760 mm Hg or
14.7 psi or
1030 cm H_2O

It is important to convert atmospheric pressure (≡ 76 cm of Hg) in CGS units. This is approximately 10^6 CGS units.

$$1 \text{ atm} \equiv 76 \text{ cm of Hg} \simeq 10^6 \text{ CGS} \simeq 1 \text{ bar}$$

It is relevant here to mention that the lungs are subject to atmospheric pressure all the time. Since the alveoli are in direct communication with the atmosphere through the tracheobronchial tree, the alveolar pressure is the same as the atmospheric pressure. The changes in alveolar pressure during inspiratory and expiratory phases of respiration are relative to the atmospheric pressure. During inspiration when the alveolar pressure is –10 cm H_2O, it implies the presence of atmospheric pressure—10 cm H_2O (i.e. 1030 – 10 cm H_2O). Similarly, when positive pressure is administered to a patient through a ventilator, the ventilator gauge pressure of 10 or 20 cm H_2O refers to a total pressure of 1040 or 1050 cm H_2O (i.e. atmospheric pressure + gauge pressure).

Partial Pressure

In a mixture of gases in a container, each gas exerts the same pressure, which it would if it alone occupied the container. There is no interference from the presence of other gas(es). The pressure exerted by each individual gas is called the partial pressure. The total pressure exerted by the mixture of gases is equal to the sum of the partial pressures of all the gases contained in the mixture (Dalton's law). The partial pressure is determined by the fraction of the concentration of the gas in the mixture.

The atmospheric air has a total pressure of 760 mm Hg when dry at sea level. The partial pressures of N_2 (79%) and O_2 (21%) therefore, are as follows:

P_{N_2} = 79% of P_{atm} = 600.4 mm Hg
P_{O_2} = 21% of P_{atm} = 159.6 mm Hg

Temperature and Heat

Temperature is the thermal state of a substance, which determines whether the substance will give or receive heat from another substance in contact. It is an indication of the level of molecular activity. Heat is the thermal energy of a substance, which can be given to or abstracted from it. Temperature is the measurement of heat.

Calorie is the unit of heat. It is defined as the quantity of heat required to raise the temperature of 1 gm of water by 1^{o}C. As an example, if one calorie is required to raise the temperature of 1 gm of water by 1^{o}C, 1000 calories will be required for 1000 gm of water. The caloric value of food is expressed by a larger heat unit, i.e. the kilocalorie (cal or kcal), which is equivalent to 1000 cal.

To raise the temperature to a given range, similar weights of different substances require different quantities of heat. The number of calories required to raise the temperature of 1 gm of that substance by 1^{o}C is the specific heat of that substance.

The specific heat depends on the state of the matter—solid, liquid or gas. Specific heat of water is 1 (It follows from the definition of 1 calorie).

For gases, such as O_2 and air, it is 0.0603 cal per cc, it is quite high when expressed per gm.

We can calculate the total quantity of heat required to raise the temperature of a given volume by multiplying the volume with specific heat and temperature rise, i.e. volume (cc) × specific heat (cal per cc) × temperature rise (^{o}C).

THE GAS LAWS

There is a definite relationship between the gas properties described above. These relationships are described in different laws to understand the behavior of gases. These laws are valid for ideal gases only, where the assumption that the gas particles are very small and do not interact with each other is valid.

Boyle's Law

Pressure (P) of a gas is inversely proportional to its volume (V) provided the absolute temperature (T) of the mass of gas is kept constant. In other words, the product of pressure and volume remains constant. It follows immediately from the ideal gas equation,

$$P \propto \frac{I}{V} \text{ or } P \times V = \text{constant, if T is constant.}$$

Or $P_1 V_1 = P_2 V_2$

The application of this law in respiratory physiology is best exemplified in the use of body plethysmography to measure total lung capacity. It is also employed in many mechanical ventilators whereby the gas is driven into patient's lungs or into the cylinder of the ventilator by the upstroke and downstroke movements of the piston.

Charles' Law

When pressure and mass of a gas are kept constant, the volume of the gas will vary directly with its absolute temperature. Again from gas equation,

= Constant (K), if P is constant

It is because of this reason that volumes measured with the help of lung function equipments (at room temperature) are a little lower than those at body temperature (37^{o}C) and need to be corrected for the same. If the temperature of a container of a gas is lowered, the volume shrinks. Therefore, more gas can be stored in the same cylinder at a lower temperature.

Gay-Lussac's Law

Temperature and pressure of a gas are directly proportional when the volume and mass are kept constant.

$P \propto T$ or = K at constant V

It implies an increase in pressure if the temperature is increased. For this reason safety valves are provided with devices using high pressure gases to vent high pressures in case there is an accidental heating.

The General Gas Law

Assume N ideal noninteracting molecules of a gas each of mass m are contained in a cube of volume V. They are in motion if the temperature is above 0^{o}K (0^{o}K = -273^o C). If the temperature is T in Kelvin, the kinetic energy from each molecule is of the order of kT, where K is called Boltzmann constant (K = 1.38 X 10^{-16} CGS units). Because of this kinetic motion, the molecules of the gas keep bombarding the walls of the cube and exert pressure. The pressure increase results in extra energy (obtainable from force X distance or p x volume relation). In this way it is quite evident that one can equate the energy because of pressure PV as resulting from kinetic energy of N molecules, PV = NkT.

If N is expressed in N_o (Avogadro No.), PV = η N_okT, where η = N/No.

This is the famous gas equation valid for all ideal gases. η is the number of moles of the gas, N_ok is also called gas constant R. R $\simeq 6 \times 10^{23} \times 1.38 \times 10^{-16}$ erg/deg K

$$\simeq 2 \text{ cal./deg K}$$

The gas equation can be used to determine how the given initial state (P_1, V_1, T_1) relates to (P_2, V_2, T_2), some final state by using P_1V_1 ($T_1 = P_2V_2/T_2$).

$$\frac{P_1 V_1}{T_1 n_1} = \frac{P_2 V_2}{T_2 n_2}$$

It may be stated here that under the conditions of lower temperature and high pressure the gas changes its state to liquid. This is because the gas molecules get attracted to each other (van der Waals forces) rather than being repelled. The higher pressure condenses the molecules and the lower temperature reduces their activity.

$$\frac{D_1}{D_2} = \frac{d_2}{d_1}$$

$$\frac{1.3}{1000}$$

The temperature at which the gas turns into liquid is the "critical temperature" of that gas. For oxygen, it is -116°C. A pressure of 50 atmospheres is required to liquefy oxygen at –116°C. To keep the oxygen in a liquid form at 1 atmosphere in a flask open to the atmosphere, the temperature is lowered to below-183°C. This principle forms the basis of the availability of oxygen in the liquid form for storage and ambulatory use.

Henry's Law

The amount of gas that enters into physical solution in a liquid is directly proportional to the partial pressure of the gas. For example, the greater the partial pressure of oxygen in the alveoli, the greater the solubility in plasma.

Graham's Law

The rate of diffusion (D) of a gas is inversely proportional to the square root of its density (d).

Therefore, a light gas (such as helium) will diffuse at a faster rate than a heavier gas (such as oxygen).

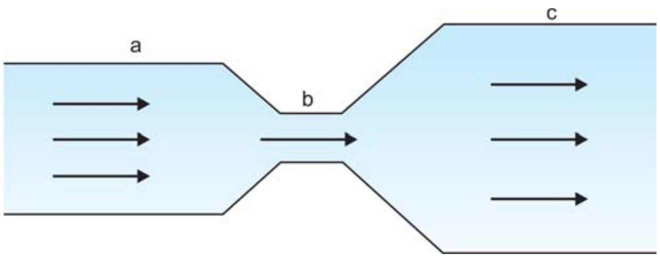


Fig. 5.2: Bernoulli's principle

Bernoulli's Principle

Flow of a gas through a partially obstructed tube can be described by Bernoulli's principle, i.e. the pressure required to produce flow is the difference in velocity at two points and the density of the gas (Fig. 5.2).

GAS SOLUTION AND TENSION

The amount of gas dissolved in a liquid is directly proportional to the pressure of the gas (Henry's law). It also varies with the temperature—lesser amount is dissolved at the same pressure if temperature is increased. A state of equilibrium is reached when no further gas dissolves in the liquid. This is a state of full saturation with the gas at a given temperature and pressure. The gas in solution is said to exert the same "tension" as the partial pressure of the gas over the liquid in equilibrium with it. For example, when the partial pressure of oxygen in alveoli is 100 mm Hg, the tension of O_2 in alveolar capillaries is 100 mm Hg. At this pressure, 0.3 cc of oxygen at NTP dissolves in 100 cc of water. The weight of oxygen dissolved in 100 cc water is

0.3 × = 0.0004 gm (1.3 gm/L is the density of oxygen).

The amount of oxygen dissolved in plasma or water is the same (0.004 gm/100 ml). This is quite sufficient to supply all the oxygen necessary for the metabolism of the body.

VAPORS

Vapor is defined as the gaseous state of a substance, which at room temperature and pressure is a liquid. On the other hand a gas at room temperature exists only in the gaseous state. Like any other gas, the molecules of a vapor are continuously in violent motion and bombard the walls of the container. The force exerted on each unit area is called the pressure of the vapor **(Vapor Pressure)**.

A vapor in a mixture of gases obeys the same laws as the gases. The partial pressure of the vapor in a mixture bears the same proportion to the total pressure as the volume, i.e. it depends on the percent (or fractional) concentration in the mixture. For example, the concentration of about 16% of water vapors in air at NTP, which is sufficient to saturate air with water vapors exerts a pressure of 16% of 760 mm Hg (47 mm Hg).

The presence of water vapors in air or oxygen is referred to as **humidity**. It is largely through the process of evaporation that the molecules of water (or any other liquid) evaporate into the overlying air (or any other gas in a container).

The molecules leave the liquid substance when their kinetic energy exceeds the surface tension of the liquid. If a liquid is kept in a closed container for long, a state of equilibrium is reached when the number of molecules returning to the liquid **(condensation)** is exactly equal to the number leaving it **(evaporation)**. This is called the saturation-point. This is further dependent upon temperature; if the temperature increases, the number of molecules leaving the liquid also increase and the saturation point is raised, i.e. there is a greater amount of vapors in the same amount of gas. Reverse happens with a fall in temperature.

The air we breathe is normally humid due to the presence of water vapor. The actual amount of water vapor present in air is expressed as "relative humidity", which is defined as the ratio of the amount of water vapor present in a given volume with the amount of water vapor, which the air (or the gas) is capable of holding at the given temperature, in the same volume.

The humidity of air varies with the atmospheric conditions. Once inhaled in the lungs, air gets fully saturated. The amount of water vapor required to saturate the alveolar air at body temperature and pressure is the body humidity.

The presence of water vapor in the inhaled air exerts its own partial pressure, and lowers the pressures of constituent gases of air—oxygen and nitrogen. Therefore, PN_2 or PO_2 is calculated as a proportion of the atmospheric pressure minus water vapor pressure, i.e. $P_{atm} - P_{H_2O}$.

When fully saturated, P_{H_2O} of atmospheric air is equal to 47 mm Hg. Therefore, $PO_2 = (P_{atm} - P_{H_2O}) \times 21\% = (760 - 47) \times 0.21 = 150$ mm Hg. The rest, i.e. 760 – (150 + 47) would be approximately the PN_2.

EXPRESSION OF GAS VOLUMES AND PRESSURES

In view of the effects of temperature, pressure and humidity on all gases, these are expressed with reference to those conditions. Some of the common expressions are:

i. Standard (or normal) temperature and pressure (STP) or NTP
   Temperature 0ºC; Pressure 760 mm Hg.
ii. STPD: D indicates "dry" = complete absence of water vapor.
iii. Ambient temperature and pressure—dry or saturated (ATPD or ATPS). Ambient implies the room conditions.
iv. Body temperature and pressure saturated (BTPS): Body temperature (usually 37ºC), ambient pressure and water vapor pressure (47 mm Hg).

Normally, gas volume measurements are made in the ambient conditions. Conversion is required to express the volume at BTPS or STPD. STPD is used for the uniformity of expression. This is done by multiplying with conversion factors. Tables of conversion factors from ATPS to STPD, STPD to BTPS, or BTPS to ATPS are available in most laboratories. Such corrections are also required to express volume of a gas (such as O_2) produced in the laboratory. The volume is expressed at STPD, which is different than that produced at ATPS.

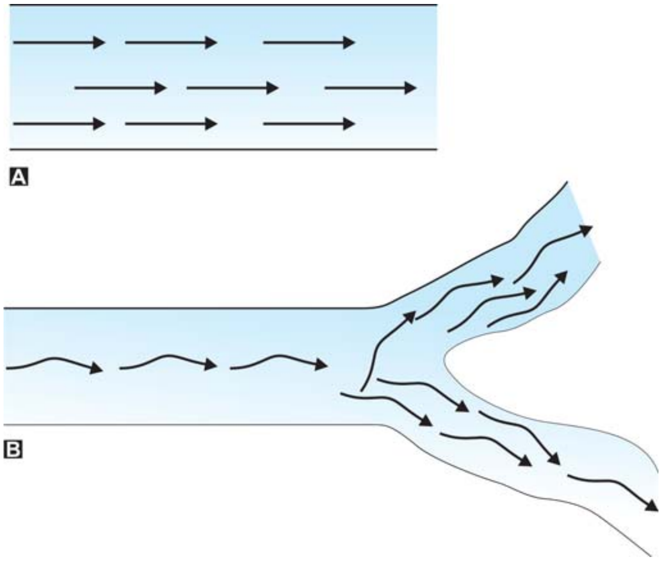
FLOW OF GASES

Flow is the movement of particles of a liquid or a gas from higher to lower pressure. It is expressed in the terms of volume per unit time, e.g. liters per minute or per second (L/min or L/sec). The movement of air into the lungs during inspiration and out into the atmosphere during expiration is accomplished by the flow of air through tracheobronchial tree. Similarly, oxygen flows from a container cylinder to the lungs or a ventilator through connecting tubes as long as there is a pressure difference.

The flow is described as laminar, if it is smooth and gas particles move along lines parallel to the walls of the tube (Fig. 5.3A). But it is turbulent if the lines of flow are irregular, broken up and disorderly (Fig. 5.3B). Whether the flow is laminar or turbulent, it has to meet a certain resistance while moving from one to the other end of the tube. The laminar flow is described by the **Hagen-Poiseuille equation**, i.e. $V = \prod \gamma^4 \Delta P)/(8\eta l)$.

Resistance

Resistance is defined by the pressure difference under given conditions, between the entry and the exit points of a tube. The resistance is dependent on the tube length (l) and diameter. It is also directly proportional to the



Figs 5.3A and B: Patterns of flow: (A) Laminar flow, (B) Turbulent flow

velocity of flow (∇) or rate in case of laminar flow. The flow is also viscosity (η) dependent and density-independent. When the flow is turbulent, the resistance rises for steeply.

In this way the laminar flow through a straight tube of uniform size is inversely proportional to the length (l) of the tube and directly to the fourth power of radius (r).

When the flow exceeds a "critical flow rate", the laminar flow is replaced by the turbulent flow throughout the length of the tube. Turbulent flow is less efficient since the ∇ P varies directly with V^2. Turbulent flow is density dependent and viscosity-independent. The critical flow varies directly with the internal diameter of the tube—the larger the diameter, the greater the flow. At a flow below the critical rate, local turbulence may occur as a result of irregularities in the pathways of the gas. During oxygen administration this may occur due to the constriction of kinking of the tubes.

Turbulence in a flowing system can also be predicted by Reynold's number. It is the ratio between inertial (density dependent, viscosity independent) and viscous (viscosity dependent, density independent) forces—a dimensionless number.

In case of pipes,

$$\textbf{Reynold's Number} = \frac{\text{Density} \times \text{Velocity} \times \text{Diameter}}{\text{Viscosity}}$$

Flow is "laminar" when the number is less than 2,000 and "turbulent" when it is more than 3,000. Turbulent flow is dominated by inertial forces producing random eddies and flow fluctuations. Between 2,000 and 3,000, the flow is transitional, i.e. neither fully laminar nor fully turbulent.

Flow Through Orifices

An orifice is a narrow opening of a tube. Unlike a tube, the diameter of the fluid pathway of the orifice exceeds the length. The greater the diameter compared to the length, the more does the opening approach the "ideal" orifice. The flow through an orifice depends on the diameter (or the cross-section area) of the orifice and the difference in pressures on either side of the orifice.

The intrinsic property of a liquid that influences its flow, which we earlier termed as resistance is called viscosity. It is attributed to the internal friction between different layers, which move at different speeds. While the laminar flow largely depends on viscosity, it is the density, which determines the flow when turbulent. The coefficient of viscosity is equal to the force per unit area necessary to maintain the unit difference of velocity between two parallel planes.

The flow through an orifice is at least partially turbulent. The lower the density, i.e. the lighter the gas, the greater is its volume flow for any given pressure difference on the either side of the orifice.

Wave Speed

Wave speed (c) is the speed at which a small disturbance (wave) travels in a compliant tube filled with a gas. In the airways, it depends upon the cross-sectional area of the airway (A). The density of the gas (p) and the slope of the pressure area curve of the airway (dP/dA):

$$c^2 = \frac{A/p}{dP/dA}$$

Maximum flow (V_{max}) of a gas in an airway is the product of the gas velocity at wave speed and the airway area (cA). It increases as the density of the gas decreases.

Thermal Conductivity

It is a measure of a substance's capacity to conduct heat. The high thermal conductivity is likely to result in a higher skin heat loss. But respiratory heat loss depends on heat capacity not conductance.

Heliox

Heliox is a mixture of oxygen with helium (He) in varying concentrations, commonly as 20% oxygen and 80%

helium. It has a lower density than that of air, i.e. oxygen (21%) with nitrogen (79%). Resistance offered to the flow of heliox is lower than that of air and of oxygen and depends on the fractional concentrations. It diffuses 1.8 times faster than oxygen. This fact is exploited in clinical practice for the treatment of acute respiratory distress of obstructive airway diseases, such as asthma when the flow is highly turbulent. Heliox diffuses fastly than oxygen through partially obstructed airways. In view of the lower resistance offered to heliox, the breathing effort is considerably reduced and the crisis tide over.

Diffusion

The molecules in a fluid (liquid or gas) unlike in a solid, move freely in all directions. The time taken by a molecule to travel a given distance depends upon its closeness to other molecules, and the intermolecular spaces. The gas molecules do not necessarily collide with the neighboring molecules when they move around or across a membrane.

Diffusion across a membrane is determined by the difference in concentrations between the two neighboring layers of the solution. The rate of diffusion is proportional to the gradient of concentration, i.e. the change of concentration per unit length in the direction of diffusion **(Fick's law)**.

Diffusion also depends on molecular movement. The rates of diffusion of gases at similar partial pressures through a porous membrane are inversely proportional to the square roots of their molecular weights **(Graham's law)**. The molecular weight of oxygen and CO_2 being 32 and 44 respectively, the diffusion ratio will be 1.2.

$$\frac{\text{Diffuse rate of Oxygen}}{\text{Diffusion rate of } CO_2} = \frac{1.2}{1}$$

It implies that oxygen diffuses 20% faster than CO_2 through a dry, porous membrane. It is because of the solubility of CO_2 in water of the moist alveolar membrane that the CO_2 diffusion is higher than O_2.

Solubility: Another factor, which determines diffusion across a wet film is the solubility of the gas. The rate of diffusion is directly proportional to the solubility of the gas in the fluid.

Permeability: A membrane is permeable, if it allows the particular molecules to pass through, i.e. across the membrane. Permeability of different membranes to the molecules of different substances (solid, liquid or gases) is variable.

Osmosis: Osmosis is the migration of molecules of a solvent across a membrane. The pressure, which stops the transfer of molecules is called the osmotic pressure of the solution. The osmotic pressure of a solution depends only on the number of dissolved particles per liter and not on the nature of the substances, which is dissolved.

The diffusion mechanisms also depend upon the pressures, volume and filtration. In respiratory system, the diffusion of gases and fluids across the alveolar membrane are critically important for normal gas-exchange functions of the lung and in the maintenance of a fluid balance (Some of these issues are discussed in Chapter 7).

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6

Respiratory Function and Mechanics

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INTRODUCTION

Oxygen is essential for the continuation of life. It is required by each human cell for its survival. It is abundantly present in the atmosphere and maintains a remarkably constant concentration of 20.9% in ambient air. Oxygen is taken up by the lungs through the act of inspiration and transported to the cells via blood. At the cellular level, oxygen is utilized for the production of energy. In this process, carbon dioxide is released and transported back via the blood to the lungs from where it is expired out into the atmosphere. The act of the exchange of oxygen and carbon dioxide is called respiration. For effective respiration, air must be drawn through the airways and distributed among approximately 400,000,000 alveolar compartments within the lung parenchyma. Although respiration is normally described as the uptake of oxygen and release of carbon dioxide by the lungs, it is essentially happening at the level of lungs ("external" respiration), as well as the tissues ("internal" respiration).

The respiratory system is made up of a gas exchanging organ (the lungs) and a pump that ventilates the lungs. The pump consists of the chest wall and the respiratory muscles, which increase and decrease the size of the thoracic cavity; the areas in the brain that control the muscles; and the tracts and nerves that connect the brain to the muscles. At rest, a normal human breathes 12-15 times a minute. About 500 ml of air per breath, or 6–8 L/min, is inspired and expired. This air mixes with the gas in the alveoli, and, by simple diffusion, O_2 enters the blood in the pulmonary capillaries while CO_2 enters the alveoli. In this manner, 250 ml of O_2 enters the body per minute and 200 ml of CO_2 is excreted.

Gas exchange by the human lungs is achieved with the help of four processes (Fig. 6.1), which are also variably interdependent:

1. *Ventilation:* To and fro movement between the atmosphere and the gas exchanging units of the lung.

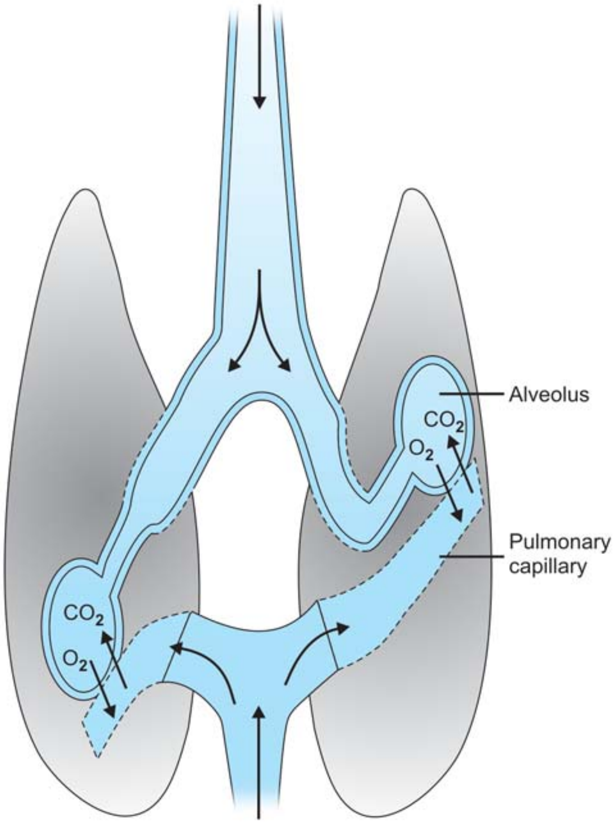

Fig. 6.1: Schematic diagram to represent different processes involved in respiration

2. *Circulation:* Supply and distribution of blood through the pulmonary capillaries.
3. *Diffusion:* The movement of O_2 and carbon dioxide across the air-blood barrier between the alveoli and the pulmonary capillaries.
4. Ventilation-perfusion relationships.

VENTILATION

Ventilation is the process of bulk movement of air from atmosphere, through the conducting airways to the terminal respiratory gas exchange units. This movement of air is made possible by the force which is generated by the effort of respiratory muscles (or a mechanical ventilator if the patient is being ventilated). Obviously, it is also dependent on the mechanical properties of the conducting airways and the lung parenchyma (i.e. the breathing units). The mechanical properties are referred to as "static" at zero (or no airflow) flow and constant volume, and "dynamic" if there is airflow.

The amount of air that moves in and out of the lungs with each inspiration and expiration respectively is called the tidal volume. The air inspired over and above the tidal volume with a maximal inspiratory effort is the inspiratory reserve volume, and the volume exhaled actively after passive expiration is the expiratory reserve volume; the air left in the lungs after a maximal expiratory effort is the residual volume. The respiratory dead space is the space in the conducting zone of the airways occupied by gas that is not involved in gas exchange. The vital capacity, the largest amount of air that can be exhaled after a maximal inspiratory effort, is a frequently measured index of pulmonary function. The fraction of the vital capacity exhaled during the first-second of a forced expiration is the FEV_1. The maximal voluntary ventilation is the largest volume of gas that can be moved into and out of the lungs in one minute by voluntary effort. There are several factors on which the aforementioned lung volume and the airflow depend: **Compliance** (a volume term), which is a measure of the elastic properties of lung, is an important determinant. Other elements include **resistance** (a flow term) and **inertance** (an acceleration term).

Inertance

Since the respired gases, the lungs and the chest wall all have appreciable mass and therefore inertia, they offer an impedance to change in the direction of gas flow. This component called inertance is extremely difficult to measure, but offers impedance that increases with frequency. Hence, inertial pressure is essentially negligible for most clinical purposes and the gas flow depends primarily on the compliance and resistance characteristics of the lung parenchyma except in situations of increased respiratory frequencies like high-frequency ventilation.

Compliance

Pulmonary compliance (or distensibility) is defined as the change in the volume of the lung per unit change in the distending pressure, which in case of lung is the transpulmonary pressure [which is defined as the pressure gradient between the alveolar (P_A) and the pleural pressures (P_{pl})]. **Elastance** is the reciprocal of compliance. Compliance is equal to the exhaled tidal volume (or a change in lung volume) divided by the alveolar pressure minus the pleural pressure (or a change in the transpulmonary pressure).

$$C = \Delta V_L / \Delta (P_A - P_{pl}),$$

where C = lung compliance, ΔV_L = change in lung volume, $\Delta (P_A - P_{pl})$ = change in transpulmonary pressure.

The interaction between the recoil of the lungs and recoil of the chest can be demonstrated using body plethysmography. The technique is described in detail in the chapter on pulmonary function testing.

The lung pressure volume relationship is a curvilinear graph. The elastic recoil pressure of lung always tends to collapse the lung even at the residual volume. Theoretically therefore, if removed from the thoracic cage, the lungs collapse to almost an airless state. The pressure-volume curve is also slightly greater when measured during deflation than when measured during inflation, a property called hysteresis (Fig. 6.2). Hysteresis is affected by the elasticity of lung parenchyma (in fact, hysteresis is a universal property of all elastic materials) and the surface tension of alveolar spaces. Pulmonary compliance is normally measured in the pressure range where the relaxation pressure curve is steepest. However, compliance depends on lung volume with highest compliance at residual lung volume and low compliance at high lung volumes.

Recruitment

This is a unique phenomenon observed in lung due to the closure of some small airways at lower lung volumes. As the transpulmonary pressure rises, the closed airways open sequentially. Thus, the recruitment of additional lung units in the initial phase of inspiration starting from lower lung volumes also contributes to hysteresis. Two other important factors affecting lung compliance are the surface tension and the physical nature of lung tissues.

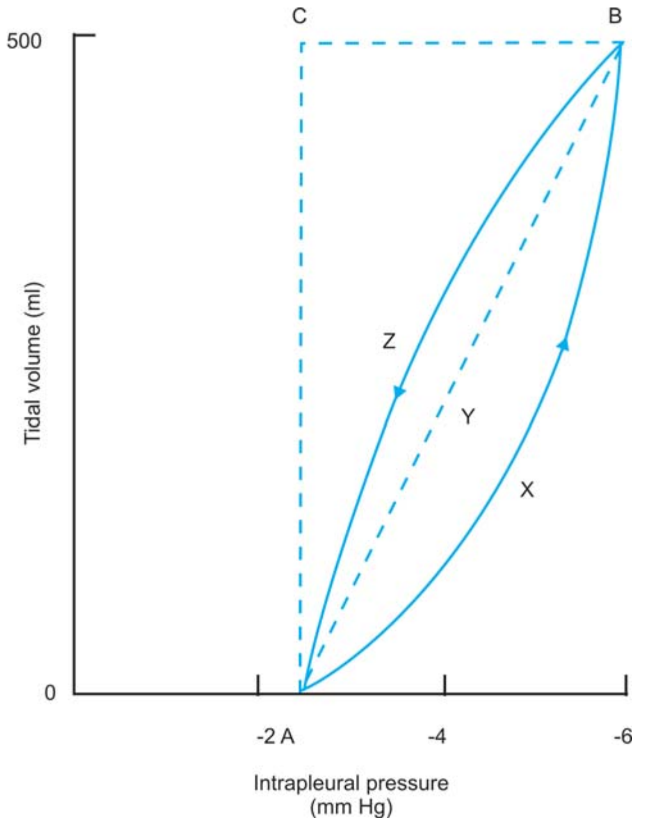

Fig. 6.2: Diagrammatic representation of pressure and volume changes during quiet inspiration (line AXB) and expiration (line BZA) is the compliance line

Surface tension exerted by the air fluid interface is reduced by surfactant—a surface active compound of phospholipids produced by type II alveolar cells. Surface tension is further lowered at lower lung volumes thereby increasing the compliance and decreasing the force required during the next inflation. Also by the Laplace law (Pressure = 2 × surface tension/radius), as the diameter of the alveoli is decreased, the pressure would increase and this would create an unstable system; this is also prevented by the surfactant, which decreases surface tension with decreasing radii of the alveoli, and allows gas to flow from the larger to the smaller alveolus and stability is maintained. This phenomenon is also mandatory for the maintenance of stability of alveoli at lower lung volumes.

Physical elastic properties of lung tissue per se, are due to the presence of elastic fibers in the pulmonary interstitium. Expansion in lungs is probably more due to unfolding and geometric rearrangement of elastic fibers rather than the actual lengthening. Ageing alters the elastin and collagen fibers in lungs and thus increases the compliance. Compliance is also increased in emphysema due to the loss of elastic fibers of alveolar walls. It is reduced wherever there is the stiffness and thickening of alveolar septae by processes such as fibrosis.

Elastic Properties of Chest Wall and Lung-Chest Wall Interactions

The resting volume of the thoracic cage is approximately equal to 70% of TLC. It implies that if thoracic cage is opened and support of lung withdrawn, it expands from FRC (the resting position of the respiratory system at which the inward elastic recoil of the lungs is exactly balanced by the outward recoil of the thoracic cage) to a volume of about 70% of TLC. At volumes less than 70% (including FRC) the thoracic cage has a tendency to expand and elastic recoil pressure is opposite to that of lungs, and is directed outwards.

The total compliance of the respiratory system is analogous to the electrical capacitance with the compliances of the lung and the thoracic wall arranged in series. Thus, the reciprocal of total compliance is the sum of reciprocals of the individual compliances, i.e.

1/total compliance = 1/lung compliance +
1/chest wall compliance

Instead of compliance, we may consider its reciprocal, elastance and the relationship is much simpler:

Total respiratory system elastance =
lung elastance + chest wall elastance

Resistance

Resistance is the opposition to motion and in the respiratory system opposition to the flow of gas. In the lung, resistance to air flow is of two types: tissue and airway. The former, also known as elastic resistance (resistance from tissues or tissue resistance), occurs when no gas is flowing, and is due to elastic resistance of lung tissue and chest wall and the resistance imparted from surface forces at the alveolar gas/liquid interface. Approximately 80% of the pulmonary resistance is due to airway resistance or non-elastic resistance.

Resistance to airflow is computed by the simultaneous measurements of airflow, and the driving pressure that is required to achieve the flow, i.e.

Resistance = Driving pressure/Flow = P/V

Most non-elastic resistance is provided by frictional resistance to airflow and thoracic tissue deformation, with small contributions from the inertia of gas and tissue and compression of intrathoracic gas.

Airway Morphology

Airways are the tubular structures designed to carry air to the alveolocapillary membrane for gas exchange. The tracheobronchial tree consists of several branches, which arise by dichotomous divisions of the parent bronchus. The airway divisions from trachea to the alveoli are not uniform and may vary between 10 and 25 in different areas—divisions being less near the hilar regions and more at the bases. The diameter, angulation and course of the bronchial divisions are also different in different lung zones. For example, the air passages to alveoli at the lung bases are straighter and have large cross-sectional areas. This asymmetric pattern of branching is referred to as "irregular dichotomy". It has a bearing on the distribution of ventilation and deposition of inhaled material.

Airways are classified into two types—conducting and respiratory airways. The conducting or central airways do not participate in gas exchange. They are larger than 2 mm in diameter, have cartilaginous support, are lined by ciliated columnar epithelium and are supplied by systemic bronchial circulation. They are also able to change their diameter in response to several neurohormonal and chemical stimuli due to the presence of smooth muscles in their walls and vagal innervation. The respiratory bronchioles or terminal airways are situated beyond the conducting airways. They are less than 2 mm in diameter, lack cartilaginous support, are lined by cuboidal epithelium and are supplied by pulmonary circulation. Due to their structural properties, they are susceptible to compression and closure in response to changes in the intrapulmonary pressures.

The geometric features of airway divisions have a direct relationship with the partitioning of resistance and hence distribution of ventilation. There is a progressive narrowing and shortening of airways as the division progresses from trachea to the peripheral airways. Despite the reduction in the diameter of daughter airways, the total cross-sectional area increases tremendously as we go peripherally. This is because the total number of airways increases geometrically with each division and the diameter of each daughter airway is more than half of the parent airway. This results in almost 2,000 fold increase in total cross-sectional area from trachea to peripheral airways.

Physical Principle of Gas Flow and Resistance

The geometric features described above are important in the distribution of resistance within the lung. Since flow is inversely proportional to the diameter of the tube, it decreases progressively as air moves down the bronchial tree to the peripheral zones. In the terminal bronchioles, flow is reduced to almost zero. It is the Brownian motion of the molecules, which facilitates diffusion across the alveolocapillary membrane. As the flow velocity decreases, the driving pressure and resistance also fall. It has been calculated that 80% of total measurable resistance at mouth is contributed by the central or conducting airways.

The precise relationship between pressure difference and flow rate depends on the nature of the flow, which may be laminar, turbulent or a mixture of the two. With laminar flow, gas flows along a straight unbranched tube as a series of concentric cylinders that slide over one another, with the peripheral cylinder stationary and the central cylinder moving fastest, the advancing cone forming a parabola. The advancing cone front means that some gas will reach the end of the tube despite the volume of gas entering the tube being less than the volume of the tube. This has relevance in patients being ventilated using the high frequency ventilation where there is significant alveolar ventilation despite the tidal volume being less than or equal to the anatomical dead space.

In a straight unbranched tube, the Hagen-Poiseuille equation allows gas flow to be quantified:

$$\text{Flow rate} = \Delta P \times \pi \times (\text{radius})^4 / 8 \times \text{length} \times \text{viscosity, where}$$

ΔP is the pressure gradient and equals the product of flow rate and resistance:

Thus, resistance = $8 \times \text{length} \times \text{viscosity} / \pi \times (\text{radius})^4$

In this equation, the fourth power of the radius explains the critical importance of narrowing of the air passages. With constant tube dimensions, viscosity is the only property of gas that is relevant under the conditions of laminar flow. Helium has a lower density, but a viscosity close to that of air, and thus will not improve gas flow if the flow is laminar.

On the other hand, turbulent flow occurs when gas flows at high rates through unbranched or irregular tubes, resulting in the formation of eddy currents. In contrast to laminar flow, it has a square front and the volume of gas entering the tube is equal to the volume of the tube, the so called bulk flow. The relationship is different from the laminar flow in that the driving pressure is proportional to the square of the gas flow rate and the density of gas, but independent of its viscosity and the required driving pressure is inversely proportional to the fifth power of the radius of the tubing (Fanning's equation).

The change in flow from laminar to turbulent characteristics is determined by a dimensionless number, the

Reynolds' number (N_R), which is N_R = density × velocity × diameter/viscosity. The property of gas that affects N_R is the ratio of density to viscosity. Flow is laminar with N_R less than 2,000, and changes from laminar to turbulent when the N_R exceeds 4,000. Between N_R of 2,000 and 4,000, both types of flow coexist. There is also a critical length of tubing before the parabolic pattern of laminar flow is established, and thus for gases with low N_R not only will resistance be less during turbulent flow, but also laminar flow will become established more quickly after narrowed airways. In principle, turbulence occurs only in the larger airways and not in the smaller airways because of the large cross-sectional area, the small diameter and the slow velocity of the small airways. Heliox has a density/viscosity ratio of 0.31 compared to one for oxygen. If thus has a lower N_R and higher potential for laminar flow, explaining its usefulness in patients with large airway diseases.

Total and Alveolar Ventilation

The total amount of air inhaled with each inspiration gets distributed in the lungs depending upon the regional resistance and compliance of the different lung units. Ventilatory requirements for adequate supply of oxygen and removal of carbon dioxide depend on the metabolic demands of the body. The resting ventilatory requirements are small and are met with minimal expenditure of energy. A normal individual can maintain gas exchange with a ventilation of about 80 ml/kg/minute, which is about one-tenth of the maximum ventilatory capacity. Therefore, there is a vast reserve in ventilatory capacity and problems of gas exchange would not occur, if all the inspired volume is available to the gas exchange units. However due to cyclical nature of ventilation, a significant proportion of the inspired gas never reaches the alveoli—a volume known as the dead space volume. So, the total ventilation is contributed by the dead space ventilation (V_D) and alveolar ventilation (V_A), i.e. the air that reaches the alveoli to take part in gas exchange. The dead space ventilation in mL is roughly around the individual's body weight in pounds.

The volume of conducting airways, which constitute the anatomical dead space is relatively fixed, i.e. about one-third of the tidal resting ventilation. Its relative proportion to the total ventilation decreases as the total ventilation increases, for example on exercise. On the other hand, a decrease in tidal volume and increase in respiratory rate (e.g. rapid shallow breathing) markedly increases the proportion of dead space ventilation thereby affecting the gas exchange.

Dead space is also increased when there is presence of lung units, which are adequately perfused, but not ventilated, the so called physiological dead space. It is important to distinguish between the anatomic dead space (respiratory system volume exclusive of alveoli) and the physiologic dead space (volume of gas in the alveoli not equilibrating with blood, i.e. wasted ventilation). As will be discussed subsequently in this chapter, ventilation has to be matched by the perfusion of blood in the alveolar capillaries for adequate gas exchange to occur. Ventilation and perfusion are not homogeneously distributed throughout the lung, and areas which receive more ventilation relative to perfusion result in wasted ventilation and thus add to "dead space" ventilation. The sum of the dead space ventilation by these two mechanisms constitutes "total dead space" and is given the formula:

V_D/V_E = $1 - P_ECO_2/P_ACO_2$, where
V_D = total dead space
V_E = minute ventilation
P_ECO_2 = partial pressure of carbon dioxide in the expired air
P_ACO_2 = partial pressure of carbon dioxide in the alveolar air (which in practice is measured by the arterial PCO_2)

The relationship of total and alveolar ventilation was first described by Christian Bohr and is also known as "Bohr dead space".

Distribution of Ventilation

The alveolar ventilation is distributed throughout the lungs. With each inspiration around 500 ml of air is distributed to around 300 million alveoli such that each alveolus receives an appropriate share of the inspired gas. This fine distribution of air is essentially a function of the "time constants" of the regional lung units. Time constant is the product of regional compliance and resistance and thus is also called the RC time constant. The relative distribution of ventilation between two neighboring lung units can be understood better with the two compartment lung model. In health, the resistance and compliance of two adjacent units of lung are essentially equal and thus their RC time constant is normal with the normal distribution of ventilation. However in a diseased lung, different portions of the lung may have abnormal time constants as a result of either the diseased airway lumen (increased resistance) or because of stiffness of alveolar walls (increased compliance) or both. Thus, ventilation will be maldistributed in a lung unit with abnormal RC time constant with more ventilation to areas with relatively normal time constant than other areas. A lung unit with a large time constant (i.e. greater resistance and compliance) does not completely fill by the end of inspiration and empties slowly during expiration. In contrast, a lung unit with a small time constant (i.e. smaller resistance and compliance) fills and empties rapidly.

When a lung unit with a large time constant is located adjacent to a lung unit with a small time constant, the unit with the large-time constant may withdraw gas from the adjacent lung unit with a short-time constant rather than fresh inspired gas. This "to and fro" behavior is known as pendelluft, and it can occur in abnormal lungs. In addition, a lung unit with a small time constant may receive a higher proportion of dead space gas, which reduces its alveolar ventilation. This effect is prominent in chronic obstructive lung disease, in which compliant lung units with extremely large time constants behave essentially as dead space. The higher the respiratory rate, the greater is the discrepancy in filling and emptying between these two kinds of units, and thus greater the inhomogeneity of ventilation.

Another reason for uneven ventilation of small lung units is a gradient of gas concentration along the small airways, a condition called stratified inhomogeneity. Inspired gas reaches near the region of the terminal or respiratory bronchioles by convective flow, but gas flow over the rest of the distance to the alveoli is accomplished primarily by molecular diffusion within the airways. When airway calibers are altered, as in emphysema, the process of gas diffusion may be incomplete for each breath. Thus, alveoli more distal to the conducting airways are less well ventilated than proximal alveoli.

Several mechanisms tend to preserve the uniform distribution of ventilation in the lung. One of these mechanisms is the pendelluft phenomenon described above. Another mechanism is gas exchange through collateral air channels between adjacent lung units. Collateral ventilation can occur between alveolo-alveolar pores of Kohn, bronchioloalveolar canals of Lambert, and bronchiolobronchiolar foramina of Martin. Another factor that tends to improve the uniformity of ventilation is the interdependence of peripheral lung units, which stems from the observation that contiguous lung units are attached integrally to each other by the connective tissue framework of the lung parenchyma. The behavior of one unit must therefore influence the behavior of its neighbors. This framework serves to offset the tendency for regional differences in compliance to make lung units larger or smaller than they should be for optimal performance.

Role of Gravity

Gravity also plays some role in the distribution of ventilation. In the upright position, ventilation per unit lung volume is greater at the base of the lung than at the apex. The reason for this is that at the start of inspiration, intrapleural pressure is less negative at the base than at the apex, and since the intrapulmonary-intrapleural pressure difference is less than at the apex, the lung is less expanded. Conversely, at the apex, the lung is more expanded; i.e. the percentage of maximum lung volume is greater. Because of the stiffness of the lung, the increase in lung volume per unit increase in pressure is smaller when the lung is initially more expanded, and ventilation is consequently greater at the base.

The ventilation differences tend to disappear in the supine position, and the weight of the lung makes the intrapleural pressure lower at the base in the upright position. However, the inequalities of ventilation and blood flow in humans have been found to persist to a remarkable degree in the weightlessness of space. Therefore, other as yet unknown factors apparently also play a role in producing the inequalities. It should also be noted that at very low lung volumes, such as those after forced expiration, intrapleural pressure at the lung bases can actually exceed the atmospheric pressure in the airways, and the small airways such as respiratory bronchioles collapse (airway closure). In older people and in those with chronic lung disease, some of the elastic recoil is lost, with a resulting decrease in intrapleural pressure. Consequently, airway closure may occur in the bases of the lungs in the upright position without forced expiration, at volumes as high as the functional residual capacity.

PULMONARY CIRCULATION

The circulation of the entire cardiac output through the lungs is ideally suited for rapid gas exchange. The pulmonary vascular bed resembles the systemic circulation, except that the walls of the pulmonary artery and its large branches are about 30% as thick as the wall of the aorta, and the small arterioles, unlike the systemic arterioles, have relatively little muscle in their walls. There is also some smooth muscle in the walls of the postcapillary venules. Also, the pulmonary capillaries are large with multiple anastomoses, so that each alveolus sits in a capillary basket. The blood from the right side of the heart flows through an intricate network of pulmonary capillaries around the alveoli.

After getting oxygenated, blood drains back into the left atrium through four pulmonary veins. The pulmonary bed is characteristically a low-pressure circuit. There is a dense network of capillaries around each alveolus. Rough estimates put the total number of capillaries at about six billion or two thousand capillaries per alveolus. Not all the capillaries are perfused under resting conditions. An increased blood flow due to an increased cardiac output (as much as 25 liters per minute during exercise in contrast to five to six liters during resting conditions) can be accommodated easily in the pulmonary circulation without an increase in the pulmonary arterial pressure. This is made possible as a result of two major mechanisms that include recruitment, which is the opening of previously unperfused pulmonary capillaries in the upper lung zones, and distension in the entire pulmonary vasculature due to increased transmural pressure gradient. The best example of the ability of pulmonary vasculature to adapt to increased blood flow is following pneumonectomy, when the remaining lung will normally take the entire resting pulmonary blood flow without an increase in pulmonary arterial pressure.

Distribution of Perfusion

The distribution of pulmonary blood flow is non-uniform from apex to base. In the upright position, the upper portions of the lungs are well above the level of the heart, and the bases are at or below it. Consequently, there is a relatively marked pressure gradient in the pulmonary arteries from the top to the bottom of the lungs, because of the effect of gravity, and a resulting linear increase in pulmonary blood flow from the apices to the bases of the lungs. The following three concepts about pressure in the pulmonary vessels are important to understanding the behavior of the pulmonary circulation.

Intravascular Pressure

This is the blood pressure inside the lumen of the vessel relative to the atmospheric pressure. The pulmonary arterial pressure (P_a) and pulmonary venous pressure (P_v), can be measured directly by placing catheters into the bloodstream at specific points, and in clinical practice, capillary pressure can be estimated by wedging a catheter into a lobar branch of pulmonary artery. The “wedge” pressure measured under the conditions of “no flow” reflects the pressure downstream of the next freely communicating channels, that is, pulmonary capillaries or small pulmonary venules.

Transmural Pressure

This is the difference between the pressure inside a vessel and the pressure in the tissue around it. For example, the pressure around the pulmonary arteries and veins is approximately equal to the intrapleural pressure. The pressure around the capillaries is approximately the intra-alveolar pressure (P_A). It is this difference in transmural pressure that leads to the different behavior of alveolar and extra-alveolar vessels under conditions such as lung inflation. At the capillary level, the transmural pressure is also an important determinant of the rate of transudation of fluid across the capillary bed.

Pulmonary Driving Pressure

This is the difference in intravascular pressure between one point in the circulation and another point downstream, and is the pressure involved in overcoming the frictional resistance that impedes blood flow between two points. The driving pressure for the pulmonary circulation is the difference between the intravascular pressure in the main pulmonary artery and that immediately after the pulmonary circulation in the left atrium.

The intravascular pressures of the pulmonary circulation are influenced by the hydrostatic pressure created by gravity and the alveolar pressures significantly affect the intra-alveolar capillaries. As alveolar pressure is relatively independent of gravity, the relationships among pulmonary arterial, pulmonary venous and alveolar pressures must also influence the distribution of pulmonary blood flow. West subdivided the lung into four zones with differing patterns of blood flow (Fig. 6.3). In ***zone 1***, near the apex of the lung, wherein the alveolar pressure exceeds both the pulmonary arterial and venous pressures ($P_A > P_a > P_v$), and thus the alveolar vessels are collapsed and there is no pulmonary blood flow. In ***zone 2***, the pulmonary arterial pressure exceeds the alveolar pressure, but alveolar pressure exceeds venous pressures ($P_a > P_A > P_v$). Under these conditions, the resistance to blood flow is determined by the difference between pulmonary arterial and alveolar pressures, rather than by the expected arterial-venous pressure difference. This behavior has been referred to variously as the waterfall or sluice effect. Also in ***zone 2***, blood flow increases progressively down the lung because of the increasing hydrostatic effect on pulmonary arterial pressure, which increases the driving pressure in this region (pulmonary arterial pressure minus alveolar pressure).

In ***zone 3***, the pulmonary venous pressure exceeds alveolar pressures ($P_a > P_v > P_A$), and blood flow is dependent on the pressure difference between P_a and P_v, and is maximal. There is also a progressive increase in the perfusion because of the progressive “distension” of vessels due to increase in P_a and P_v, while P_A remains

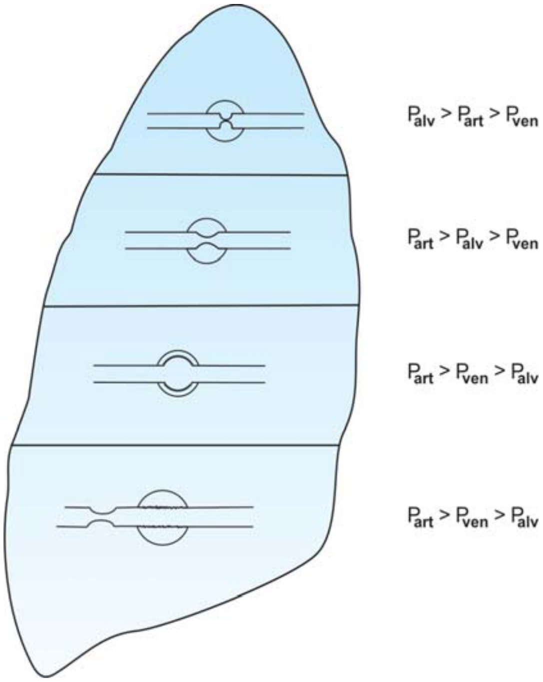
$P_{alv} > P_{art} > P_{ven}$
$P_{art} > P_{alv} > P_{ven}$
$P_{art} > P_{ven} > P_{alv}$
$P_{art} > P_{ven} > P_{alv}$

Fig. 6.3: West zones of perfusion

constant. In ***zone 4***, the relationships between intravascular and alveolar pressures are the same as in zone 3, but the blood flow decreases slightly. Zone 4 occurs in the lowermost region of the upright human lung and diminishes as lung volume increases. Conversely, as lung volume decreases, this region of reduced blood flow extends farther and farther up the lung, so that at FRC blood flow decreases progressively down the bottom half of the lung. At residual volume, zone 4 extends nearly all the way up the lung, so that blood flow at the apex exceeds that at the base. This condition obviously cannot be explained by the interactions among the pulmonary arterial, venous and alveolar pressures. Instead, the reduced blood flow in zone 4 is probably due to the narrowing of extra-alveolar vessels at the lung base that result from lower lung inflation due to airways closing down at the "closing volume". The increased contribution of extra-alveolar vessels to pulmonary vascular resistance results in the presence of a zone of reduced blood flow in that region. Zone 4 would be expected to increase in the presence of interstitial pulmonary edema, because the edematous fluid increases interstitial pressure in the vascular sheath and thereby narrows the extra-alveolar vessels. This is a plausible mechanism for the inverted distribution of blood flow (cephalization of pulmonary vasculature on chest X-ray) in pulmonary edema.

However, not all the inhomogeneity of blood flow in the lung can be explained by gravitational effects. Indirect measurements of inhomogeneity (monitoring the magnitude of cardiogenic oscillations on the expired carbon dioxide tracing) of pulmonary blood flow have been made in astronauts in space shuttles, and a striking reduction in inhomogeneity of blood flow was detected during weightlessness compared with that observed in the upright posture before or after the flight. Interestingly, substantial inhomogeneity of blood flow still remained, indicating that some gravity-independent mechanism was also present. Another situation where the gravitational model fails is the situation of prone position ventilation, where the perfusion is probably more homogeneous and not dependent on gravity.

DIFFUSION

Diffusion is the rate at which oxygen from the alveolus is transferred across the alveolocapillary barrier to combine with hemoglobin in the red blood cells of pulmonary capillaries (Fig. 6.4). The situation in lungs can be visualized as a two chamber model with different partial pressures of oxygen and a liquid barrier separating the two (Fig. 6.4). The transfer of gases from

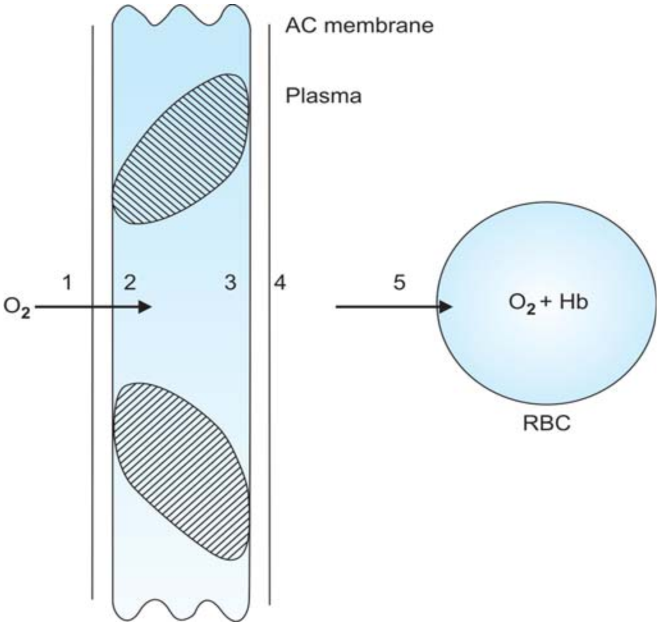

Fig. 6.4: Schematic diagram representing diffusion across the alveolocapillary membrane into the red blood cell. 1 and 2 represent the inner and outer layer of the alveolar epithelium, 3 and 4 represent the inner and outer layer of the capillary endothelium, 5 represents the red blood cell membrane

the alveoli to the capillary blood during the pulmonary transit time of 0.75 seconds depends on their reaction of the molecules with hemoglobin in the blood. For example, nitrous oxide (N_2O) does not react, and reaches equilibrium in about 0.1 seconds. In this situation, the amount of N_2O taken up is not limited by diffusion, but by the amount of blood flowing through the pulmonary capillaries; i.e. it is flow-limited.

On the other hand, carbon monoxide (CO) is taken up by the hemoglobin in the red blood cells at such a high rate that the partial pressure of CO in the capillaries stays very low and equilibrium is not reached in 0.75 seconds till the blood is in the pulmonary capillaries. Therefore, the transfer of CO is not limited by perfusion at rest and instead is diffusion-limited. Oxygen is intermediate between N_2O and CO; it is taken up by hemoglobin, but much less avidly than CO, and it reaches equilibrium with capillary blood in about 0.3 seconds. Thus, its uptake is also perfusion-limited. The diffusing capacity of the lung for a given gas is directly proportionate to the surface area of the alveolocapillary membrane and inversely proportionate to its thickness. The factors that influence the movement of gas from the area of higher partial pressure (alveolus) to the area of low partial pressure (capillaries) are governed by the Fick's law:

V = Ad/T (P1 - P2), where
V = volume of gas diffusing per unit time (ml/minute)
A = area available for diffusion (cm^2)
P1 - P2 = pressure difference of gas on two sides (mm Hg)
d = diffusion coefficient of the barrier (cm^2/minute/mm Hg)

This **diffusion coefficient** "d" is further related to the solubility of the gas within the liquid barrier and the square root of the molecular weight of the gas. Other factors being constant, the driving pressure is the most important factor determining the flow of oxygen across the alveolocapillary membrane. When this pressure falls, such as travel at high altitudes, the oxygen delivery to the tissues becomes diffusion limited. Similarly, diffusion is inversely proportional to the thickness of the membrane.

Although diffusion is reduced in the presence of thickened alveolocapillary membrane (e.g. interstitial lung disease) or the loss of gas exchange areas (e.g. chronic obstructive airway disease); however, it is rarely the sole factor responsible for hypoxemia encountered in these conditions. The reason is that the transfer of oxygen and carbon dioxide is perfusion limited. The normal capillary transit time across the alveolar walls is usually 0.75 seconds, but in healthy individuals only 0.25 seconds is required for gas exchange to be completed. Thus, there is an adequate time for gas exchange to occur even in the presence of a diffusion defect. The gas exchange however becomes diffusion dependent during conditions, which increase cardiac output, such as exercise, anxiety, etc. when the capillary transit time is significantly reduced.

VENTILATION-PERFUSION (V/Q) RELATIONSHIPS

The ratio of pulmonary ventilation to pulmonary blood flow for the whole lung at rest is about 0.8 to 1 (4-6 liters/minute ventilation divided by 5–6 L/minute blood flow), and this matching of distribution of ventilation and perfusion is the most important determinant of gas exchange. The ventilation-perfusion mismatch is the final common pathway to cause hypoxemia in most pulmonary diseases (Fig. 6.5). An area of lung that is well perfused, but under ventilated acts as a right to left shunt (physiological shunt) whereas an area that is well ventilated, but under perfused acts like a dead space (physiological dead space). The spectrum of $\dot{V}/\dot{Q}$ ratios in a healthy lung would vary between zero (perfused, but not ventilated) to infinity (ventilated, but not perfused).

The ideal $\dot{V}/\dot{Q}$ratio of one indicates perfectly matched ventilation and perfusion. Although $\dot{V}/\dot{Q}$ mismatch includes both physiologic shunt and physiologic dead space, but in clinical parlance, the term generally denotes physiologic shunt as physiologic dead space, is rarely, if ever the cause of hypoxemia. In an alveolar-capillary unit with a $\dot{V}/\dot{Q}$ ratio of 0 (physiologic shunt), the blood

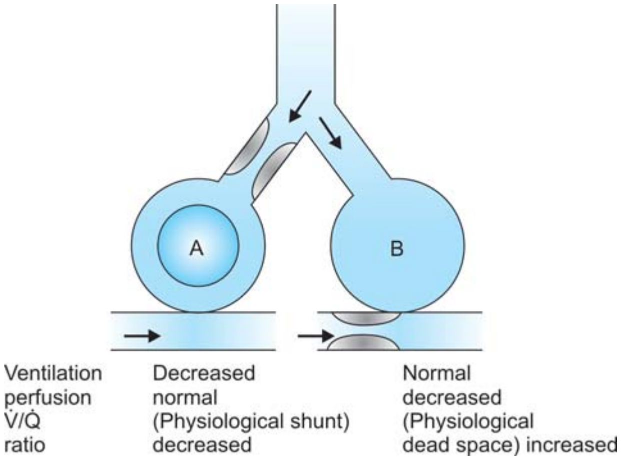

Fig. 6.5: Mismatching of ventilation and perfusion: Model A (diminished ventilation) and B (decreased perfusion)

leaving the unit has the composition of mixed venous blood entering the pulmonary capillaries, i.e. PO_2 of 40 mm Hg and PCO_2 of 46 mm Hg whereas in an alveolar-capillary unit with a high $\dot{V}/\dot{Q}$ ratio (physiologic dead space) the small amount of blood leaving the unit has partial pressures of O_2 and CO_2 are 150 mm Hg and 0 mm Hg approaching the composition of inspired gas.

Because of the sigmoid shape of the oxyhemoglobin dissociation curve, it is important to differentiate between the partial pressure and the content of oxygen in the blood. Hemoglobin is almost fully (> 90%) saturated at a PO_2 of 60 mm Hg, and little additional O_2 is carried by hemoglobin even with a substantial elevation of PO_2 above 60 mm Hg. On the other hand, significant O_2 desaturation of hemoglobin occurs once PO_2 falls below 60 mm Hg and onto the steep descending limb of the curve. As a result, blood coming from regions of the lung with a high $\dot{V}/\dot{Q}$ ratio and a high PO_2 has only a small elevation in O_2 content and cannot compensate for blood coming from regions with a low $\dot{V}/\dot{Q}$ ratio and a low PO_2, which has a significantly decreased O_2 content. Although $\dot{V}/\dot{Q}$ mismatching can influence PCO_2, this effect is less marked and is often overcome by an increase in overall minute ventilation.

The alveolar PO_2 appears to be the most important factor involved in regulating the distribution of ventilation-perfusion within the lung. In this respect, hypoxic pulmonary vasoconstriction can be considered as part of a negative feedback loop. For example, in lung units with low $\dot{V}/\dot{Q}$ ratios, there is a fall in the local alveolar PO_2, and constriction of the associated microcirculation reduces the local pulmonary blood flow. This tends to restore the loca $\dot{V}/\dot{Q}$ ratio toward its normal value. This effect can be appreciated in the residents of high altitudes, who are exposed constantly to lower ambient O_2 concentrations. Residents of high altitudes have better $\dot{V}/\dot{Q}$ matching than sea level residents, as reflected by a smaller alveolar-arterial PO_2 difference. The intensity of hypoxic pulmonary vasoconstriction varies among different lung regions, and probably depends on the smooth muscle tone in different vessels. More recently, a role for nitric oxide in regulating local ventilation-perfusion matching has been suggested as nitric oxide is a selective pulmonary vasodilator (no systemic effects), and inhibits hypoxic pulmonary vasoconstriction. Theoretically, the inhalation of nitric oxide can cause selective pulmonary vasodilation in adequately ventilated areas and improve gas exchange. The nitric oxide-mediated mechanism may also be important in patients with inflammatory lung diseases, in whom the production of nitric oxide is increased. The loss of local hypoxic vasoconstriction would worsen ventilation-perfusion mismatch.

CONTROL OF VENTILATION

The active inspiratory process facilitates expansion of the lungs. It involves the contraction of intercostals muscles and diaphragm to move the chest upwards and outwards. By doing so the intrathoracic and alveolar pressures are lowered and the flow of the air into the lungs is facilitated. Expiration is usually a passive process. The lungs and chest collapse under their own elastic recoil and raise the intrathoracic and alveolar pressures. The air flows out of the lungs.

Ventilation is controlled tightly through three components—sensors (or receptors), central controllers and effectors (muscles of respiration). The respiratory control mechanisms operate through both neuronal and chemical receptors. While the former are peripherally located (airway, lung, chest wall, blood vessels), the latter are both peripherally and centrally located. Control centers in the brain put together information from all these receptors, and fine-tune the neuronal drive to respiratory musculature, which in turn controls the level of ventilation.

Neuronal Receptors

The neuronal receptors vary greatly in their location and response characteristics. Some are rapidly adaptive to change in lung volume or irritation by noxious agents or inflammatory mediators. Receptor signals are mediated through the vagus nerve to the respiratory center, and have variable effects like increase in ventilation, cough and/or bronchoconstriction. Others like stretch receptors or muscle spindles in airway smooth muscles adapt slowly to lung volume changes. These get activated by lung overdistension and signal the respiratory center to discontinue the stimulation of the inspiratory muscles, allowing expiration to begin. This response is called the inflation (Hering-Breuer) reflex. Juxtacapillary (or J) receptors located in alveolar walls sense the engorgement of the pulmonary capillaries and cause rapid shallow breathing.

Peripheral Chemoreceptors

The main location for peripheral chemoreceptors is in the aortic and carotid bodies, although they may be present in other areas as well. Carotid bodies are located bilaterally at the bifurcation of common carotid arteries, and are the major receptors in adult life. They mainly respond to arterial hypoxemia, and also to hypercapnia, by transmitting signals to the nucleus tractus solitarius through the ninth cranial nerve, resulting in hyperventilation. Other chemoreceptors in the central nervous system adjust ventilation to maintain acid-base homeostasis. The more important receptors are located near the ventral medullary surface and the retrotrapezoid nucleus. These receptors respond to pH changes in the cerebrospinal fluid resulting from the diffusion of carbon dioxide through the blood-brain barrier.

Respiratory Center

The various positive and negative signals from all these receptors are integrated at the level of respiratory control centers in the medulla and pons, and result in appropriate modifications in frequency, depth and/or pattern of respiration. The dorsal medullary inspiratory center generates rhythmic neuronal impulses that result in the contraction of inspiratory muscles. Exhalation is largely a passive process, though it can be actively controlled through the ventral respiratory group of neurons in the medulla. The medullary center is controlled by pontine centers. The pneumotaxic center is located in the dorsal and superior pontine area, and is inhibitory to the medullary ventilatory drive. The apneustic area in the lower pons can stimulate respiration if the pneumotaxic center is blocked, but its function is not well understood.

Ventilatory Responses

The ventilatory response to carbon dioxide elevation in the blood is largely centrally mediated and results in a proportional increase in ventilation that attempts to correct the anomaly, although normocapnia may not be achieved. The relationship between respiratory minute volume and the alveolar carbon dioxide is essentially linear. The ventilatory response to hypoxia is not so linear. Although mild hypoxemia increases discharge from the peripheral chemoreceptors, the corresponding hypocapnia from any increase in ventilation, as well as a slight alkalosis from the lesser amount of oxyhemoglobin, prevent any sustained hyperventilation. An increase in minute ventilation is only seen when arterial oxygenation falls substantially. The composite effects of hypoxemia, hypercarbia and acidosis are much more complex.

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7

Gas and Fluid Exchange in the Lung

Marc Zelter

GAS EXCHANGE

The oxygen needed by cell mitochondria for tissue respiration is extracted from atmospheric air by a succession of processes,[1] including external ventilation between the lung and the air, gas distribution and gas exchange in the lung, transport of oxygen by blood and transfer to the tissues (Fig. 7.1). Carbon dioxide, one of the two main by-products of tissue respiration, the other one being water, follows the reverse pathway. The flow process is possible because the partial pressure of oxygen decreases from one step to the next, creating the physical conditions necessary for the transfer of gas from the lung to the cell (Fig. 7.2). The series of steps or pressure changes in oxygen from one step to the next are not even. Each of the steps involved can be characterized by what is called its "conductance," defined as the maximum quantity of oxygen that can be transferred from one step to the next, per unit of time and per unit of oxygen pressure difference. The actual mechanisms by which oxygen follows these steps may vary from one step to the other: Forced convection between atmosphere and alveoli; passive diffusion across the alveolar wall and plasma; diffusion and reversible chemical bondage between plasma and intracellular red cells hemoglobin; forced convection from the lung to tissues via the systemic circulation; and passive diffusion from red cells to the tissue interstium and then by diffusion to tissue cells and mitochondria. The oxygen that has not been extracted by tissues follows the reverse pathway back to the lungs. Two of these steps require energy expenditure: ventilation and circulation.

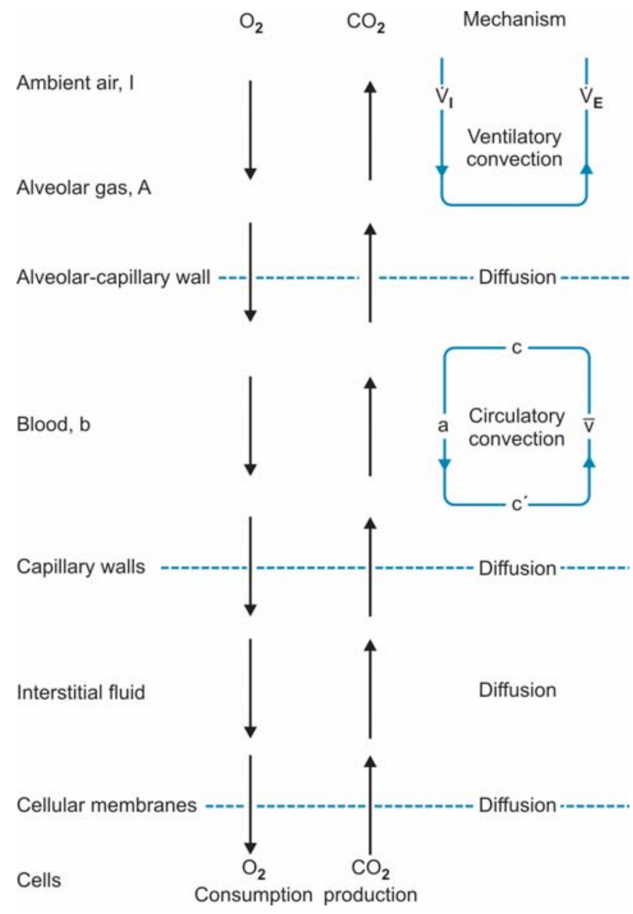

O_2
CO_2
Mechanism
Ambient air, I
$\dot{V}_I$
$\dot{V}_E$
Ventilatory convection
Alveolar gas, A
Alveolar-capillary wall
Diffusion
c
Blood, b
a
Circulatory convection
$\bar{v}$
c´
Capillary walls
Diffusion
Interstitial fluid
Diffusion
Cellular membranes
Diffusion
Cells
O_2
CO_2
Consumption
production

Fig. 7.1: Schematic representation of the steps and mechanisms of gas exchange from air to tissues
Modified from Dejours[1]
$\dot{V}_I$: inspiratory flow; $\dot{V}_E$: expiratory flow; a: arterial, c: capillary, $\bar{v}$: mixed venous, c': end-capillary blood

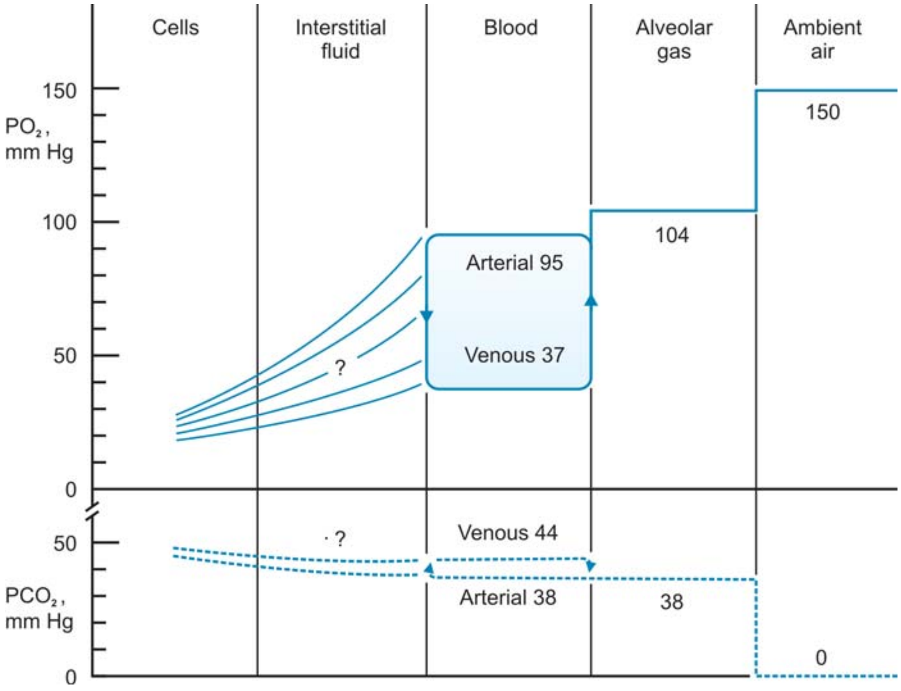


Fig. 7.2: Partial pressures for O_2 and CO_2 from ambient air to cells. Pressures in the interstitial fluid and in cells are still to be determined reliably
Modified from Dejours[1]

Whatever the transport mechanisms, the system is built and regulated in such a way that the amount of oxygen used for metabolism by the cells in stable conditions is always equal to the amount extracted by the lung; the amount of carbon dioxide expired by the lungs per unit of time equals the amount produced by the cells. The two processes are called the “oxygen consumption” and “carbon dioxide production.” Both are independent of changes in ventilation as long as enough oxygen is made available to the tissues. For instance, hyperventilation as such has no influence on oxygen consumption or carbon dioxide production provided the tissue metabolism is not modified, although the amount of oxygen entering the lung per unit of time is higher than during normal ventilation. The amount of oxygen that enters the lung and is contained in the inspired air per unit time (the oxygen intake) is always larger than the amount transferred from the alveoli to the blood (the oxygen consumption). What is left is expired during the next breath. The same does not apply to carbon dioxide, as there is no carbon dioxide in the inspired air, so the amount expired per unit of time is that actually produced at tissue level, provided conditions have remained stable.

The same reasoning applies to both gases in the blood. The amount of oxygen present in the blood at the output of the lung is higher than what is needed by the tissues, but the tissues extract only what correspond to their consumption so that the quantity extracted from the blood by the tissues is equal to what has been extracted from the alveoli by the blood. What remains is brought back to the pulmonary artery, which is the lung input. The volume of carbon dioxide leaving the blood in the lung is equal to the carbon dioxide produced in the tissues, which is always less than what is transported by the pulmonary artery so that there is always carbon dioxide left in the oxygenated blood leaving the lung via the pulmonary veins. The design of the system is such that the amount of oxygen present at the output of the lung is almost always the maximum in a normal individual. The concentration of oxygen in the blood leaving the lung is, therefore, fixed and independent of oxygen consumption. It is called the arterial blood oxygen concentration (CaO_2), as it is the concentration of oxygen reaching the systemic arteries. The amount of oxygen actually present in the arterial blood is routinely evaluated by measuring the partial pressure of oxygen (PaO_2) rather than the concentration; this pressure is a precious index of the ability of the lung to saturate the blood in oxygen. It is also a good index that blood can carry enough oxygen to the tissues presuming that hemoglobin concentration in the blood and blood flow are adequate.

Inspired Gas

Inspired gas is best described in terms of pressure and composition. Gas is inspired at barometric pressure P_B. At sea level, pressure is about 760 mm Hg (100 kPa); it diminishes with altitude and rises during diving or during hyperbaric treatment. Inspired gas contains essentially atmospheric air, a defined chemical mixture of oxygen (21%) and nitrogen (79%) with no carbon dioxide, plus a variable amount of water vapor. Atmospheric air composition does not change with barometric pressure. Its composition remains the same at altitude and at sea level. What varies is the pressure at which it is inhaled. Composition of air may be expressed in terms of fractions of gas mixture: the fraction (F) is the percentage of one of the components in the mixture (F_IO_2 = 0.21 for oxygen, in inspired air). It may be expressed as partial pressure. Partial pressure is the fraction of total pressure due to each component of the gas mixture: P_{O_2}= 0.21× P_B = 160 mm Hg for dry air. Pressure of water vapor in the atmosphere varies with meteorological conditions. Inspired atmospheric gas is immediately heated up to body temperature (37° C) and saturated with water vapor in the trachea. Therefore, the actual inhaled gas mixture consists of dry air and water vapor. Physical laws determine the maximum amount of water vapor that can mix with air at 37° C without condensation; it depends only on temperature. The saturated water partial pressure at body temperature is 47 mm Hg. Barometric pressure being unchanged, the saturated partial pressure of water vapor being 47 mm Hg, the partial pressure of air in the inhaled mixture is P_B-47 = 713 mm Hg and consequently P_IO_2= 0.21 × 713= 150 mm Hg.

Expired Gas

After loosing oxygen to, and gaining carbon dioxide from the blood, the gas is expired from the alveoli. Because each molecule of oxygen consumed is not necessarily replaced by one molecule of carbon dioxide produced, the number of molecules expired per unit time and Volume may vary with the $\dot{V}CO_2$ /   ratio, called the respiratory quotient (R). This quotient is a function of the nutriments burnt by the tissues. R = 1, 0.7 or 0.8 respectively when the diet consists only of carbohydrates, lipids or proteins. The average value is 0.84 for a standard diet. Therefore, for each mole of oxygen consumed, only 0.84 mole of carbon dioxide is produced so that fewer molecules are present in the expired gas compared to the inspired gas. This represents a change of fraction of 0.03 and is generally neglected unless focus is on metabolic exchange or oxygen consumption. Therefore, although expired gas flow ($\dot{V}_E$) is lower than inspired gas flow ($\dot{V}_I$), they are considered equal in routine measurements.

The composition of expired gas depends also on the composition of inspired gas, normally dry air and water vapor. It may change if the subject is given oxygen therapy, or with metabolic activity(   ), with R if diet changes, and on ventilation. Ventilation (   ) is the flow produced by the action of the respiratory muscles on the thoracic cage and, therefore, on the lung. The flow is the product of the volume of each inspiration, also called the tidal volume (V_T), multiplied by the number of expirations per unit of time, the ventilatory frequency (f.   = V_T × f).

DEAD SPACE AND ALVEOLAR GAS

Gas exchange between inspired gas and blood occurs at the alveolar level, so gas has to be transported from the mouth to the alveoli by conducting airways. Conducting $\dot{V}O_2$ airways do not participate in gas exchange. They are part of what is called the "Dead Space" (V_D), around 150 ml. Functionally, the lung is therefore separated by a compartment, the dead space, which does not participate in gas exchange, but drives gas to where exchange occurs, and a compartment that participates in gas exchange called the Alveolar Volume (V_A).   and   are disposed in series. These definitions are physiological and do not strictly correspond to any precise anatomical volumes: Indeed the conducting airways are part of V_D but that is also true of part of the anatomical alveolar volume, because only a fraction of the anatomical alveoli participate in gas exchange at a given time. Consequently, V_A is always smaller than the anatomical alveolar volume.

The fraction of inspired gas flow that truly contributes to gas exchange is the flow that ventilates the functional part of the alveolar volume, called Alveolar Ventilation (   ). It is the useful part of   . The Inspired Flow (   ) is the sum of   and   . The end result is that during each cycle of 450 ml of tidal volume, 150 ml serve to ventilate dead space and only 300 ml participate in the exchange process. The composition of inspired gas does not change during inspiration and the composition of expired gas varies in time during expiration. First, the volume of gas contained in the dead space is expired.

TABLE 7.1: Normal values of pressures in inspired, expired, alveolar gas and in blood (mm Hg)

	I	*E*	*A*	*a*	$\bar{v}$
P_{CO_2}	0	26	39	39	44
P_{O_2}	150	118	102	91	38
P_{N_2}	563	569	572	572	572
P_{H_2O}	47	47	47	47	47
P_{total}	760	760	760	749	701

a: arterial blood, $\bar{v}$: mixed venous blood

It is the gas that was inspired at the end of the previous inspiration and because it had remained in the dead space, it did not participate in gas exchange. Its composition is that of inspired gas. Then, a mixture of inspired gas and alveolar gas and finally pure alveolar gas are successively expired. Alveolar gas composition can be reasonably approximated in a normal subject by sampling either the end tidal gas (gas at the end of a normal expiration) or better yet, the end forced expiratory gas.

The normal values for inspired, expired and alveolar gas are given in Table 7.1.

Ventilation equations can be computed from what is called the monocompartment alveolar model. The model consists of a fully functional monoalveolar lung and a single dead space.[2]

The equations are:

$$= [(0.863 \times \qquad [1–F_IO_2\ (1–R)]]/(P_IO_2\text{-}P_AO_2) \qquad (1)$$

$$= (0.863 \times R \times \qquad)/P_ACO_2 \qquad (2)$$

(The 0.863 constant results from correcting volumes and flows for pressure and temperature conditions)

Equation 2 shows that alveolar ventilation at a given metabolic rate is the unique function of PCO_2 in normal circumstances and therefore, PCO_2 and not PO_2 is the regulating factor of ventilation.[3]

TRANSFER OF GAS ACROSS THE ALVEOLAR CAPILLARY MEMBRANE

Gases pass through the complex structure of the alveolar membrane consisting of the alveolar epithelium lined by lipoproteins, the epithelial basal membrane, the interstitium, the endothelial basal membrane and the capillary endothelium to reach the plasma. Gas enters the membrane by dissolving almost instantaneously either in the lipid layer or directly in the aqueous components of the cells in proportion of its solubility, which varies from very low for helium to high values for diethyl ether, which are at the extremes of the scope of gases utilized in respiratory studies. For a given partial pressure, a soluble gas reaches a higher concentration at the surface within the alveolar cell than a less soluble one. The rate of diffusion will, therefore, be greater. The site of gas exchange within the lung is difficult to define anatomically, but confined to that part of the alveolar membrane bounded by the ventilated alveoli and on the other side by microvessels that contain blood and which is believed to represent half of the alveolar membrane surface.

Other factors that contribute to gas exchange, apart from solubility and surface area, are molecular weight and thickness of the membrane and indeed the difference of partial pressures across the membrane.[4]

The overall transfer rate is:

$$Dm = k\ [(A/d \times s)/\sqrt{M}]$$

Where D is the transfer rate of the gas in volume per unit of pressure gradient per unit of time, k the diffusion coefficient in cm^2 per unit time, A the surface area, d the membrane thickness in cm, s the solubility of the gas in volume/volume per unit gas partial pressure and M the molecular weight of the gas. Dm is generally called the “diffusing capacity” of the gas across the membrane.

$\dot{V}\dot{O}\dot{O}$ $_{A\ 2\ 2}$

To achieve the transfer from alveoli to blood in the case of oxygen and in part for carbon dioxide, the gas after crossing the membrane and reaching the plasma must diffuse from plasma to erythrocytes and then combine chemically with hemoglobin. The gas crosses the erythrocyte membrane by facilitated diffusion due to the migration of hemoglobin molecules between the surface area and the interior of the cells. The reversible reaction by which gas combines to hemoglobin is not instantaneous and the amount of gas bound will depend on the hemoglobin concentration. The overall rate is the product of the reaction rate, the driving pressure, the volume of blood and the blood flow in the microvessels. The transfer rate for the gas from plasma to hemoglobin can be approximated from a complex equation to:

$$D' = \beta Q + \theta V_C$$

Where β is the “capacitance coefficient” in mmol per l of blood per unit of pressure at 37° C, θ the rate of the chemical combination, V_C the capillary volume.

Because Dm and D′ have the dimension of a flow rate per unit of pressure, their inverse have the dimension of a “resistance” so the total resistance offered against the flow of gas from the alveoli to hemoglobin is the sum of the resistance from the alveoli to plasma and from plasma to hemoglobin:

$$1/T_L = 1/Dm + 1/(\beta Q + \theta V_C)$$

T_L is called the "transfer factor" of the lung. The rate at which the gas leaves the plasma to combine with hemoglobin is fast compared to the rate at which it dissolves in circulating blood for carbon monoxide and nitric oxide and to a lesser extent for oxygen so that βQ can be neglected so:

$$1/T_L = 1/Dm + 1/\theta V_C$$

The transfer factor is often called the diffusing capacity, but as demonstrated it incorporates resistive terms related not only to diffusion, but also to chemical bonding, expressing the complexity of the transfer of oxygen from the alveoli to the blood. The speed at which the bonding of oxygen to hemoglobin occurs is relatively fast compared to the time it takes for an erythrocyte to cross the lung, so that it is not a limiting factor in the transfer of oxygen from alveoli to capillaries, at least until blood flow is very high.[5]

The physical properties of oxygen and carbon monoxide in terms of diffusion are not very different. The plasma concentration of CO remains negligible when a small quantity is breathed because of the high affinity of CO for hemoglobin so that the measurement of TLCO is easy and a good approximation of the oxygen transfer factor.[6]

GAS TRANSPORT TO AND FROM THE PERIPHERY

Oxygen Transport by the Blood

The relationship between cardiac output , arterial and mixed venous concentrations of oxygen in blood and oxygen consumption is:

$$= (\dot{Q})\ (CaO_2\text{-}C\bar{v}O_2).$$

The mixed venous concentration ($C\bar{v}O_2$) is the concentration of oxygen in the pulmonary artery, just before cardiac output enters the lung, where all venous blood from the various organs mix together. This equation states that the amount of oxygen consumed by the tissues is the difference between the total amount of oxygen brought to them by cardiac output from the lung ($\dot{Q} \times CaO_2$) and the amount that is left over and brought back to the lung by cardiac output . As stated before, in a normal subject, CaO_2 always reaches its maximum value after lung oxygenation and does not depend on the subject activity unless in extreme situations. Venous blood concentration depends on the organ activity. It varies from one organ to the other.[7,8]

Oxygen is carried in the blood in two forms, dissolved in plasma (1.5%) and combined to hemoglobin (98.5%). The amount of oxygen dissolved in the blood obeys Henry's law for dissolution of gas into liquids. It is proportional to partial pressure, but the dissolution coefficient for oxygen being very low, the amount of oxygen that can be transported per unit of volume of blood and per unit of time is very limited (0.3 ml/100 ml of blood). It is inadequate to cover metabolic needs. This amount rises to 2 ml/100 ml when breathing pure oxygen. The essential mechanism of oxygen transport is chemical reversible bondage to hemoglobin. The total amount of oxygen present in the blood is the sum of the dissolved and combined oxygen concentration (Table 7.2). Dissolved oxygen is usually neglected in most calculations, but dissolved oxygen is the form that allows oxygen to be transferred from erythrocytes to mitochondria in organs. It is also the physical state allowing the measure of PaO_2 by electrochemical methods.

$(\dot{Q} \times C\bar{v}O_2)$

TABLE 7.2: Normal partial pressures and concentrations of oxygen and carbon dioxide in blood

Oxygen		*a*	*v̄*	*(a – v̄)*
PO_2	mm Hg	**91**	**38**	
dissolved	mmol/L	0.12	0.005	+ 0.07
HbO_2	mmol/L	8.60	6.01	+ 2.59
Total	mmol/L	**8.72**	**6.01**	**+ 2.66**
Carbon dioxide		*a*	*v̄*	*(a – v̄)*
PCO_2	mm Hg	**39**	**44**	
dissolved	mmol/L	1.19	1.37	– 0.18
HCO_3^-	mmol/L	19.60	20.96	– 1.36
$HbCO_2$	mmol/L	1.09	1.72	– 0.63
Total	mmol/L	**21.88**	**24.05**	**– 2.17**

a: arterial blood, v̄: mixed venous blood, (a – v̄): arterio-venous difference

Normal adult hemoglobin (Hemoglobin A) is a conjugated protein consisting of four polypeptide chains (globins) and of an iron porphyrin compound (heme). Oxygen binds to the heme in various successive stages, up to four molecules of oxygen per heme. These stages explain the sigmoid shape of the relationship between PaO_2 and oxygen concentration. A small percentage of total circulating hemoglobin is not functional because it is under the form of Methemoglobin (MetHb) or because some carboxyhemoglobin has been formed in the presence of traces of carbon monoxide (HbCO). The normal concentration of hemoglobin is 9 mmol/l, equivalent to 14.6 g/100 ml, and can carry up to 20 ml of oxygen per 100 ml of blood (1.39 ml per gram if only functional hemoglobin is considered, 1.36 ml if total

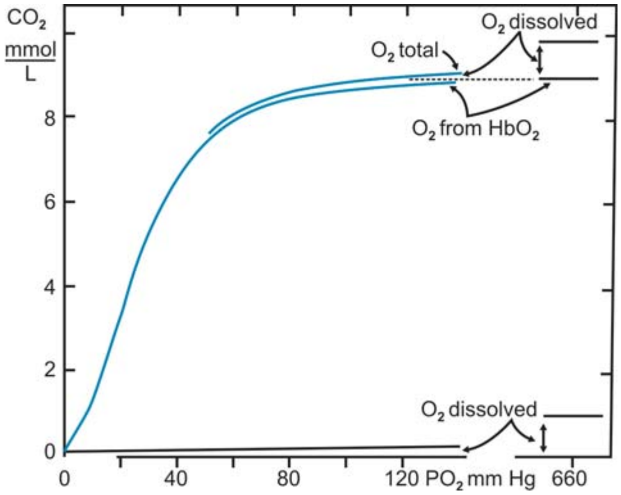


Fig. 7.3: Dissociation curve for oxygen and total oxygen content (CO_2): Total content of oxygen is the sum of oxygen dissolved in plasma and of oxygen combined to blood hemoglobin. Dissolved oxygen is low at atmospheric pressure breathing ambient air, but can rise significantly if ambient pressure (hyperbaric condition) or oxygen fraction is raised (breathing gas with a high oxygen fraction). Content can be given in ml oxygen/100 ml of blood or mmol/L (see Table 7.2)

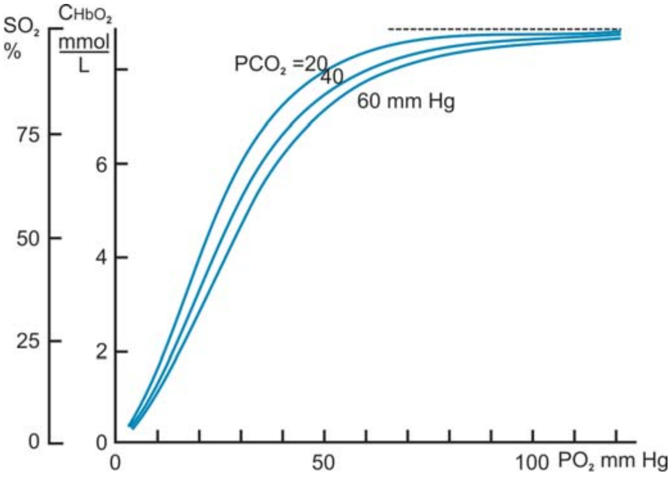


Fig. 7.4: Dissociation curve for oxygen for different PCO_2 in blood: Note that an increase in PCO_2 induces a shift to the right of curve. For the same PO_2 value, less oxygen can be combined to hemoglobin. The process facilitates the release of oxygen to the tissues as metabolism induces a rise of local PCO_2. Note that when hemoglobin concentration is known, the curve is the same for saturation and content

hemoglobin is considered). The maximum volume of oxygen that can be carried by 100 ml of blood is called the total oxygen capacity. The concentration of oxygen in the blood is usually given in ml of oxygen per 100 ml of blood or in mmol/L. It is called the "oxygen content."

The O_2 saturation is defined as the ratio of O_2 combined with hemoglobin (oxyhemoglobin) to O_2 capacity. Normal arterial saturation is 97.5% for a PO_2 of 100 mm Hg at normal temperature and H^+ concentration. Normal mixed venous blood saturation is around 75% for a PO_2 of 40 mm Hg. Because of the sigmoid shape of the concentration and saturation curves (Fig. 7.3), there is no simple relationship between saturation, content and oxygen partial pressure; for example, doubling the pressure does not double saturation. The shape of the curve is beneficial to physiological functions. Because the curve is almost flat in its upper part, a fairly large variation of PAO_2 will not change the loading of oxygen to much extent. The difference in oxygen pressure between blood and alveoli will remain high all along pulmonary capillaries facilitating the rapid diffusion of oxygen between alveoli and erythrocytes. Conversely, because the lower part of the curve is steep, a small drop in pressure will ensure a large flow of oxygen from the erythrocytes to the capillaries and then to the tissues.

The affinity for oxygen of the hemoglobin molecule is modified when its stereo chemical conformation changes, which happens, for example, when $[H^+]$ or PCO_2 changes or when another gas or molecule (carbon monoxide for example) can compete with the O_2 receptor sites.

The hemoglobin dissociation curve is shifted to the right by a rise in $[H^+]$, of temperature and of PCO_2 (Fig. 7.4). This means that under these circumstances, hemoglobin combines with less oxygen and can release more of the oxygen that was already fixed. This facilitates the release of oxygen in organs where metabolism raises the temperature, PCO_2 and $[H^+]$. Organic phosphates present in the erythrocytes (2,3-diphosphoglycerate, DPG) also facilitate the release of oxygen when their concentration rises, as seen in chronic hypoxia (altitude). A useful indicator of the position of the inflexion point of the dissociation curve is the value of P_{50}, the oxygen pressure at which saturation is 50%. The normal value is 26 mm Hg. It is elevated when the dissociation curve is shifted to the left, i.e. when hemoglobin can combine to more oxygen per gram and falls when it can combine to less (right shift).

Oxygen reaches the mitochondria by passive convection and diffusion from the plasma. The P_{O_2} at tissue level and in the mitochondria is very low, but oxygen flow is high. Mitochondrial respiration does not stop until oxygen pressure is at extremely low levels.

The stores of oxygen in the body are very limited, in the form of combined oxygen in the blood (HbO_2) and of MbO_2 in muscles and amounts to 900 µMol/kg of body mass in a normal 70 kg man at rest. These stores allow only a few minutes of survival.

Transport of CO_2 by the Blood

The blood transports carbon dioxide in three forms: Dissolved in plasma; bicarbonate, and in combination with proteins (Table 7.2).

Because the solubility of CO_2 is 20 times higher than that of oxygen, the amount of dissolved CO_2 is more significant in the terms of transport (5% in arterial blood versus 90% for bicarbonates and 5% for proteins).

CO_2 can be transformed in bicarbonate by the following reaction:

$$\begin{array}{c}\text{CARBONIC ANHYDRASE}\\ \downarrow \\ CO_2 + H_2O \quad H_2CO_3 \quad HCO_3^- + H^+\end{array}$$

The speed of transformation of dissolved CO_2 into carbonic acid is very slow in plasma, but greatly facilitated by a specific enzyme, carbonic anhydrase, in erythrocytes. The ionization of carbonic acid occurs quickly and is spontaneously reversible. When bicarbonate concentration increases in the cell, the bicarbonate ion diffuses freely from the erythrocytes to plasma, but H^+ cannot, because the membrane is little permeable to cations. Chloride Ions (Cl^-) move from plasma membrane into the erythrocytes to maintain electrical neutrality in the cells, according to the Gibbs-Donnan equation.

A significant part of the free H^+ can bind to hemoglobin releasing oxygen:

$$H^+ + HbO_2 \rightleftharpoons H^+\text{-}Hb + O_2$$

This facilitates, as said previously, the release of oxygen and the uptake of CO_2 in the tissue capillaries. The facilitation of CO_2 uptake by the release of oxygen in the tissues is called the Haldane effect. The symmetrical facilitation of O_2 uptake by release of CO_2 in the lung is called the Bohr effect.[9]

CO_2 can combine with the terminal amine groups of some blood proteins and in particular with the globins of hemoglobin forming carbaminoproteins and more specifically carbaminohemoglobin (Fig. 7.5). This reaction again facilitates the release of O_2 in the tissues (Fig. 7.6).

Altogether, dissolved CO_2 constitutes 10% of the venous-arteriolar difference for CO_2 against 30% for carbaminoproteins and 60% for bicarbonate.

The dissociation curve for CO_2 differs markedly from the dissociation curve for oxygen. It is steeper than the oxygen dissociation curve for oxygen, especially in 40–50 mm Hg range where CO_2 content varies as much as 4.7 ml/100 ml against 1.7 ml/100 ml for oxygen (Fig. 7.6).

As stated before, CO_2 content increases when the oxygen saturation of hemoglobin decreases, which facilitates gas exchange at the tissue level. The opposite occurs at lung level. Because of these interactions, the gas contents cannot be proportional to partial pressure. This is figured when O_2 and CO_2 dissociation curves are plotted together on a PCO_2 versus PO_2 diagram (Rahn diagram),[2]: The lines of equal O_2 pressure and equal CO_2 pressure (isopleths) are neither straight nor parallel to the axes (Fig. 7.7).

The stores of carbon dioxide in the body are very large because of the high capacitance of all tissues, including the bone. CO_2 is stored mainly in the form of bicarbonates and carbamino compounds. They amount to more than 10,000 µMol/kg of body mass in a normal 70 kg man at rest. These stores change slowly except in the blood and soft tissues so that they can quickly compensate for hypocapnia or hypercapnia.

VENTILATION PERFUSION RATIO

The global efficacy of the lung exchanger depends strongly on the adequacy between alveolar ventilation and capillary blood flow, ensuring that ventilated zones are well perfused, and vice-versa. The relationship between ventilation and perfusion is characterized by the ventilation-perfusion ratio $\dot{V}_A/\dot{Q}$.[10,11] The ratio can be computed from the ventilation equations and the oxygen transport equation in the blood:[12]

$$\dot{V}_A/\dot{Q} = 0.963 \times R\ [(CaO_2 - C\bar{v}O_2)/P_ACO_2]$$

It is noteworthy that this ratio is a function of the respiratory quotient (R). There is a different ratio for each metabolic level (Fig. 7.8). The equation gives the average ratio value for the entire lung. In fact the ratio presents regional variations because ventilation and perfusion are inhomogeneous within the lung (Fig. 7.9). Furthermore, regulation mechanisms, such as hypoxic vasoconstriction may locally modify perfusion and ventilation.

Most of the heterogeneity can be attributed to the effects of gravity on the lung. The influence of gravity on ventilation and perfusion differs in the term of mechanism and amplitude.

The effect of gravity on ventilation is secondary to the elastic structure of the lung. Mechanically, the lung can be seen as suspended to the trachea so that at each level, it is expanded by the weight of its own underlying levels (Fig. 7.10). Consequently, the weight bearing on one level is inversely proportional to that level and

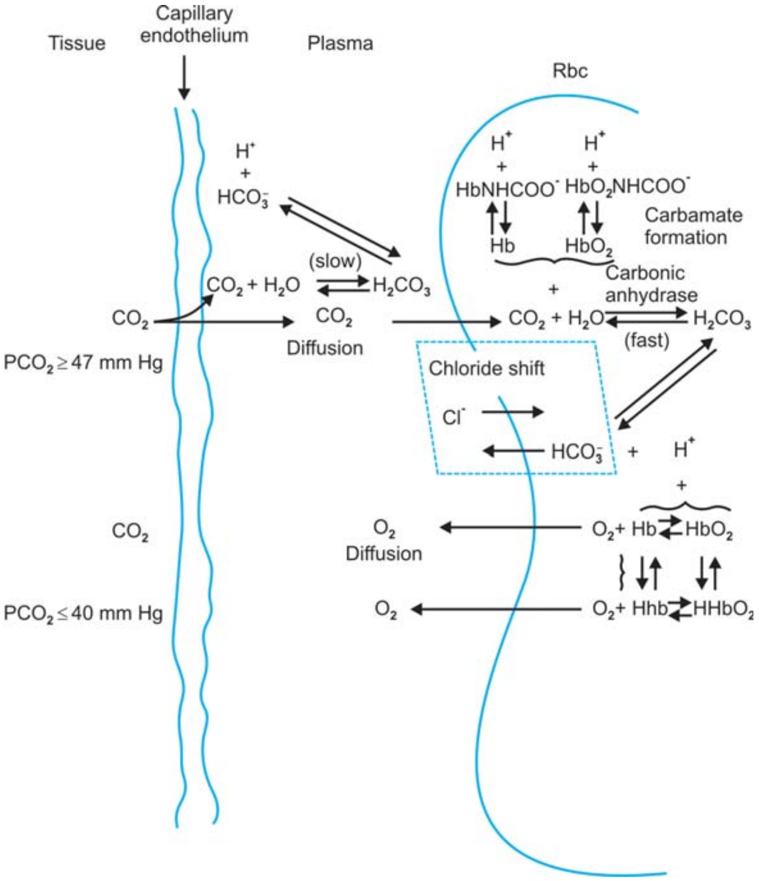

Tissue
Capillary endothelium
Plasma
Rbc
H^+ + HCO_3^-
H^+ + $HbNHCOO^-$
H^+ + HbO_2NHCOO^-
Hb
HbO_2
Carbamate formation
Carbonic anhydrase
(slow)
$CO_2 + H_2O \rightleftarrows H_2CO_3$
CO_2
CO_2
Diffusion
$CO_2 + H_2O \rightleftarrows H_2CO_3$
(fast)
$PCO_2 \geq 47$ mm Hg
Chloride shift
Cl^-
HCO_3^- + H^+
CO_2
O_2
Diffusion
$O_2 + Hb \rightleftarrows HbO_2$
$O_2 + HHb \rightleftarrows HHbO_2$
$PCO_2 \leq 40$ mm Hg
O_2

Fig. 7.5: Transport mechanisms for oxygen and carbon dioxide between erythrocytes and tissue (see text for explanations)

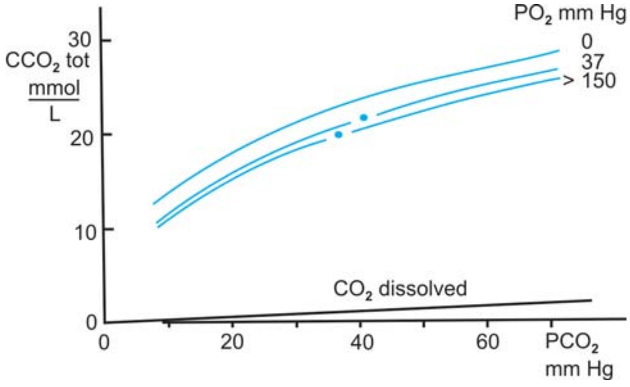


Fig. 7.6: Dissociation curve for carbon dioxide in blood. The shape of the curve is quite flat. The amount of dissolved CO_2 cannot be neglected. A rise in PO_2 induces a shift of the curve downwards. The process facilitates the release of CO_2 in the lungs. This is why there is a shift from one curve to the other, when venous blood looses CO_2 in the lung capillaries and takes up oxygen
a: arterial blood, $\bar{v}$: mixed venous blood
Modified from Dejours[9]

distension increases from bottom to top so that the size of alveoli increases from bottom to top. Because of the relationship between pulmonary volume and transpulmonary pressure, compliance will be lower at the apex compared to bottom so that for a given change of transpulmonary pressure during the ventilatory cycle, ventilation will be higher at the bottom compared to the apex. Alveolar ventilation increases from top to bottom.

The effect of gravity on perfusion is due to the increase in hydrostatic pressure from top to bottom within the elastic vessels of the lung that is not compensated on the external side because the vessels are exposed on that side to the atmospheric pressure of the alveoli instead of a water column that would compensate for hydrostatic pressure at each level as this is the case in the systemic vessels. The rise in internal hydrostatic pressure results in an increase in transmural pressure, so that vessel section rises and perfusion follows. Alveolar perfusion increases from top to bottom.

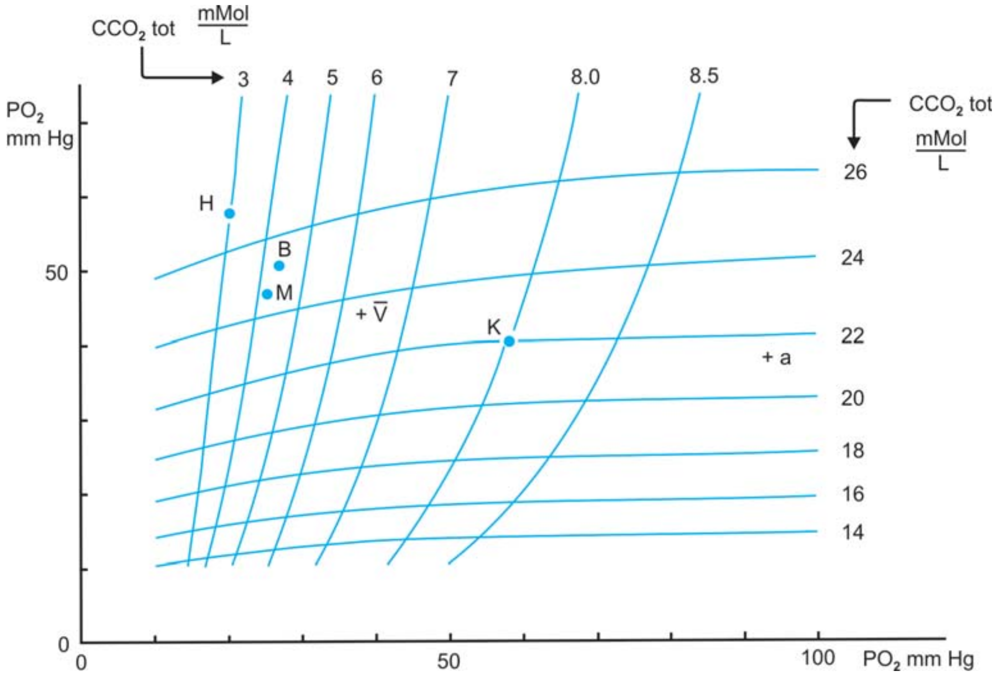


Fig. 7.7: The PO_2-PCO_2 diagram combines the dissociation curves for both gases. The lines represent the isopleths, the pressure curves for one gas at a given concentration of the other one. If there were no interactions between the two gases, all curves for one gas would be flat and parallel to the axis. The changes of partial pressures and of concentrations for both gases can be read on a single diagram when going from arterial to venous blood

A: arterial blood; v̄: mixed venous blood; c: coronary; e: encephalic; m: muscle; r: renal venous blood. The venous blood of all these organs and others, mix when reaching the pulmonary artery to form mixed venous blood, v̄.

Modified from Rahn et al[2]

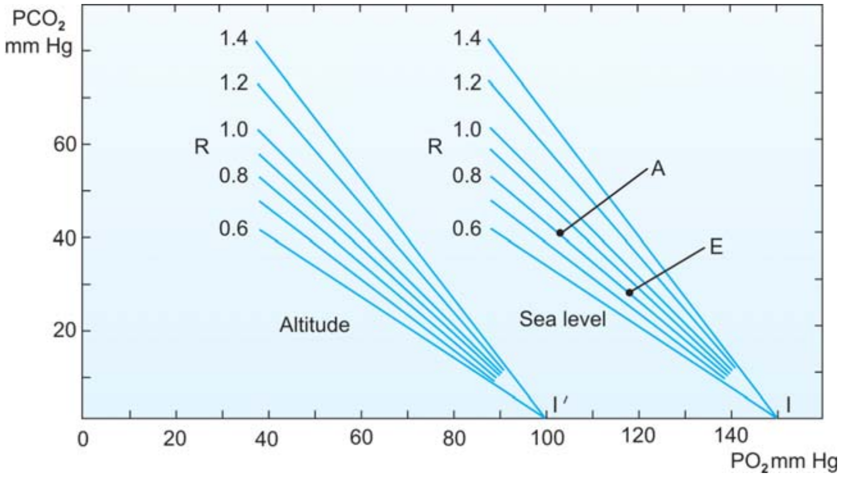


Fig. 7.8: Representations of R lines on the PO_2-PCO_2 diagram: On the right: set of R lines at sea level (PO_2 = 150 mm Hg). On the left: set of R lines at altitude (PO_2 = 100 mm Hg). For each metabolic level represented by the ratio of CO_2 production to O_2 consumption R, possible values of PO_2 and PCO_2 are coupled and must be on the corresponding R line. For each PO_2 value there is only one PCO_2 value. The slope of the relationship is not modified by a change in pressure in ambient air, for example, by altitude (in this example 3000 m, P_B = 526 mm Hg).

A: alveolar, E: expiratory, I: inspiratory gas.

Modified from Dejours[1]

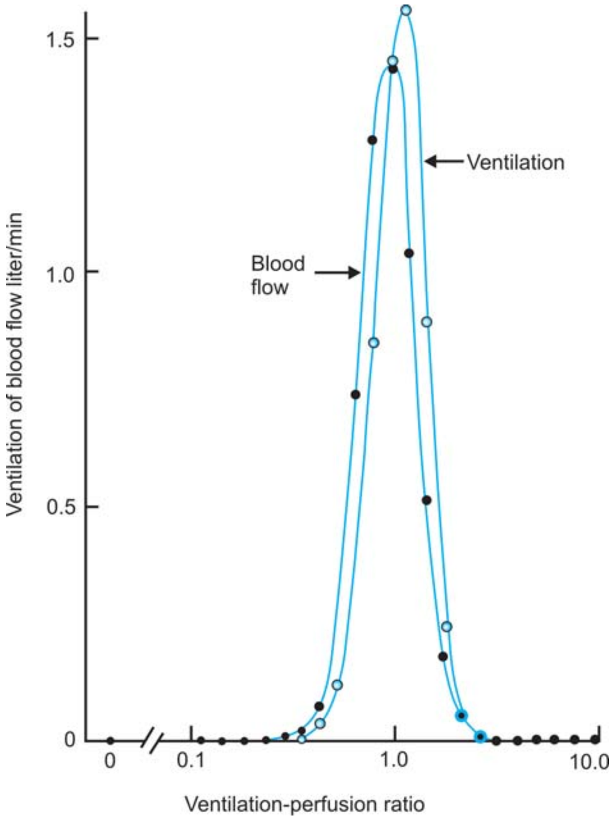


Fig. 7.9: Distribution of blood flow and ventilation in function of V_A/Q in a normal young: subject: note that the horizontal scale is logarithmic. Both distributions are positioned about a ratio close to 1, but are not superimposed.
Modified from Wagner et al[11]

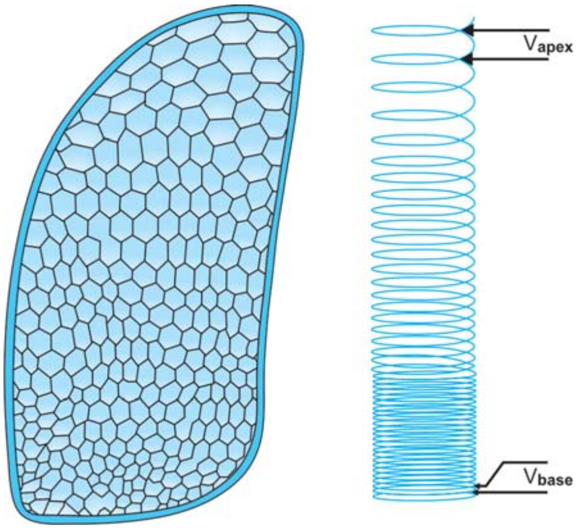


Fig. 7.10: Because the lung behaves like a suspended elastic structure, the weight bearing on any level is that of the structure below it and therefore increases from base to apex. The resulting structure of the lung is pretty much that of a suspended spring. Distension increases from base to apex and so does the volume of the alveoli

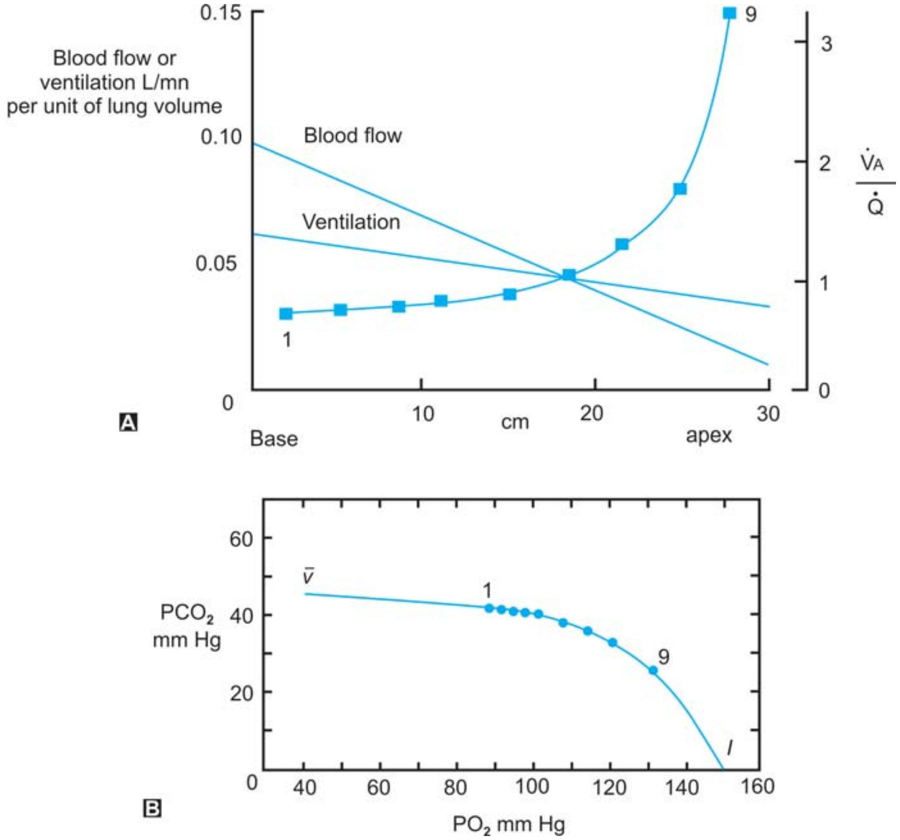
Although, both ventilation and perfusion increase linearly from top to bottom, the increase in ventilation is not proportional to that of circulation. The resulting relationship of the ratio to height is curvilinear (Fig. 7.11A). In theory $\dot{V}_A/\dot{Q}$ may vary from zero (a perfused zone with no ventilation) to infinity (a ventilated zone with no perfusion) (Fig. 7.12). The average lung value is 0.84.

For a given ventilation-perfusion ratio, there is only one possible quantitative relationship between P_AO_2 and P_ACO_2 and thus between P_aO_2 and P_aCO_2. In other words, for any given P_AO_2 or P_ACO_2, there is only one possible P_aCO_2 or P_aO_2. The possible paired values can be represented as a distribution curve on a P_{O_2}-P_{CO_2} diagram (Fig. 7.11B). Each level of the lung has its own $\dot{V}_A/\dot{Q}$ value so that the $\dot{V}_A/\dot{Q}$ of a given level corresponds to a specific paired value (Fig. 7.13).

The range of variation of P_{O_2} is almost of 40 mm Hg against only 14 mm Hg for CO_2. This asymmetrical nature of the distribution curve is a consequence of the very different relationship between pressure and concentration for each gas, relatively flat for CO_2, but sigmoid for O_2 and also because of the predominating role of PCO_2 in the regulation of ventilation. The largest variations of the $\dot{V}_A/\dot{Q}$ ratio are observed in the upper regions of lung. This is mostly due to the fall of local perfusion in these regions. $\dot{V}_A/\dot{Q}$ gets below its average value when going towards the bottom of the lung; the P_ACO_2-P_AO_2 diagram shows little changes in P_ACO_2, but an important drop in P_AO_2. $\dot{V}_A/\dot{Q}$ gets above 0.84 when going towards the apex; P_ACO_2 tends very quickly to very low values while PO_2 almost reaches inspired air O_2 partial pressure. Consequently, the PaO_2 of blood is higher and the $PaCO_2$ lower at the apex compared to the bottom, meaning that blood oxygenation is more efficient at the apex. However, proportionally, most perfusion and ventilation take place towards the base, therefore, most of the alveolocapillary exchange is located there, although it is less efficient.

Gas Exchange and $[H^+]$

The relationship between PCO_2, HCO_3^- and $[H^+]$ implies a close relationship between these parameters and ventilation. In fact, the role of ventilation on pH regulation in the organism is essential. The physiology of gas exchange cannot be fully understood unless acid-base status is known.



Figs 7.11 A and B: (A) Blood flow and alveolar ventilation per unit of lung volume decrease linearly from top to bottom, but not with the same slope. The ratio of one to the other is therefore curvilinear. (B) For each $\dot{V}_A/\dot{Q}$ value in diagram A (1 to 9), everything being equal, there is only one possible pair of PO_2-PCO_2 values as shown in diagram B (1 to 9). The continuous line gives all the possible PO_2-PCO_2 paired values from inspired gas (I) to mixed venous blood (v). Each dot on this line gives the pair corresponding to each of the $\dot{V}_A/\dot{Q}$ dots of figure A.

The end results of ventilation and blood-gas exchange can be shown on the P_AO_2-P_ACO_2 diagram on which the O_2 and CO_2 dissociation curves can be superimposed, the $\dot{V}_A/\dot{Q}$ ratio values and the R lines (Fig. 7.14). The figure shows that when only two of these values are known, all others are fixed. For example, for a given R and a given inspired P_{O_2}, there is only one possible combination of $\dot{V}_A/\dot{Q}$, P_ACO_2, P_AO_2, and R.[2]

FLUID, SOLUTES AND PROTEIN EXCHANGE IN THE LUNG

An average of 300,000 ml of blood flows per hour through the microvessels of a human lung and 299,990 ml reach the pulmonary venous system.[13] Although pulmonary vascular pressure is maintained at a low level, which permits high flow at low resistance, the large endothelial surface area still forms an imperfect barrier, leaking water, small molecules and even proteins in all circumstances. There is therefore a permanent, albeit limited outflow flux of around 10 ml per hour of fluid and proteins towards the lung interstitium (Fig. 7.15). The lymphatic vessels due to the respiratory movements can drain this flow from the interstitium. Normally, fluid is prevented to reach the alveoli from the interstitium because of the very low permeability to fluid of the alveolar barrier and because the lymphatic ducts can generally handle excess fluid, upto atleast 10 times the normal value, so that fluid does not accumulate in the lung interstitium or flood the alveoli.[14]

The liquid and protein exchange in the lung are not confined to the alveolar wall capillaries, but also occurs

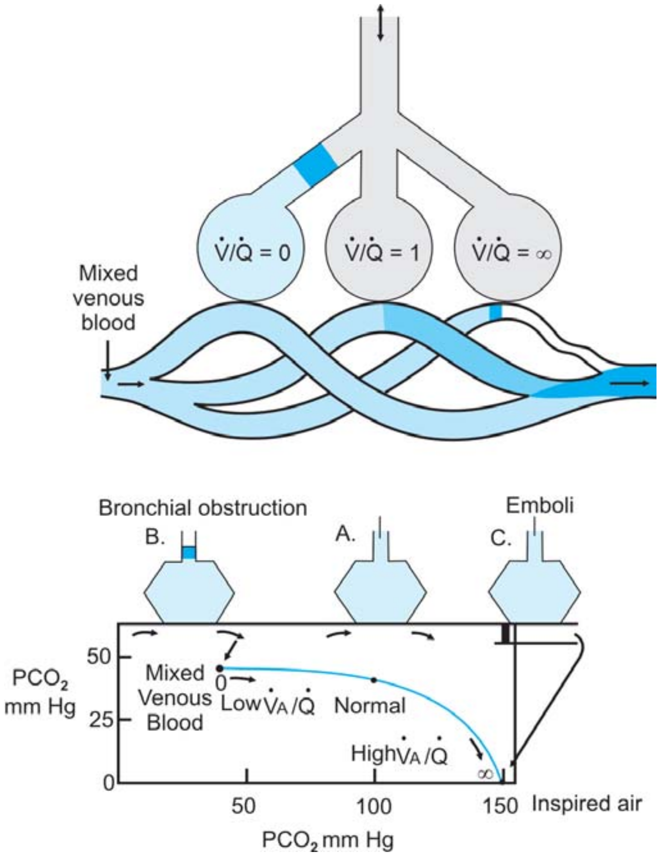


Fig. 7.12: Range of $\dot{V}_A/\dot{Q}$ ratio in case of impaired ventilation and perfusion. In case of bronchial obstruction, there is no ventilation, but perfusion is maintained and mixed venous blood does not participate in alveolar exchange. $\dot{V}_A/\dot{Q} = O$ In case of emboli, there is no perfusion, but ventilation is maintained, $\dot{V}_A/\dot{Q} = \infty$. No blood comes out of the alveoli.

The blood coming out of lung is composed of oxygenated blood from perfused and ventilated alveoli and of mixed venous blood from capillaries that have not been exposed to alveolar ventilation. In normal subjects, the percentage of such capillaries is very low (less than 5%). In fact, they correspond to what is called the physiologic shunt: blood flowing through capillaries that are too far from the alveolar membrane to participate in gas exchange. The physiological shunt explains why saturation cannot reach 100% in arterial blood. In pathological situation, the shunt may increase considerably and lower significantly PaO_2 because more blood flows through the nonventilated area.

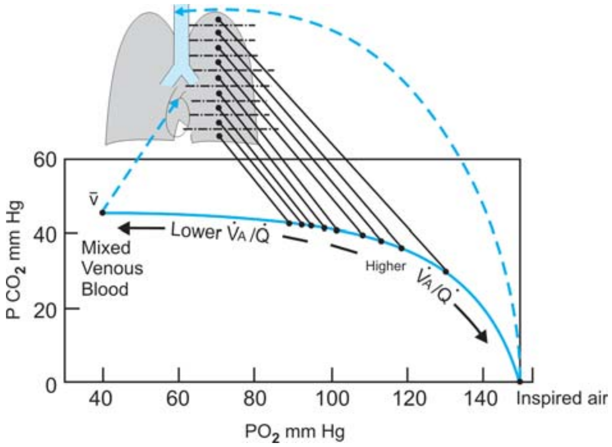


Fig. 7.13: Contribution of the different zones of the lung to the PO_2-PCO_2 curve: The highest $\dot{V}_A/\dot{Q}$ ratios occur towards the apex resulting in high PO_2 and low PCO_2, but most of the perfusion occurs at the base where $\dot{V}_A/\dot{Q}$ is lower. This explains that the average $\dot{V}_A/\dot{Q}$ ratio is 0.84

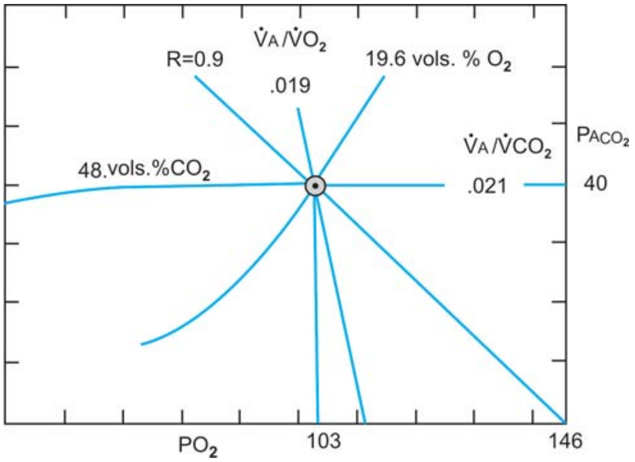


Fig. 7.14: The figure shows that when two parameters are measured all other values are determined. This results from the fact that PO_2 and PCO_2 must be simultaneously on the PO_2-PCO_2 curve, on the R lines and on the corresponding isopleths. Only one point at the junction of all curves satisfies these conditions.
From Rahn et al[2]

in the extra-alveolar lung capillaries[15] and across arterioles and venules up to two generations up or down from the capillary level (Fig. 7.16).

The liquid draining from the alveolar wall to the extra-alveolar connective tissue space does so by a direct route via the alveolar wall junctions. The initial lymphatics are situated in the adventitia of the small extra-alveolar small blood vessels,[16] within the extra-alveolar interstitium, at the junction with the alveolar space (Fig. 7.17). The fluid is drained passively by a hydraulic pressure gradient of about 3 cm H_2O. There is no evidence of any active pumping of fluid from these initial lymphatics to the general lymphatic circulation. The lymphatic flow may increase considerably, up to 10 to 20 folds in correspondence with an increase of the filtration flow at the microvascular barrier.

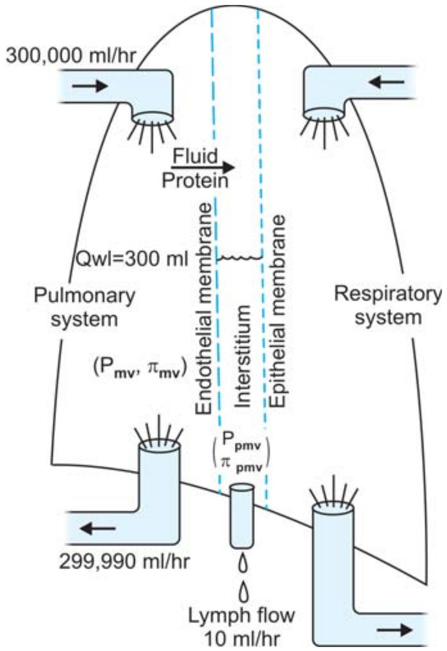

300,000 ml/hr
Fluid
Protein
Qwl=300 ml
Endothelial membrane
Interstitium
Epithelial membrane
Pulmonary system
Respiratory system
(P_{mv}, π_{mv})
(P_{pmv}, π_{pmv})
299,990 ml/hr
Lymph flow
10 ml/hr

Fig. 7.15: The lung is composed of three compartments: vascular, interstitial and alveolar.
Because the endothelial membrane is not totally impermeable to fluid and solutes, a continuous flow drains both to the interstitium according to the Starling equation. This net outward flux is drained out of the lung by the lymphatic system. The alveolar compartment remains dry due to the very low permeability of the epithelial barrier. A normal lung contains around 300 ml of water (Q_{wl}). P: pressure; pi: osmotic pressure; mv: microvascular; pmv: perimicrovascular. The osmotic pressure in the interstitium is around 0.6–0.8 that of plasma.
Modified from Blake[13]

Liquid and Solutes Transport

Transport across the microvascular endothelial barrier of the lung is qualitatively similar to that in other organs and obeys the general liquid and solute transport equations.[17] Because permeability to liquid, solutes and to proteins always vary in parallel (a change in permeability to water cannot happen without a simultaneous change in permeability to solutes and to proteins) the basic Starling equation for fluid exchange, which is a simplified expression of these general equations, characterizes reasonably well exchanges through the endothelium:

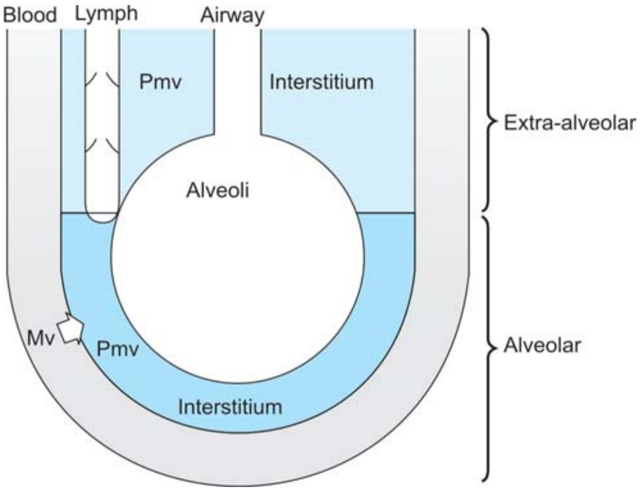

Blood
Lymph
Airway
Pmv
Interstitium
Extra-alveolar
Alveoli
Mv
Pmv
Alveolar
Interstitium

Fig. 7.16: Schematic representation of the alveolo-microvascular fluid exchange system in the lung. The interstitial compartment is drained by the lymphatics. The lymphatics start at the alveolar junctions and are therefore extra-alveolar. Filtration can occur in the alveolar and in the extra-alveolar compartments. The interstitium is drained passively from the alveoli to the hilum due to the drop in pressure along the bronchoalveolar interstitium.
Modified from Staub[15]

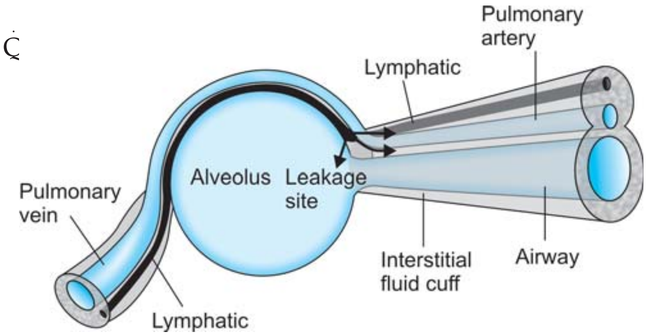

Pulmonary artery
Lymphatic
Alveolus
Leakage site
Pulmonary vein
Interstitial fluid cuff
Airway
Lymphatic

Fig. 7.17: Lymph drains normally via the lymphatics situated along the arterial, bronchial and venous trees. When lymphatics cannot drain anymore the excess filtration fluid, fluid accumulates first in the loose connective tissues of the bronchoarterial and venous cuffs. Then the alveoli are flooded. The most likely hypothesis explaining alveoli flooding during pressure edema is that overflow occurs in the zone that pumped out alveolar fluid at birth and that may constitute a zone of fragility.
Modified from Staub[16]

Where Q_f is the rate of fluid filtration, P is the fluid pressure, π the osmotic pressure, in the microvascular (mv) and perimicrovascular interstitial fluid compartment (pmv), K_f is the fluid conductance of the microvascular barrier, and sigma (σ), the reflection coefficient of the membrane. K_f is the product of the permeability to fluid and small solutes per surface unit (P) by the surface of the exchange area S. Sigma characterizes the effective osmotic pressure of solutes, i.e. the fraction of solute concentration that cannot be balanced across the barrier because a fraction of the molecules cannot cross the barrier due to restrictive permeability because of size and structure. Sigma = 0 for electrolytes crossing freely and 1 for very large proteins that cannot cross at all. The value of σ in the lung is between 0.6 and 0.8. This implies that the endothelial barrier is not fully impermeable to proteins and results in the fact that the interstitium protein concentration is about 0.8 that of plasma. It is generally believed that more than 95% of filtration fluid flows via the intercellular junctions and is therefore paracellular, and that other passive or active transcellular mechanisms are little related to bulk flow.

Types of Edema

We can deduce from the Starling equation that two types of edema may occur: i. High-pressure edema, also called hemodynamic or abusively hydrostatic edema, and ii. increased permeability edema, also called toxic edema.

In high-pressure edema, the conductance of the membrane to fluid and protein remains normal. The rise in filtration flow results solely from the rise in the difference in pressure across the membrane, due exclusively to the rise of the intravascular pressure. The composition of the filtration fluid remains the same as during normal filtration with a low protein concentration, which is reflected by the low protein concentration of the edema fluid.[18] This type of edema is representative of left ventricular failure, the rise of filtration pressure resulting from the rise in pressure in the left atrium (Fig. 7.18).

In increased permeability edema, fluid and proteins conductance of the endothelium are both modified. As stated before, K_f and σ vary together, but in opposite directions: K_f rises while σ decreases so that both fluid and proteins may move more freely across the barrier. The filtration flow increases even without any rise in pressure and the fluid is rich in protein, up to plasma concentration. This type of edema can be induced, for instance by endotoxin, regurgitation or inhalation of toxic substances such as chlorine.

In both types of edema, as long as the fluid remains interstitial, no apparent change occurs in the epithelium. When alveolar flooding occurs, the epithelium appears to become freely permeable to solutes, including proteins, irrespective of the type of edema so that the composition of interstitial and alveolar fluids are identical.[19] It will be low in pressure edema and almost identical compared to plasma in permeability edema. Therefore, the concentration in protein in the alveolar edema fluid reflects that of the type of edema. This explains why the type of edema may eventually be diagnosed from the protein content of fluid sampled at the trachea level.

In fact in most cases, permeability edema is preceded or associated with a transient or persistent rise of pulmonary arterial pressure inducing an additional rise in filtration and possibly a pressure edema as in endotoxic shock, for instance (Fig. 7.19). When this occurs, the rate of filtration becomes very high,[20] as the rise in filtration pressure is associated with a change in membrane permeability (Fig. 7.20). In practice, this implies that ideally, filtration pressure should be maintained as low as possible when permeability changes are suspected, a requirement conflicting in many cases with the need to sustain cardiac function through perfusion and vasoactive drugs.

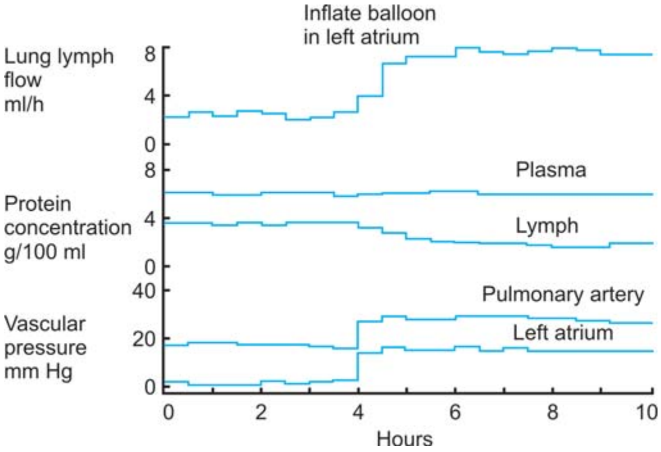


Fig. 7.18: Experimental design showing the effect of a rise in pressure in the right atrium by balloon inflation in a sheep: The rise in pressure in the left atrium causes almost instantaneously a rise in pressure in the pulmonary circulation. The rise of intramicrovascular pressure results in a rise of fluid and small molecules filtration through the endothelial barrier, shown by the increase in lymphatic flow. Because the endothelial membrane remains intact, proteins do not cross the barrier in significant amount and a protein poor fluid filtrates to the lymph so that the ratio of lymph to plasma protein concentration drops with time. This is characteristic of pressure edema.
Modified from Bland et al[18]

Sequence of Fluid Accumulation in the Lung

Clinically, pulmonary edema is defined as the stage when liquid enters the alveolar space. Whatever the type of edema, alveolar filling is believed to be an all or none process, alveoli being filled completely at once. However much before this final and dramatic stage happens, various protective drainage mechanisms offer protection against flooding. The first step for filtration fluid is drainage along the interstitial compartment.

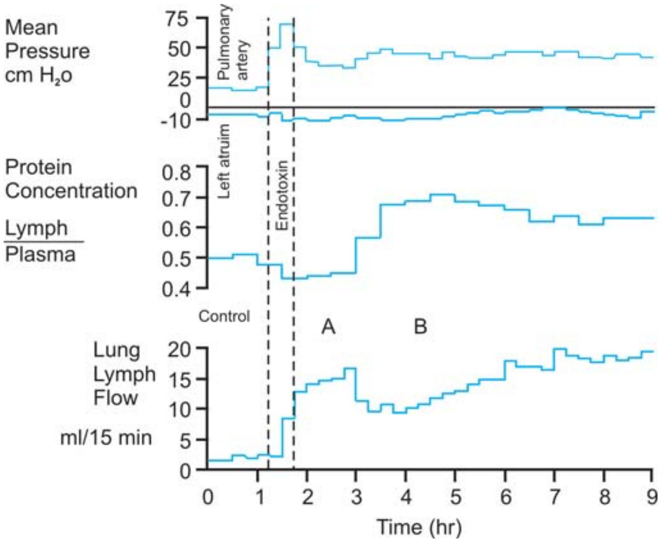


Fig. 7.19: Experimental design showing the succession of pressure and permeability edema in a sheep after administration of endotoxin: In the few hours following administration, pressure rises in the pulmonary artery, lymph flow increases rapidly and the lymph to plasma protein concentration ratio decreases suggesting a typical pressure edema (A). However, if the animal is monitored long enough, pulmonary artery pressure decreases to slightly above normal level, lung lymph, flow increases slowly over several hours to reach a late high plateau, although pressure has remained stable. Lymph to plasma protein ratio which has dropped initially comes back to normal slowly (B). This is interpreted as the emergence of a permeability edema characterized by a moderate pulmonary arterial pressure, a very high lymph flow and a normal lymph to plasma protein ratio suggesting the filtration of plasma and not of a protein poor fluid as in pressure edema. The slow time course is due to the necessary activation of the various biological processes leading to endothelial membrane alterations.
Modified from Robbins et al[19]

Liquid and protein conductance in the interstitium do not depend on the interstitium structure although the constituting matrix structure of the interstitium may vary with pressure and volume. The interstitium does not interfere qualitatively with the fluid when flow increases. This means that the composition of pulmonary lymph is representative of filtration fluid. Interstitial edema happens only at a late stage and is quantitatively limited. The sequence of accumulation of fluid in the lung differs somewhat between hemodynamic and permeability edema. To begin with, in both types of edema, the excess fluid is drained by the lymphatic system until it is saturated, then fluid appears to collect first in the bronchoalveolar interstitial space, the so called bronchial cuffs on the venous, as well as the arterial sides, then in the alveolar wall, and at the corners of the alveoli in the airspace, and finally fills the airspace by a mechanism that is still poorly understood.[16]

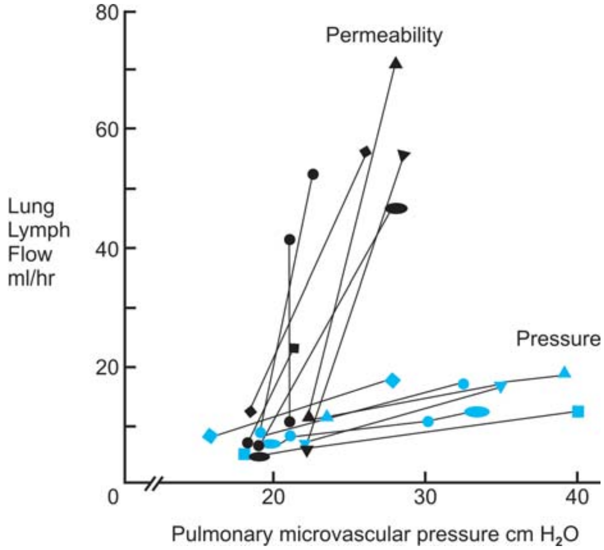


Fig. 7.20: Relationship between filtration flow across the endothelial barrier and membrane permeability in sheep: Black symbols show the change in lymph flow (filtration) with changes in microvascular pressure during permeability edema (endotoxin). Open symbols show the same change during pressure edema (intact membrane). A rise in microvascular pressure results in a dramatic increase in filtration if permeability has been altered simultaneously. A modest rise of filtration pressure in patients with toxic edema can have deleterious effects on the lung.
Modified from Brigham et al[20]

In pressure edema, it is unlikely that direct damage to the epithelium occurs except at very high pulmonary pressure (> 50 mm Hg). Changes in pressure and tension across the alveolar wall cannot explain the overflow because perialveolar interstitial pressure is far too low a driving force to overcome the high epithelial hydraulic resistance. The most likely hypothesis is that overflow occurs at the junction of the alveoli with the first bronchial segments. This zone of so-called natural weakness is precisely where fluids and proteins are reabsorbed from the alveoli to the lymphatics at birth and would play an inverse passive role due to its fragility during pressure edema (Fig. 7.17). In increased permeability edema, direct damage may occur simultaneously to the epithelial and alveolar barrier with fluid filtrating simultaneously to the cuffs and lymphatics and to the alveoli.

Effect of Blood Distribution in the Lung

Blood flow is nonuniformly distributed in the lung on both a gravitational and a local (longitudinal) basis. There is a five-fold variation of flow over the height of the lung due to the action of gravity on distensible vessels. This results in an increasing endothelial surface area towards the bottom of the lung with an increase in filtration that is matched by a proportional increase in the lymphatic drainage structure, so that there is no vertical change in fluid accumulation with height per volume unit. In the case of high-pressure edema, extra vascular fluid tends to accumulate first where pressure and exchange surface per unit volume are highest. This explains the increase in water accumulation from top to bottom. In high permeability edema, the repartition of extra-alveolar lung water is patchy, depending on the repartition of the lesions, and atleast in part, independent of the vertical pressure gradient.

Filtration across the microvascular membrane is linked to the distribution of microvascular pressure and therefore of resistance along the microvessels (Fig. 7.21). Contrary to what occurs in the systemic circulation where the drop in pressure and therefore resistance is localized at the arteriolar level, resistance is distributed longitudinally in pulmonary microvessels and may vary not only at the arteriolar level because of hypoxemia or hypoxia (hypoxemic vasoconstriction), but also all along the vessels[21] in response to various biological or pharmacological agents such as serotonin on the arterial side or histamine on the venules side. Consequently, the filtration pressure at the filtration site is dependent on the distribution of resistance between the prefiltration and postfiltration sites (Fig. 7.22). If the resistance is mostly on the prefiltration vessels, then filtration pressure will be low compared to arteriolar pressure and well reflected by the measure of wedged capillary pressure. If resistance is mostly localized on the postfiltration side, then filtration pressure will be only slightly less than arteriolar pressure, and therefore filtration rate will be high and not evaluated correctly by wedge capillary pressure. Therefore, wedge capillary pressure may underestimate filtration pressure with the risk of under evaluating the outwards flux especially in permeability edema.[22]

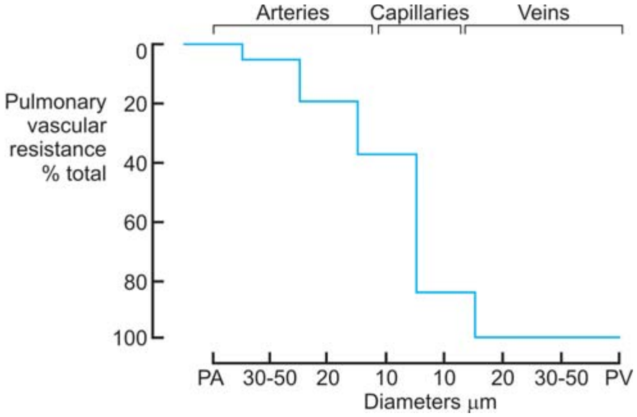


Fig. 7.21: Distribution of vascular resistance in an isolated perfused dog lung: Around half of the total resistance is distributed along the microvessels, a major difference compared to systemic microcirculation where the resistance is located at the arteriolar level.
From Bhattacharya et al[21]

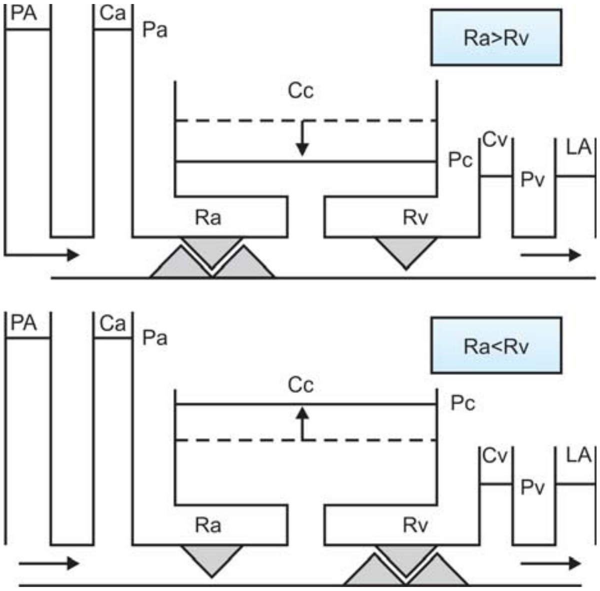


Fig. 7.22: Filtration pressure in the lungs depends on the longitudinal distribution of resistance along the microvessels. When most of the resistance is located prior to the filtration site, microvascular filtration pressure and filtration are low in the filtration compartment (Ra > Rv). When most of the resistance is located past the filtration site, microvascular filtration pressure and filtration are high (Ra < Rv). Pulmonary arterial, arteriolar, pulmonary venous and left atrial pressure are identical in both situations. Wedge capillary pressure may therefore be misleading when taken as an index of true filtration pressure during permeability edema.
AP: pulmonary artery; OG: left atrium; Ca: capillary arterial compartment; Cv: capillary venous compartment; Cc: pulmonary capillary compartment (filtration site).
From Grimbert et al[22]

Filtration through the Endothelial Barrier

The role of the microvascular wall in liquid transport is not passive. Active mechanisms capable of modifying barrier properties have been identified.[23] Some tentative signaling mechanisms that are involved in the regulation of endothelial permeability are shown in Figure 7.23. Solutes can traverse the endothelium via the transcellular and paracellular pathways. The transcellular pathway or transcytosis is a vesicle-mediated transport of plasma proteins across the endothelium by caveolar mechanisms. The bulk of filtration of fluid and solutes occurs across a

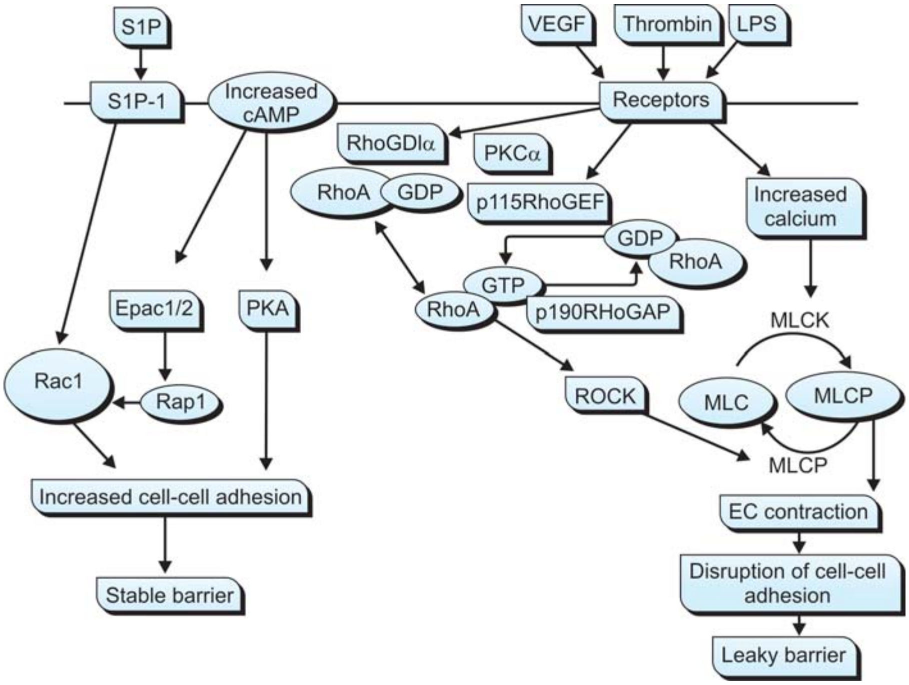


Fig. 7.23: Tentative representation of some of the signaling mechanisms that are involved in the regulation of endothelial permeability: All mechanisms may not apply to the lung microvascular endothelium as phenotypic and genetic variations are known between endothelial cell types, depending on organs and locations in organs.
This representation makes the assumption that a common final pathway exists for various types of receptors (VEGF, Thrombin, LPS). See text for details.
From Vandenbroucke et al[23]

small fraction of the total microvascular surface area formed by the minute intercellular spaces between cells.[24] This space primarily allows the convective and diffusive transport of molecules of less than 3 nm of diameter while restricting, but not totally restricting the passage of larger molecules. The permeability of the interendothelial junction depends on the adhesive properties of the structural proteins of the tight junctions and of the adhesive junctions. These junctions are not passive and can be modified by the endothelial cells in response to specific stimuli acting on them, including sheer stress and pressure changes. The integrity of the junctions is controlled by the actin cytoskeleton through actin remodelling.

Junctional permeability is modulated by inflammatory mediators, for example, thrombin, TNFα and LPS (endotoxin). Mediators act through their respective endothelial surface receptors. Receptor activation increases cytosolic Ca^{++} and activates myosin light chain kinase (MCLK), GTPases RhoA, Racl and Cdc 42. Racl and Cdc 42 reinforce the junctional assemblies while the Ca++ activation of MCLK and RhoA disrupt the junctions, increasing permeability. Other agents, such as sphingosine-1-phosphate and cAMP play a role of barrier stabilizing agents, capable of reducing increased endothelial permeability. The role on permeability of LPS, an endotoxin present on the outer membrane of gram-negative bacteria and a major factor of acute lung injury, exemplify the relationship between the endothelial cell receptors and increased permeability. LPS binds to Toll-like receptor 4, resulting in the translocation of NF-κB to the cell nucleus initiating transcription of proinflammatory mediators, which increase permeability. LPS also promote the expression of an Intercellular Adhesion Molecule (ICAM-1). Cross-linking of ICAM-1 activates RhoA and actin stress fiber formation; ICAM-1 also up regulates RhoA expression, resulting in a positive feedback mechanism on permeability.

Indeed, many other mechanisms may initiate the endothelial cell response such as activation of platelets, the coagulation cascade, neutrophil or macrophage activation, and others. The activation of the inflammatory cascades will be related to the initial cause of disease and takes time to proceed. This explains why the onset of permeability edema is a slow process (hours and days) compared to the onset of pressure edema that can take only minutes to develop. It is important to note that permeability edema may be secondary to the inflammation, secondary to an initial mechanical or chemical aggression, such as thrombi or inhalation of toxic material, which per se does not increase permeability.

Resolution of Alveolar Edema

The first evidence that active ion transport is involved in fluid clearance from the air space was obtained in ventilated, anesthetized sheep. Fluid clearance of an instilled isomolar salt and water solution was shown to occur, although the alveolar protein concentration was rising well above plasma level. It was also shown that reabsorption of protein occurred very slowly and much later than that of fluid by independent mechanisms. Further evidence comes from the inhibition of alveolar fluid clearance in various species, including man by ouabaïn (90%) and amiloride (70%).

The resolution of alveolar edema depends on the active transport of sodium and chloride across the epithelial barrier.[25] Regulation occurs via alveolar epithelial type I and II cells and distal airway epithelia. The differences in hydrostatic and protein osmotic pressures implicated in the Starling equation play no direct role in the removal of excess fluid or proteins. The vectorial transport of sodium, chloride and water is the central mechanism by which alveolar fluid can be cleared at birth, as well as in the mature lung during pulmonary edema. Active sodium transport drives osmotic water transport. Inhibition of sodium transport by appropriate drugs reduces significantly, water transport from the airspace in several species, including man. Isolated epithelial cells have been shown to be capable of actively transporting ions *in vitro*, as well as *in vivo*. Reabsorption can occur at all levels of the distal airspaces; nonciliated cuboidal cells and Clara cells are involved in the mechanisms just as alveolar epithelial cells. They have all been shown to contain the required transporters.

Transport by the alveolar type II cells have been extensively studied because these cells constitute 95% of the alveolar epithelium membrane and because they are fit for *in vitro* studies. Active sodium uptake occurs on the apical cell surface through amiloride-sensitive and amiloride-insensitive channels. Na, K-ATPase pumps sodium actively from the cell basolateral surface to the interstitium. An Epithelial Sodium Channel (ENaC) has been cloned and characterized.[24] Concerning type I cell, studies conducted on fresh cells have identified the expression and presence of $\alpha 1$ and $\alpha 2$ subunits of Na, K ATPase on the basolateral surface of the cell, as well as expression of all subunits of ENaC. The $\alpha 1$ subunit of type I cells has been linked to alveolar fluid reabsorption.[22] Na uptake is sensitive to amiloride blockage. Furthermore, highly selective cation channels have been identified by patch clamp and may participate in fluid clearance.

Water passively follows the sodium-induced fluid movement. The movement of liquid is generally thought to follow intercellular pathways. The identification of specialized water transporting proteins called aquaporins in the lungs has led to the hypothesis that part of the water movement might occur via transcellular channels. The predominant lung aquaporin (aquaporin 5), is expressed in the apical surface of alveolar type I cells, which have one of the highest permeability coefficient for water, leading to the hypothesis that some movement of fluid occurs across type I cells. However, experiments show that the deletion of aquaporin does not seem to affect alveolar liquid clearance.

Endogenous release of catecholamine stimulates the reabsorption of fetal lung fluid from the airspaces at birth. Type I and type II cells both express and present β_2 receptors. Stimulation of these receptors in human lungs by terbutamol, salmeterol or epinephrine increases fluid clearance. This increase can be prevented by nonspecific β_2 antagonists, for example, by propranolol or amiloride. This demonstrates a link between increased filtration, amiloride sensitive sodium transport, and catecholamine dependent regulation of fluid clearance.

Chloride also plays a role in the upregulation of fluid clearance across the distal lung epithelium by mediating cAMP apical uptake of sodium. Cystic fibrosis transmembrane conductance regulator (CFTR) is essential for cAMP mediated upregulation of isomolar fluid clearance from both the distal airways and the alveoli so that CFTR might be the chloride channel involved in the process. Chloride channels are β_2 sensitive.

Various catecholamine-independent mechanisms have also been identified lately, including proinflammatory molecules, such as TNF and leukotrienes D4, some growth and hormonal factors acting by transcriptional or post-translational mechanisms.

CLINICAL IMPLICATIONS

Resolution of pulmonary pressure edema depends on the clearance of fluid from the alveoli, a process that requires a functional alveolar epithelium. The alveolar and distal airway epithelia are remarkably resistant to edema[17] compared to adjacent lung endothelium so that the alveolar barrier may remain functionally intact after endothelial injury. This might explain why in mild to moderate lung injury, the transport of water and sodium may remain normal or even be upregulated by stress hormones.

The rate of alveoli clearance of water has been measured during major pressure (hemodynamic) edema in several species, in ex-vivo human lungs and in patients. It was found to vary from 3% per hour to a maximum of 14% per hour and found to be generally around maximal level providing alveolar epithelium was intact. Clearance was increased in 75% of the patients. In acute lung injury (permeability edema), alveolar clearance is impaired in 56% of the patients and there is a convincing relationship between the clearance rate, extent of epithelial injury and patient's survival. This has encouraged strategies to increase alveolar fluid clearance, essentially by means of β_2-agonist therapy, but also by vasoactive agents (dobutamine, dopamine) and growth factors. However, these strategies can be meaningful only when enough of the alveolar epithelium has remained functional.[26]

MEASUREMENT OF EXTRAVASCULAR LUNG WATER

Quantification of extravascular fluid accumulation may appear a significant tool to analyze the exchange of fluids within the lung. As always in compartmental analysis, the significant approach would be to quantify the net flux of fluid and solutes across the barrier, a technical measurement that is very difficult to obtain, especially in a clinical setting. The measurement of extravascular lung water (EVLW) has been attempted by a variety of single pass indicator, thermal and osmotic dilution techniques based on compartmental models of water and solutes exchange or on washout procedures. All these methods have uncertain specificity and sensitivity and the normal range of EVLW has never been properly established. Major limitations are linked to the change in the distribution of tracers in the lung in function of the distribution of perfusion, perfusion pressure, perfusion of extracorporeal fluids, and repartition of diseased area, all factors contributing to variations of the exchange surface area and volumes of diffusion from one time to the other. Furthermore, only tracer accessible zones can be measured, therefore excluding poorly perfused or ventilated areas, resulting in underestimation. In fact, only radiological imaging methods can detect and localize in a functionally and clinically significant manner the extent and localization of extravascular fluid accumulation although it is not quantitative.[27]

CONCLUSION

Transport of fluid and solutes through the alveolar wall is a complex process requiring the active participation of the endothelial and epithelial cells. Pressure and permeability edema have different characteristics in the terms of time course and cell activation. They may occur simultaneously or successively as in gram-negative infections. Permeability edema provokes much higher levels of filtration, compared to pressure edema, and is extremely sensitive to modest changes in filtration pressure. Filtration pressure tends to be undervalued for the lack of adequate measurement technique. Treatment of pressure edema focuses successfully on the mechanical change in pressure, whereas permeability edema is dependent on our capacity to counteract the inflammatory mechanisms, this with limited success so far because of their complexity.

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8

Tissue Oxygenation

Puneet Malhotra, SK Jindal

INTRODUCTION

The final link in the transport of oxygen from the atmosphere to the cells is known as internal respiration or tissue oxygenation, which involves the exchange of gases between capillaries and tissue cells (Fig. 8.1).

More than 90% of the body's oxygen consumption is utilized by a single enzyme, cytochrome oxidase during the process of oxidative phosphorylation, which generates adenosine triphosphate (ATP). This is the most efficient means of producing ATP, since a total of 38 molecules of ATP are generated per molecule of glucose. Aerobic cellular respiration depends on the efficient supply of oxygen to the mitochondria, which is a function of the coordinated interaction between the respiratory and circulatory systems. When oxygen supply is inadequate, anaerobic metabolism sets in and generates only 2 molecules of ATP per molecule of glucose (Fig. 8.2). In addition H^+ ions are formed, which can lead to a systemic metabolic acidosis. Tissue oxygenation is often impaired in critically ill patients, who have poor cardiopulmonary reserve and optimizing oxygen delivery to meet oxygen demand, has the potential to improve outcomes in these patients.

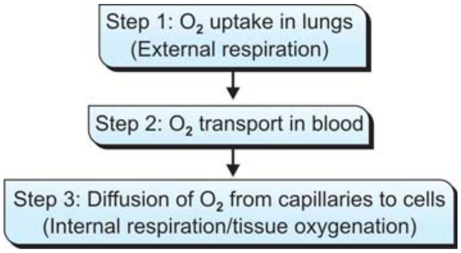
Step 1: O_2 uptake in lungs
(External respiration)
Step 2: O_2 transport in blood
Step 3: Diffusion of O_2 from capillaries to cells
(Internal respiration/tissue oxygenation)

Fig. 8.1: The delivery of oxygen to tissue for cellular metabolism is a three-step process

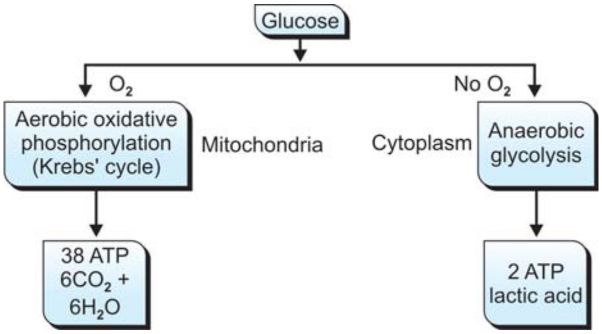
Glucose
O_2
No O_2
Aerobic oxidative phosphorylation (Krebs' cycle)
Mitochondria
Cytoplasm
Anaerobic glycolysis
38 ATP
$6CO_2$ +
$6H_2O$
2 ATP
lactic acid

Fig. 8.2: Aerobic metabolism via oxidative phosphorylation in the mitochondria produces 19 times more energy (ATP) than anaerobic glycolysis

The main determinant of tissue oxygenation is a balance between oxygen delivery (DO_2) and oxygen consumption (VO_2). An imbalance between the two results in oxygen debt.

OXYGEN DELIVERY (DO_2)

Calculation of DO_2

Tissue oxygen delivery depends on two factors: i) arterial O_2 content (CaO_2), and ii) cardiac output (Q) (Fig. 8.3).

$$DO_2 = Q \times CaO_2$$

The normal range for DO_2 is 520–570 ml/min/m^2 and under normal physiological conditions, DO_2 is considerably in the excess of the oxygen consumption

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*Sources Jindal SK. Oxygen Therapy. Chapter 5, SK Jindal, Ritesh Agarwal (Eds.). New Delhi: Jaypee Brothers Medical Publishers; 2008. pp. 71-85.

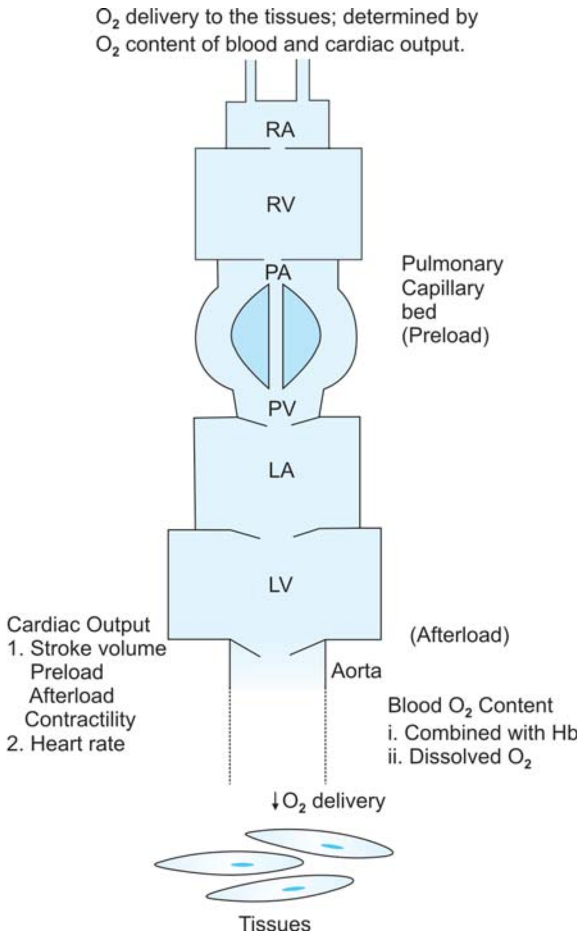

Fig. 8.3: O_2 delivery to the tissues; determined by O_2 content of blood and cardiac output

(110–160 ml/min/m^2). This "spare capacity" enables the body to cope with a fall in oxygen delivery without initially compromising aerobic respiration.

Factors Influencing DO_2

Arterial O_2 Content (CaO_2)

It is the total amount of O_2 present in blood, i.e. combined with hemoglobin (Hb) and dissolved in plasma.

$$CaO_2 = (1.34 \times Hb \times SaO_2) + (0.0031 \times PaO_2)$$

The contribution of Hb is described by the first part of the equation. This relationship states that each gram of Hb will bind 1.34 ml of O_2, when it is fully saturated with oxygen. The SaO_2 is expressed as a fraction, not a percentage (i.e. 1.0 instead of 100%). Therefore, at a Hb level of 15 g/dL and an SaO_2 of 98%, the oxygen carried by Hb will be:

$$1.34 \times 15 \times 0.98 = 19.7 \text{ ml/100 ml}$$

From the second part of the equation one can infer that, at a PaO_2 of 100 mm Hg, the expected concentration of dissolved O_2 in blood is

$$0.0031 \times 100 = 0.3 \text{ ml/100 ml}$$

Therefore, the total concentration of O_2 in arterial blood is 19.7 + 0.3 = 20 ml/100 ml. Thus, it is clear that CaO_2 primarily depends on Hb and SaO_2 and to a lesser extent on PaO_2.

Cardiac Output

In critically ill patients, cardiac output can be measured by invasive, as well as noninvasive methods:

i. *Invasive methods:* These include direct and indirect Fick methods, which require pulmonary artery catheterization and intubation respectively.
ii. *Noninvasive methods:* These include Electrical Impedance Cardiography (EIC) and Transesophageal Echocardiography (TEE).

DO_2 is directly related to changes in cardiac output, which is the product of heart rate and stroke volume. Any alteration in either of these two parameters alters the cardiac output. Stroke volume, the amount of blood ejected per beat is affected by the following factors:

a. *Preload:* It is the load imposed on a muscle before the onset of contraction and is synonymous with the initial length (or stretch) of cardiac fibers. An increase in preload, augments muscle length and leads to a more forceful cardiac contraction (Frank-Starling phenomenon). In fact, in the normal heart, the diastolic volume/preload is the principal force that governs the strength of ventricular contraction. This emphasizes the value of avoiding hypovolemia and correcting volume deficits promptly when they exist. The relationship between preload and cardiac output is however not linear and is also influenced by changes in ventricular compliance and geometry. Since ventricular end-diastolic volume is not easily measured at the bedside; End-Diastolic Pressure (EDP) and Central Venous Pressure (CVP) are more commonly used as reflections of preload in clinical practice.
b. *Afterload:* It is the sum of all forces opposing ventricular ejection. It is influenced by aortic and pulmonary arterial pressures, systemic and pulmonary vascular resistance, and compliance of ventricular muscle. As the determination of these forces is complex, systolic left ventricular pressure is usually used as a reasonable measure of afterload. In addition, since afterload is a transmural force, it is influenced by the pleural

pressures at the surface of the heart. Positive pleural pressures can promote ventricular emptying by facilitating the inward displacement of the ventricular wall during systole and this is one of the mechanisms by which noninvasive positive pressure ventilation is beneficial in cardiogenic pulmonary edema.

c. *Contractility:* It refers to the intrinsic contractile property of cardiac myocytes and is influenced by catecholamine levels, as well as extracellular calcium concentration. Cardiac contractility is measured indirectly by impedance cardiography and Doppler echocardiography.

Steps Involved in DO_2

The final link in the delivery of O_2 to cells, involves two steps: (i) cellular O_2 supply and (ii) cellular O_2 utilization.

i. Cellular O_2 supply: Although all arteries in the body carry virtually identical concentrations of O_2, the distribution of O_2 is not equal to all cells. This is because of the following factors:

a. *Differences in regional blood flow:* The gatekeeper of blood supply to a capillary network is the local arteriole. Arterioles may dilate or constrict in response to various local and central regulatory factors. Local factors causing dilatation include hypoxia, increased CO_2, increased temperature and decreased pH. The release of catecholamines is a central mechanism that attempts to preferentially distribute blood to vital organs when DO_2 is compromised. When the body is confronted with a declining DO_2, both central and local mechanisms are stimulated. In the short term, central effects predominate while if the O_2 shortage persists, local effects override and generalized vasodilatation occurs.

b. *Differences in capillary architecture:* Some cells are simply closer to capillaries than others. Because movement of O_2 depends on pressure gradients, the cells farthest away from capillaries are most vulnerable to hypoxia. In addition, many capillaries are normally closed and open only when perfusion to that particular region increases. For example, an actively contracting muscle may have 10 times more open capillaries than a resting muscle.

ii. Cellular O_2 utilization: Metabolic utilization of O_2 in cells occurs by the oxidation of pyruvic acid in the Krebs cycle (Fig. 8.2). This series of reactions takes place in mitochondria and results in the production of 38 molecules of ATP. The availability of O_2 is crucial in the production of ATP from Adenosine Diphosphate (ADP) in the Krebs' cycle. The actual process of ATP formation is called oxidative phosphorylation as phosphate is added to ADP by using the energy from oxidation. In the absence of O_2, metabolism is less efficient and only 2 molecules of ATP are generated by the metabolism of glucose (anaerobic glycolysis). Furthermore, anaerobic metabolism results in the production of lactic acid, which may lead to systemic metabolic acidosis.

OXYGEN CONSUMPTION (VO_2)

Calculation of VO_2

Oxygen consumption refers to the rate of uptake of O_2 by tissues from the microcirculation. It is a product of the cardiac output and the difference in oxygen content between arterial and venous blood.

$$VO_2 = Q \times (CaO_2\text{-}CvO_2)$$
$$VO_2 = Q \times 1.34 \times Hb \times (SaO_2\text{-}SvO_2)$$

The normal range for VO_2 is 110–160 ml/min/m^2 and it can be measured in three ways:

1. Using Fick's equation given above, which requires the placement of a pulmonary artery catheter.
2. By measurement of inspired and expired minute ventilation (Vi and Ve) and of fractional concentrations of O_2 (FiO_2 and FeO_2) in the two samples. This is a noninvasive method, but is relatively unreliable in mechanically ventilated patients on high FiO_2.

$$VO_2 = (Vi \times FiO_2) - (Ve \times FeO_2)$$

VO_2 can also be measured directly with the help of a rebreathing spirometer system filled with oxygen; the expired CO_2 is absorbed from the system and any change in the volume of gas in the spirometer reflects the VO_2.

Calculated Versus Measured VO_2

The VO_2 is usually derived from Fick's equation and not directly measured. The derivation is based on four measured variables: Cardiac output (Q), hemoglobin concentration (Hb), arterial O_2 saturation (SaO_2) and mixed venous O_2 saturation (SvO_2). Each of these measurements varies and their summed contribution can lead to considerable variability in the final calculated VO_2. Therefore, to be considered a physiologically significant change, the calculated VO_2 should change by atleast 15%.

O_2 Extraction Ratio (O_2ER)

It is the ratio of oxygen uptake to oxygen delivery (VO_2/DO_2), and reflects the fraction of O_2 delivered to the microcirculation that is taken up by the tissues. The

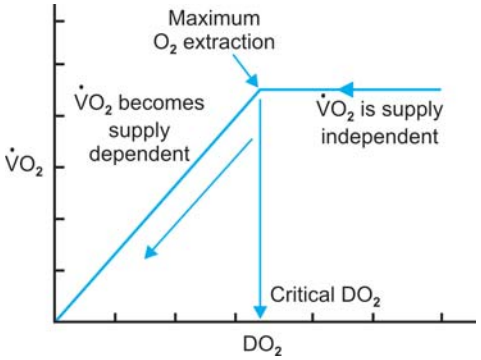

Fig. 8.4: Graph describing the relationship between delivery (DO_2) and O_2 uptake ($\dot{V}O_2$). As DO_2 decreases below normal, O_2 extraction increases proportionally to keep $\dot{V}O_2$ constant and therefore, "supply independent". When DO_2 falls below a critical level, $\dot{V}O_2$ becomes "supply dependent"

O_2ER varies between different organs. For example, the brain has an O_2ER of 34% while exercising muscle can remove all O_2 from its microcirculation and thus have an O_2ER approaching 100%. Overall, the normal O_2ER is 20 to 30%. Thus, only a small fraction of the available O_2 delivered to the capillaries is taken up into the tissues. Oxygen extraction is adjustable, and in conditions where O_2 delivery is impaired, the O_2ER can increase up to 50-60%.

The DO_2-$\dot{V}O_2$ Curve

The relationship between O_2 delivery and O_2 uptake is described by the curve in Figure 8.4. As DO_2 decreases below normal, the O_2ER increases proportionally to keep $\dot{V}O_2$ constant. When O_2ER reaches its maximum level (50 to 60%), further decreases in DO_2 result in proportional decreases in $\dot{V}O_2$. Since under normal physiological conditions, DO_2 is considerably in excess of the $\dot{V}O_2$, tissue oxygenation to a large extent is supply-independent. However, when DO_2 falls below a certain critical level, $\dot{V}O_2$ becomes supply dependent and this condition, in which cellular metabolism is limited by the supply of O_2 is called dysoxia. This *critical O_2 delivery point* (critical DO_2) varies between 150–1000 ml/min/m^2 in critically ill patients, though on an average it is approximately 300 ml/min/m^2. When DO_2 falls below this level, tissue hypoxia ensues, blood lactate increases and prognosis becomes poor. Thus, maintenance of DO_2 in excess of the critical delivery point is crucial in the management of critically ill patients. This is particularly true when Positive End-Expiratory Pressure (PEEP) is being used because PEEP may be associated with a fall in DO_2 despite improvements in PaO_2 because of its effect on cardiac output.

Factors Influencing $\dot{V}O_2$

Causes of Decreased $\dot{V}O_2$

1. *Decreased blood supply to tissues:* Shock (Cardiogenic/hypovolemic).
2. *Cytotoxicity:* An intrinsic defect in O_2 utilization at the cellular level is seen in carbon monoxide and cyanide poisoning, as well as in sepsis.
3. *Increased O_2 demand:* This is seen in most critically ill patients with increased metabolic rates, e.g. acute pancreatitis, burns, etc.

It is noteworthy that tissue hypoxia in sepsis involves all the three mechanisms mentioned above: i) decreased blood supply as a result of redistribution of blood flow due to pathologic capillary dilatation and arteriovenous shunting, as well as microvascular occlusion due to platelet and fibrin microthrombi, ii) disruption of cellular metabolism by cytokines and free radicals, and iii) increased O_2 demand.

Causes of Increased $\dot{V}O_2$

Whenever stress or tissue injury occurs, there is an increase in metabolic rate and $\dot{V}O_2$. In normal subjects exercise increases $\dot{V}O_2$, almost simultaneously with the onset of work. Most of this increase is accounted for by increase in cardiac output. A relative hemoconcentration and therefore increased O_2 content may also occur with the high levels of exercise. The $\dot{V}O_2$ may increase 10 to 15 folds during exercise. In addition, O_2 extraction (see above) may also increase to as much as 80% of $\dot{V}O_2$ in order to meet the additional O_2 requirement. This is made possible by capillary dilatation and recruitment in exercising muscles.

Causes of increased $\dot{V}O_2$ in sick patients include fever, tachypnea, shivering and seizures. In a very ill patient, even innocuous activities, such as chest physiotherapy, getting up or turning in bed and tracheal suctioning can increase $\dot{V}O_2$ and tilt the already precarious O_2 balance.

Oxygen Debt ($\dot{V}O_2$ Deficit)

Oxygen debt or $\dot{V}O_2$ deficit is the difference between the metabolic demand for O_2 and the actual $\dot{V}O_2$. As demand increases, $\dot{V}O_2$ must increase to preserve aerobic metabolism. This is met with by increasing DO_2 either by physiological compensation, e.g. an increase in cardiac output or O_2ER or by therapeutic interventions such as intravenous fluids or inotropes. If this increase in DO_2 is delayed, O_2 debt continues to grow and a stage is reached from where recovery is not possible. Studies of the O_2 debt after resuscitation from hemorrhagic shock and in postoperative patients, show a direct relationship between the magnitude of O_2 debt and the risk of multi organ failure and death. This indicates that the early correction of VO_2 deficits is warranted to limit the severity of tissue ischemia.

ASSESSMENT OF TISSUE OXYGENATION

Unlike hypoxemia, which denotes a low PaO_2 and has standard normal and abnormal values, there are no normal values for tissue PO_2 and it cannot be routinely measured at the bedside. Tissue hypoxia is defined as abnormal O_2 utilization by cells and should be distinguished from other terms, such as hypoxic, anemic, histotoxic and stagnant hypoxia, which can lead to but are not synonymous with tissue hypoxia. There are three ways to detect tissue hypoxia.[4]

Clinical Assessment

Clinical examination should be the first step in assessing tissue oxygenation. A number of well-known signs (mental obtundation, oliguria, abnormal vital signs, delayed capillary refill) often indicate specific organ dysfunction as a sequel of tissue hypoxia. However, clinical signs are often insensitive as they occur late during the course of tissue hypoxia. Direct or indirect measurements of local tissue oxygenation of an organ suspected to suffer from hypoxia will facilitate the assessment. Local tissue oxygen probes have been used in critical care areas in some instances (e.g. brain).

Physiological Parameters

Mixed Venous O_2 Saturation (SvO_2)

Mixed venous blood represents blood returning from all the venous beds of the body, "mixed" together in the right ventricle. It is obtained from the distal end of the pulmonary artery with the help of a specialized pulmonary artery catheter, the tip of which emits infrared light and records light reflected back from hemoglobin in circulating erythrocytes. This technique is called *reflectance spectrophotometry* (whereas pulse oximeters use *transmission spectrophotometry*). SvO_2 can also be measured intermittently by withdrawing blood from the catheter. In the proximal part of the pulmonary artery, blood from the two venae cavae and coronary sinus is not fully blended and therefore does not represent total body venous gas values. SvO_2 is a marker of the balance between whole body oxygen delivery and O_2 demand, and is normally between 65 to 75%, i.e. O_2 demand is usually about 25 to 35% that of O_2 delivery.

Causes of decreased SvO_2

a. Decrease in DO_2: This may occur due to hypovolemia, decreased cardiac output, low Hb, low PaO_2 and SaO_2.
b. Increase in O_2 demand: Critical illness, sepsis, thyrotoxicosis, etc.

Causes of increased SvO_2

a. Increased DO_2: Increased cardiac output (e.g. exercise, use of ionotropes), increased Hb (hypertransfusion).
b. Decrease in O_2 demand: Deep sedation and paralysis in ventilated patients.
c. Decreased tissue O_2 utilization: Cyanide and CO poisoning, sepsis.
d. Left-to-right shunts: These can usually be diagnosed by an abnormal "step-up" of SvO_2 at the level of the defect as the pulmonary artery catheter is passed into the right atrium or ventricle.

A limitation of SvO_2 as a parameter for assessing tissue oxygenation is that normal or increased values do not always mean that tissue oxygenation is adequate. For example, in sepsis and CO poisoning, impaired tissue O_2 utilization results in a normal or high SvO_2. In addition, pathologic vasodilatation and increased cardiac output in sepsis also tend to increase SvO_2 even though tissue hypoxia is ongoing.

Dual Oximetry

By simultaneously measuring SaO_2 by pulse oximetry, one can get a continuous measurement of whole body O_2 extraction, i.e. $SaO_2 - SvO_2$. This method is known as dual oximetry and its normal value is 20 to 30%.

DO_2/VO_2 Measurements

The measurement of changes in VO_2 in response to changes in DO_2 has been suggested as a sensitive method of determining whether tissue hypoxia exists. However it entails multiple measurements at baseline and after various interventions carried out to increase DO_2 (such as the administration of fluids and inotropes) and is therefore impractical.

Biochemical Parameters

Blood Lactate Level

Blood lactate levels increase when tissue hypoperfusion results in anaerobic metabolism. This is known as Type A lactic acidosis and is different from Type B or non-hypoxic causes of lactic acidosis, e.g. delayed clearance of lactate due to liver disease, thiamine deficiency (blocks pyruvate metabolism) and metabolic alkalosis (stimulates glycolysis). A blood lactate value higher than 4 mmol/L is generally taken as abnormal. It is easy to measure and can be followed sequentially to assess prognosis, as well as response to therapy. Recent studies indicate that blood lactate concentrations are a better prognostic indicator than oxygen-derived physiological variables.

Gastric Tonometry

Physiological variables of oxygen transport detailed above and lactate are the indices of global tissue oxygenation and cannot identify oxygen deficits in individual organs. This leads to the development of gastric tonometry to measure regional perfusion in the gut that employs a balloon in the stomach to measure intramucosal pH (pHi). Despite its complexity, tonometry is a reasonably good prognostic indicator in critically ill patients.

Sublingual Capnography

Recently capnography in the sublingual area, a technique that is less invasive and easier to use has been shown to yield tissue PCO_2 measurements that correlate with those obtained by gastric tonometry.

Nuclear Magnetic Resonance Spectrometry

This laboratory technique, not applicable at the bedside, can measure biochemical processes at the cellular level, e.g. levels of ATP, NADH and cytochrome oxidase. Radionuclide imaging, such as Positron Emission Tomography (PET) scanning has emerged as an important tool to characterize tumor oxygenation to optimize and individualize therapy for cancers.

Most of the different parameters of *in vivo* oxygen measurements measure different things and differ in their sensitivity, accuracy and repeatability. It has been proposed that a proper model that relates the various measurements to each other can serve as a powerful tool to assess tissue oxygenation. Unfortunately, such a functional model is not available as yet (Table 8.1).

RECENT DEVELOPMENTS

Hemodynamic monitoring, which relies on physical signs, such as pulse rate, blood pressure, urine output and mentation is inadequate for detecting tissue hypoxia. It has recently been shown that the measurement of central venous oxygen saturation ($Sc\bar{v}O_2$), and its manipulation in patients with severe sepsis has improved survival. In a trial examining $Sc\bar{v}O2$ in severe sepsis, patients with $Sc\bar{v}O2$ levels higher than 70% had lower serum lactate levels, higher pH and base deficit and improved mortality (26% vs 42%). Also, $Sc\bar{v}O_2$ has been shown to correlate well with $S\bar{v}O_2$ measurements and both serum lactate and $Sc\bar{v}O2$ appear to be independent predictors of poor outcome. The advantage of $Sc\bar{v}O_2$ lies in the fact that it can be easily measured by the insertion of a catheter in the internal jugular or subclavian vein, whereas the measurement of $S\bar{v}O_2$ requires the placement of a pulmonary arterial catheter.

TABLE 8.1: Normal values and equations of tissue oxygenation parameters

Parameter	*Equation*	*Normal range*
Arterial O_2 content (CaO_2)	CaO_2 = (1.34 x Hb x SaO_2) + (0.0031 x PaO_2)	20 ml/dL
Cardiac output (Q)	Q = hr x sv	4-8 L/min
Cardiac index (CI)	CI = Q/ BSA	2.4-4.0 L/min/m^2
Oxygen delivery (DO_2)	Q x 1.34 x Hb x SaO_2	900-1000ml/min
Oxygen delivery index (DO_2 index)	DO_2/ BSA	520-570 ml/min/m^2
Oxygen uptake ($\dot{V}O_2$)	Q x 1.34 x Hb x (SaO_2-SvO_2)	180-280 ml/min/m^2
Oxygen uptake index (VO_2 index)	$\dot{V}O_2$/ BSA	110-160 ml/min/m^2
Oxygen extraction ratio (O_2ER)	(SaO_2 - SvO_2/Sao_2) x 100	20-30%

BSA: body surface area; Hb: Hemoglobin; hr: heart rate; PaO_2: partial pressure of O_2 in arterial blood; SaO_2: arterial O_2 saturation, SvO_2: mixed venous O_2 saturation; sv: stroke volume.

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9

Respiratory Physiology in Specific Physiological States

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INTRODUCTION

The respiratory system performs the essential function of gas exchange and plays its assigned role in the maintenance of the acid-base homeostasis to perfection with its basic mechanisms of the control of breathing, lung mechanics, gas diffusion and transport, and regulation of pulmonary circulation in a coordinated and integrated manner under a wide range of environmental conditions and physiological states of the body. Together with the cardiovascular system and aided by an appropriate response from other systems, the human body can adapt to these variations from the normal state without any adverse consequences. These adaptations may sometimes resemble changes in pathological conditions and hence the knowledge of physiological changes in these specific states is necessary to avoid an erroneous interpretation of symptoms and signs. However, adaptations have a limit in the time course over which they develop and in the range of deviations from the normal resting state at the sea level. Due to these limits, the adaptations may fail and manifest as pathological conditions. The following sections are devoted to changes in respiratory physiology and allied systems in specific physiological states such as exercise, pregnancy, high altitude and deep diving.

EXERCISE[1-14]

While exercising, the muscles are required to perform greater work and thus require more energy. This is provided by increased aerobic metabolism and thus increased oxygen consumption. The oxygen consumption in the muscles increases with the rising intensity of exercise. An integrated response of the cardiovascular and respiratory systems is required to meet the increased demand for oxygen by the muscles and to eliminate the excessive amount of CO_2. This response requires an increase in the heart rate, cardiac output, regional blood flow in the exercising muscles, oxygen extraction by the tissues and ventilation to washout extra CO_2. It is coordinated and related to the workload and meets the requirements of the exercising muscles. The acute respiratory and cardiovascular responses to exercise are complimented by changes and responses in the muscles, as well as neurological and endocrinal systems in an effort to survive through a wide range of severity of exercise without adverse consequences. The physiological changes occurring in the cardiorespiratory systems on exercise are summarized in Table 9.1.

Respiratory System

Increased extraction of oxygen in the exercising tissues results in a fall in the mixed venous PO_2 of blood reaching the right side of the heart, from a normal of 40 mm Hg to 25 mm Hg or even less. This increases the alveolo-capillary gradient, even though the alveolar PO_2 is not changed. As a result, the amount of oxygen entering the blood in the lungs is increased. The increased alveolo-capillary gradient for oxygen is aided by an increase in the diffusion capacity that may be up to threefold on exercise. This results from the recruitment of underperfused pulmonary capillary beds due to increased blood flow and pulmonary artery pressures, thus providing a greater surface area across which oxygen can diffuse into

TABLE 9.1: Physiological changes in the cardiorespiratory systems on exercise

- Increased rate of oxygen consumption
- Increased CO_2 excretion
- Increased alveolocapillary gradient for oxygen
- Increased diffusion capacity
- Increased blood flow and pulmonary artery pressure
- Recruitment of underperfused pulmonary capillary beds
- Increased ventilation
- Decreased airway resistance
- Decreased ratio of Dead Space (V_D) to tidal volume (V_T)
- Rightward shift of the oxygen-hemoglobin dissociation curve
- Increased extraction of oxygen in the muscles
- Dilatation and recruitment of the capillary bed of the muscles
- Increased blood flow to muscles
- Increased arterial blood pressure
- Increased stroke volume
- Increased heart rate
- Increased venous return
- Increased cardiac output

the blood. The pulmonary blood flow increases from a normal of 5.5 L/min to as much as 20–35 L/min.

Those athletes who require greater amount of oxygen per minute have higher diffusion capacities. It is not clear how much of this increase is genetic and how much is acquired through training. Normally, there is a mild degree of ventilation-perfusion inequality due to relative underperfusion in the upper zones of the lung. During moderate exercise, this is reduced because of the more uniform distribution of blood flow in upper zones, providing another adaptation to facilitate oxygen uptake. On the other hand, in athletes performing strenuous exercise, a mild degree of interstitial pulmonary edema related to increased pulmonary artery pressures may develop leading to mild ventilation-perfusion inequality.

The total amount of oxygen entering the blood increases from 250 ml/min at rest to values as high as 3000 to 4000 ml/min. In a marathon runner, it may exceed 5000 ml/min, a 20-fold increase. The rate of oxygen usage under maximal aerobic metabolism is written as Vo_2 max. The Vo_2 max of a marathoner may thus be 40 to 50% greater than that of an untrained person. Training does increase the Vo_2 max, but only to a limited extent of about 10% over two to three months. However, longer periods of training may increase the Vo_2 max further, and it is also probably genetically determined. The oxygen saturation, PaO_2 and the oxygen content of the blood (CaO_2) leaving the lungs remain the same as at rest. This is dictated by the oxygen hemoglobin dissociation curve, as well as the hemoglobin levels. The CO_2 excretion also increases from 200 ml/min to as much as 8000 ml/min.

Oxygen consumption and total pulmonary ventilation at different levels of exercise increase with a linear relationship depending on the intensity of the exercise up to a limit. Above this limit, the aerobic metabolism in the muscles is unable to synthesize energy stores at a pace matching their utilization, and thus anaerobic metabolism sets in (anaerobic threshold). The oxygen consumption levels off, an oxygen debt is incurred and the blood lactate level rises.

Ventilation increases abruptly and sharply with the onset of exercise followed by a further, more gradual increase. The initial rise in ventilation occurs primarily because of an increase in the tidal volume. Though the limit for tidal volume is the vital capacity, it plateaus off at around 50 to 60% of the vital capacity. The tidal volume encroaches into the Inspiratory Reserve Volume (IRV) and, to a smaller extent, into the Expiratory Reserve Volume (ERV). During light and moderate exercise, the contribution of an increase in the respiratory rate to minute ventilation is minimal and gradual. Ventilation decreases abruptly when exercise ceases, and is followed after a brief pause by a more gradual decline to pre-exercise values.

The increase in ventilation is proportional to the increase in oxygen consumption. It is likely that multiple mechanisms are involved in the stimulation of ventilation. The initial sharp increase at the start of an exercise is presumably due to cerebral input to the respiratory center in the anticipation of the increased needs depending on the past experiences and afferent impulses from proprioceptors in muscles, tendons and joints. The subsequent more gradual increase is probably humoral in origin. However, the arterial pH, PCO_2, and PO_2 remain constant during moderate exercise. The increase in body temperature may also play a role. Stimulation of the peripheral chemoreceptors by exercise-induced temperature rise, the plasma K^+ level, increased sensitivity of the neurons controlling the response to CO_2 and increased respiratory fluctuations in arterial PCO_2 (even though the mean arterial PCO_2 does not rise) are some of the proposed mechanisms. Oxygen may also play some role, despite the lack of a decrease in arterial PO_2, since during the performance of a given amount of work, the increase in ventilation while breathing 100% oxygen is 10 to 20% less than the increase while breathing air.

When exercise becomes more intense, there is liberation of CO_2 due to the buffering of the increased amount of lactic acid that is produced in the muscles. This further increases ventilation. With increased production of acid, the increase in ventilation and CO_2 production remain proportional, and thus the change in alveolar and arterial CO_2 is relatively little (isocapnic buffering). The increase in ventilation produced by the acidosis is due to the stimulation of carotid bodies. The alveolar PO_2 increases because of hyperventilation. With the further accumulation of lactic acid, the increase in ventilation becomes out of proportion to the CO_2 production, alveolar PCO_2 and arterial PCO_2 fall. The decline in arterial PCO_2 is a respiratory compensation for the metabolic acidosis produced by the additional lactic acid.

While the level of maximum ventilation achieved is dependent on the intensity of exercise, it is seldom beyond 20 times the resting level, i.e. upto 100 to 110 L. The maximum breathing capacity is about 150 to 170L in an average person. Thus, even on intense exercise, only about 50 to 60% of the reserve is used. There is still sufficient reserve available for extreme circumstances such as exercise at high altitudes and in extreme environments. Further, as oxygen supply from the lungs under normal circumstances is always sufficient, respiratory system response is never the limiting factor for exercise.

The recovery of the respiratory rate after exercise to basal level is delayed until the oxygen debt is repaid. This may take as long as 90 minutes. The stimulus to ventilation after exercise is the elevated arterial H^+ concentration due to the lactic academia. The arterial PCO_2, which is normal or low, or the arterial PO_2, which is normal or high, play no role. The magnitude of the oxygen debt is the amount by which its consumption exceeds basal consumption from the end of exertion until it has returned to pre-exercise basal levels. During the repayment of the oxygen debt, its concentration in muscle myoglobin rises slightly. ATP and phosphorylcreatine are resynthesized, and lactic acid is removed. Eighty percent of the lactic acid is converted to glycogen and twenty percent is metabolized to CO_2 and H_2O. Buffering of lactic acid during strenuous exercise increases the CO_2 liberation and therefore, respiratory exchange ratio (R: the ratio of CO_2 production to oxygen consumption) rises, reaching 1.5 to 2.0. After exertion, while the oxygen debt is being repaid, the R falls to 0.5 or less. Typically, the R rises from about 0.8 at rest to 1.0 on aerobic exercise. This increase reflects a greater reliance on carbohydrate rather than fat to produce the required energy.

Airway resistance decreases owing to bronchodilation as soon as exercise begins. Likewise, the ratio of dead space (V_D) to tidal volume (V_T) decreases. The drop in V_D/V_T is moderate at low-to-moderate exercise intensities. The V_D itself changes minimally with bronchodilation, the change in ratio being largely due to the increased V_T. This is advantageous, as it results in greater alveolar ventilation for given minute ventilation.

Changes in the Muscle

The rate at which oxygen is transported to the mitochondria in the exercising muscle is a limiting factor for the maximum oxygen uptake. As pointed out above, the lungs are never the limiting factor for oxygen uptake in health. During exercise, because of greater oxygen extraction, the tissue and the venous PO_2 drop sharply. There is a dilatation and recruitment of the capillary bed of the contracting muscle, facilitating the delivery of oxygen from blood to cells. The blood flow to muscles during exercise increases markedly, about 25-fold during the most strenuous exercise. This results from intramuscular vasodilatation caused by the direct effects of increased muscle metabolism, and also a moderate increase in the arterial blood pressure on exercise. Muscle contractions temporarily decrease the muscle blood flow by the compression of the intramuscular blood vessels; therefore, strong tonic muscle contractions can cause rapid muscle fatigue because of the lack of delivery of enough oxygen and other nutrients during the continuous contraction.

The oxygen-hemoglobin dissociation curve is steep in the PO_2 range below 60 mm Hg, and a relatively large amount of oxygen is supplied per mm Hg fall in PO_2. Oxygen off loading is further facilitated by the rightward shift of the curve due to the accumulation of CO_2, the rise in temperature and a rise in red blood cell 2,3-diphosphoglycerate (2,3-DPG). The net effect is a threefold increase in oxygen extraction from each unit of blood. As the local redistribution and increased cardiac output result in a 30-fold or greater increase in blood flow, it permits the metabolic rate of muscle to rise by as much as 100-fold during exercise.

Cardiovascular System

The work output, oxygen consumption, and cardiac output during exercise are directly related to each other, linearly. The increased blood flow to the muscles to meet the demand for increased oxygen consumption increases the venous return and hence the cardiac output. Normally, in an untrained person, the cardiac output can increase a little over four fold, and in the well-trained athlete, about six fold. Marathoners can achieve maximal cardiac outputs that are about 40% greater than those achieved by untrained persons. This occurs because of a nearly 40% increase in the cardiac muscle mass, as well as in the size of the chambers, and is observed only in the endurance types, not in the sprint types, of athletic training. At rest, a marathoner with a large heart has the same cardiac output as that of an average person. However, given the increased stroke volume, he can maintain the required cardiac output with a slower heart rate. At rest, a non-athlete person has an average stroke volume of 70–75 ml pumped at around 70 beats per minute while a marathoner has a stroke volume of around 100 ml and thus requires only 50 beats per minute to achieve the same cardiac output.

The increase in stroke volume is also greater on exercise in the marathoner and may reach 150–160 ml (about 50% increases over the resting value). At a maximal heart rate of around 180 beats per minute (up from the resting of 50 beats per minute, an almost 250% change), he will have a much greater cardiac output than a non-athlete in whom the stroke volume increases moderately to around 100–110 ml on exercise. Thus, a marathoner can increase the cardiac output to about 27–30 L per minute while a non-athlete can increase it to around 18–20 L per min. The increase in the cardiac output till about halfway is largely accounted for by the increase in stroke volume and subsequently by the increase in heart rate as the stroke volume gets limited earlier.

During maximal exercise, the cardiac output can reach 90% of its maximum possible value, whereas as noted above, the maximum ventilation achieved is only 50 to 60% of the maximum capacity. Therefore, cardiovascular system is normally much more limiting on V_{O_2} max than is the respiratory system, because oxygen utilization by the body can only be up to the rate at which the cardiovascular system can transport oxygen to the tissues.

PREGNANCY[15-26]

Pregnancy induces major physiological changes affecting all systems of the body. These occur early in the pregnancy and continue throughout gestation, with complete reversal after delivery. Several of these changes would be considered pathological if these were to occur in the nonpregnant state and may even cause symptoms. However, in pregnancy, these changes are considered physiological because they serve to ensure a successful gestation. An understanding of these changes is necessary since inappropriate diagnosis and interventions may occur in the absence of this knowledge. Considering the scope of this chapter, the following discussion is limited to changes in the respiratory system and related cardiological and hematological aspects. These changes are summarized in Table 9.2.

TABLE 9.2: Physiological changes in cardiorespiratory and hematological systems during pregnancy

- Bronchial smooth muscle relaxation
- Reduced TLC, FRC, RV, ERV
- Increased IC
- Increased dead space ventilation
- Increased tidal volume
- Increased respiratory rate
- Increased minute ventilation
- Increase in the oxygen consumption
- Increased blood volume
- Increased red blood cell mass
- Increased left atrial size
- Increased left ventricular end-diastolic dimension
- Increased left ventricular wall thickness
- Increased left ventricular mass
- Increased cardiac output
- Decreased systemic vascular resistance
- Decreased systemic blood pressure
- Increased pulse rate

Respiratory System

Hormonal changes in pregnancy, the increased estrogen, cause edema, capillary congestion and hyperplasia of the mucus glands. It affects the mucosa of the upper respiratory tract, including the larynx, producing hyperemia, mucosal edema, hypersecretion, and increased mucosal friability. This causes the voice to change along with nasal congestion. It leads to the worsening of pre-existing rhinitis. The muscosal changes in the larynx also make endotracheal intubation more difficult, should the need arise. Respiratory infections and pre-eclampsia aggravate these symptoms. As the uterus enlarges, the diaphragm is elevated by as much as 4 cm, the rib cage is displaced upwards and widens, increasing the lower thoracic diameter by 2 cm and the thoracic circumference by up to 6 cm. Abdominal muscles have a decreased tone and are less active during the pregnancy, causing respiration to be more thoracic and less diaphragmatic. The subcostal angle increases from 60–70 degrees to around 100–110 degrees.

Pregnancy causes significant changes in the pulmonary mechanics. The dead space volume increases due to the relaxation of the musculature of the trachea and the bronchi by progesterone. The bronchial smooth muscle relaxation may decrease asthma symptoms in some patients. A state of hyperventilation occurs and the Tidal Volume (V_T) increases gradually (by 35 to 50%) as the pregnancy progresses. The Total Lung Capacity (TLC) is reduced slightly (4 to 5%) by the elevation of the diaphragm. Due to anatomical changes in the thoracic cage, the Functional Residual Capacity (FRC), Residual Volume (RV), and Expiratory Reserve Volume (ERV), all decrease by about 10 to 20%. The increased tidal volume and the smaller residual volume cause an increase in the alveolar ventilation (up to about 65%) during pregnancy.

Inspiratory Capacity (IC) increases by 5 to 10%. Although there is no change in the lung compliance, there is an overall decrease in the chest wall and total respiratory compliance. The Forced Vital Capacity (FVC) is largely unaltered till later in pregnancy as the widened chest diameters counter the effects of the raised diaphragm. Airway function is not affected and FEV_1 remains at the same level as the pre-pregnancy state. The FEV_1/FVC ratio is usually not affected. Therefore, the dyspnea of normal pregnancy is not responsive to bronchodilators.

There are other stimuli that increase the ventilation, including increased metabolic carbon dioxide production, as well as the high serum progesterone that has a direct effect on the respiratory center. The respiratory changes include a slight increase in the respiratory rate, and a progressive increase in the oxygen consumption of up to 15 to 20% above the prepregnant levels by term (due to increased maternal BMR and increased fetal energy demands). With the increase in respiratory tidal volume associated with a normal or increased respiratory rate, there is an increase in respiratory minute volume of approximately 26%. As the respiratory minute volume increases, "hyperventilation of pregnancy" occurs, causing a decrease in the alveolar CO_2. The $PaCO_2$ decreases to around 30 mm Hg in late pregnancy and the renal loss of bicarbonate compensates to maintain the pH in the normal range. This maternal hyperventilation is considered a protective measure that prevents the fetus from exposure to the excessive levels of CO_2.

At the time of labor, the Functional Residual Capacity (FRC) decreases further. The ventilation increases, which is also driven by pain and anxiety resulting in marked hypocapnia and respiratory alkalosis. This may have adverse consequences for the fetus oxygenation by reducing the uterine blood flow. On the other hand, severe pain and anxiety can lead to rapid shallow breathing with alveolar hypoventilation, atelectasis, and mild hypoxemia in some patients. Preoxygenation is less effective and desaturation is likely to occur much faster than in the nonpregnant patient. A preoxygenation period of 3 to 5 minutes is advisable.

Hematological and Cardiovascular Systems

The most striking maternal physiologic alteration that occurs during pregnancy is the increase in the blood volume that varies according to the body mass of the woman, the parity, and the number of fetuses. This occurs due to the effect of progesterone and estrogen on the kidneys, leading to the activation of the renin-aldosterone-angiotensin pathway resulting in renal sodium retention and an increase in the total body water. The increase in blood volume is progressive, starting from the 6th week. The average increase in volume is 45 to 50% by 30–32 weeks; the level being static thereafter till term. The increased volume serves to maintain adequate feto-maternal tissue perfusion, as well as preparing the body to compensate for maternal blood loss during delivery.

The increase in plasma volume parallels the increase in the whole blood volume, the maximum extent being 50%. The red blood cell mass also increases by about 20 to 30%, stimulated by the rise in erythropoietin levels. There is a mild increase in the total leukocyte and platelet count. Simultaneously, platelet consumption is also increased. As plasma volume increases early in pregnancy and at a faster rate than the red blood cell volume, the hematocrit falls until the end of the second trimester, after which the increase in the red blood cells matches the increase in the plasma volume. This hemodilution results in the "physiological anemia of pregnancy." The hematocrit then stabilizes or may even increase slightly near the term. The initial hemodilution is advantageous as the reduced blood viscosity ensures adequate gaseous exchange to the fetus. The increased blood volume also delays the onset of symptoms of hypovolemia in the case of excessive bleeding during delivery. By two weeks postpartum, the hematological changes revert to prepregnancy status.

During pregnancy, as the uterus enlarges and the diaphragm becomes elevated, the heart is displaced upwards and somewhat to the left with rotation on its long axis, so that the apex beat is moved laterally. The cardiac capacity increases by 70–80 ml; this may be due to increased volume or hypertrophy of the cardiac muscle. The overall size of the heart appears to increase by about 12%. The left atrial size increases and correlates with the change in blood volume. The left ventricular end-diastolic dimension increases while the left ventricular end-systolic size might decrease somewhat as a result of the changes in the cardiac contractility. The left ventricular wall thickness increases by 28%, and the left ventricular mass increases by 52%.

A systolic murmur may be audible in the aortic or the pulmonary areas due to hemodilution and torsion of the great vessels. The cardiac output also starts to rise from the 5th week and increases approximately by 30 to

40% at 20–24 weeks gestation, reaches a maximal value of 10 to 30% above baseline values by 32 weeks and continues at this level until term. The cardiac output is lowest in the sitting and supine position and highest in the right or left lateral or the knee-chest position. In the supine position, the gravid uterus may compress the inferior vena cava reducing the venous return to the heart leading to a fall in the cardiac output, maternal blood pressure and placental perfusion. The descending aorta can also be compressed by the uterus causing a reduction in the uterine blood flow. Aortocaval compression is a cause of maternal hypotension from the end of the first trimester onwards, though usually it occurs after 20 weeks of gestation.

The systemic vascular resistance decreases by around 20% due to the effect of progesterone, nitric oxide, prostaglandins and atrial natriuretic peptide. The systemic blood pressure declines slightly during pregnancy. The diastolic pressure is reduced by approximately 5–10 mm Hg from about 12–26 weeks and increases thereafter to prepregnancy levels by about 36 weeks. There is an increase in the pulse rate of about 15 to 25%, a reflex due to reduced blood pressure and extrasystoles may occur. The pulmonary vascular resistance also decreases by 20 to 30%.

During labor, uterine contractions cause a 7 to 25% increase in the maternal cardiac output, a 7 to 15% decrease in the heart rate, and a resultant 7 to 33% increase in the stroke volume. The central venous pressure increases in parallel with the intensity of uterine contractions and increases the intra-abdominal pressure. Additionally, cardiopulmonary blood volume increases by 300 to 500 ml during contractions.

HIGH ALTITUDE[27-42]

Ascent to high altitude represents a physiological stress on the body. The concept of high altitude is arbitrary. Above 1500 m, physiological changes due to hypobaric hypoxia are detectable. With ascent, the barometric pressure falls leading to a lower atmospheric partial pressure of oxygen (PO_2), that in turn leads to a lower alveolar PO_2, although the composition of air remains the same. The pressure at 5,800 m (19,000 ft) is only one-half of the normal 760 mm Hg and the PO_2 of moist inspired gas is 70 mm Hg. On the peak of Mount Everest (altitude 8,848 m, or 29,028 ft), the inspired PO_2 is only 43 mm Hg. At 19200 m (63,000 ft), the barometric pressure is 47 mm Hg, so the inspired PO_2 is zero. Yet, more than 150 million people live at altitudes over 2,500 m (8,000 ft), and even higher than 4,900 m (16,000 ft) in the Andes.

TABLE 9.3: Physiological changes at high altitude

Acute Changes

- Increase in the minute ventilation
- Increase in diffusion capacity of lungs
- Respiratory alkalosis and fall in PCO_2
- Increased pulmonary vascular resistance and perfusion
- Increased heart rate
- Increased cardiac output
- Increase in the regional blood flow by vasodilatation
- Decrease in circulating volume due to water diuresis
- Increase in the number of erythrocytes
- Leftward shift in the dissociation curve

Chronic Effects

- Ventilation diminishes, but still more than at sea level
- Resting $PaCO_2$ increases towards normal, but still low
- Increased vital capacity
- Increased pulmonary vascular resistance and perfusion
- Decreased heart rate
- Increased stroke volume
- Decreased blood pressure
- Cardiac output tends to decrease back to normal
- Increased recruitment of the systemic capillary units
- Increase in the hematocrit values (polycythemia)
- Leftward shift in the dissociation curve

Climbers have lived for several days at altitudes that would cause unconsciousness within a few seconds if the human body did not have the capacity for acclimatization. Respiratory changes and adaptations follow ascent, and are associated with changes in other systems of the body, especially hematological and cardiovascular that allow survival. Table 9.3 summarizes the acute and chronic physiological adaptations on ascent to high altitude. It should be appreciated that these adaptations have regional, ethnic and gender variations. The physiological changes occurring in the body can be classified into acute and chronic, depending on the duration of exposure and stay at high altitude.

Acute Effects of Hypoxia

Respiratory

The minute ventilation increases to minimize the fall in alveolar Po_2 as the barometric pressure decreases. The ventilatory response increases initially on ascent as the PaO_2 falls below 60 mm Hg due to carotid chemoreceptor stimulation, then stabilizes over hours and weeks, and finally declines with deacclimatization on descent. The neural discharge from the whole carotid sinus nerve is related hyperbolically to decreasing Pao_2. Immediately following acute exposure to a very low PO_2, and lasting for perhaps half an hour, a transient "roll off" phenomenon or a hypoxic ventilatory decline may be there. Later, hypoxic stimulation of the peripheral chemoreceptors increases the alveolar ventilation to a maximum of about 1.65 times the normal. The increased ventilation allows alveolar CO_2 to be lowered and thus for a given FiO_2, a higher alveolar PO_2 can be achieved, as dictated by the alveolar gas equation. In extreme cases, ventilation may increase five-fold lowering alveolar CO_2 to as low as 8 mm Hg though usually in high altitude residents at 15,000 ft, it is around 33 mm Hg.

The acute increase in ventilation is inhibited by the resulting respiratory alkalosis and the fall in PCO_2 at the medullary and peripheral chemoreceptors. After a day or so, the Cerebrospinal Fluid (CSF) pH is brought partly back towards normal by the movement of bicarbonate out of the CSF, and after two or three days, the pH of the arterial blood is returned to near normal by the renal excretion of bicarbonate. The inhibition of ventilation is then reduced, allowing it to increase. In addition, there is evidence that the sensitivity of the carotid bodies to hypoxia increases during acclimatization. Over the next two to five days, the chemoreceptors increase the ventilation gradually to over five times the normal. However, the measurement of blood pH has revealed that alkalosis persists as ventilation increases. On the other hand, the cerebrospinal fluid pH may return to normal or even be relatively acidotic, causing sustained hyperventilation. The interstitial fluid around central chemoreceptors has also been found to be acidic inspite of the alkalinity of the CSF. It is possible that some mediator(s), other than H^+, may sustain the hyperventilation during the stay at high altitude.

High-altitude inhabitants exhibit a different long-term response that results in lower ventilation at any given altitude as compared to people experiencing similar altitudes for the first time suggesting that they have a diminished ventilatory response to hypoxia. The vital capacity decreases in the first 24 hours, with an increase in the residual volume and in the slope of the alveolar plateau of the single-breath nitrogen test. These changes are compatible with an increased interstitial fluid volume, resulting in airway narrowing, gas trapping, and delayed emptying of some lung units.

Cardiovascular

The initial increase in ventilation during acute hypoxia is accompanied by an increase in the cardiac output (as much as 30%) and pulmonary perfusion. This helps to sustain oxygen delivery inspite of the decreased arterial oxygen content. The increase in cardiac output is largely a result of an increased heart rate with little change in the stroke volume. This is mediated by an increase in the release of, and sensitivity to, catecholamines that override the augmented parasympathetic tone. Over the next few days at high altitude, the cardiac output decreases, primarily as a result of a decrease in the stroke volume as decreasing plasma volume reduces preload.

The hypoxic pulmonary vasoconstriction causes pulmonary hypertension. The increase in the pulmonary artery pressure starts as the alveolar PO_2 drops below 70 mm Hg, and then sharply below that. This is advantageous as it improves ventilation-perfusion matching by the redistribution of blood flow to areas of the lung that are usually poorly perfused. The increased pulmonary perfusion also improves the diffusion of oxygen.

Hematological

Hemoglobin concentration increases within one or two days of ascent and continues to rise for a number of weeks. The initial rise is due to hemoconcentration following the diuresis that occurs on initial ascent. Later, erythropoietin increases rapidly within 24 to 48 hours to stimulate the red blood cell production and then starts to decline within three weeks as acclimatization progresses. This increase allows the oxygen content to increase even though PaO_2 and saturation are diminished. The erythropoiesis however carries a disadvantage as it also increases the viscosity. There is a rightward shift of the O_2 dissociation curve due to an increase in the concentration of 2,3-diphosphoglycerate following respiratory alkalosis at moderate altitudes, that aids in unloading of O_2 in tissues at a given PO_2. At higher altitudes, there is a leftward shift in the dissociation curve caused by the respiratory alkalosis, and this assists in the loading of O_2 in the pulmonary capillaries.

Chronic Effects of Hypoxia or Acclimatization

Compensatory mechanisms come into play on ascent to high altitudes and allow a person to sustain and work without the deleterious effects of hypoxia on the body. This process is called acclimatization. Ventilation continues to increase for a few weeks. A number of factors, such as regulation of brain pH, metabolic rate and turnover of neurotransmitters, might contribute to this hyperventilation. However, with residence at high altitude, ventilation diminishes, and the resting $PaCO_2$ settles at a higher level, though still lower than at sea-level. This blunting is associated with hypertrophy of the carotid bodies. The decreased energy expenditure of the lower ventilation is an advantage as it reduces the overall oxygen consumption making it easier to sustain at the lower alveolar PO_2.

Chronic exposure causes the vital capacity to increase in high-altitude natives. The increase in vital capacity is dependent on the age at which the subjects start living at high altitude. Natives born at these heights develop larger vital capacities than those who move to high altitude later in life. This is understandable as the lung growth occurs mostly till the age of 8 years. With long-term residence at high altitude, diffusion capacity of the lung increases. This may be due to increased surface area consequent upon higher lung volume and the increase in pulmonary arterial pressure, promoting more blood flow through the alveolar capillaries.

On a prolonged stay at high altitude, the parasympathetic tone plays a role in the decreased heart rate. Downregulation of α-receptors in the myocardium results in lower heart rate on exercise even though norepinephrine levels rise. This does not compromise oxygen delivery as the stroke volume is also increased. The blood pressure is generally lower in high-altitude natives that may be secondary to a primary vasodilatory effect of hypoxia on the arterial wall muscle, as well as its negative inotropic effect on the cardiac muscles. With a more gradual increase in the hemocrit values, lower resting heart rate and higher stroke volume, the cardiac output tends to decrease back to normal. Another hemodynamic change that occurs is the increased recruitment of the systemic capillary units in the nonpulmonary tissues that increases the tissue blood flow and hence the oxygen delivery.

Chronic exposure to high altitude results in an increase in the pulmonary vascular resistance and pulmonary hypertension (primarily at the site of pulmonary arterioles) that may be compounded by polycythemia and hypoxic vasoconstriction and be severe. The continued increase in hemoglobin results from increased red blood cell production (erythropoesis) as part of acclimatization; this adaptation helps sustain oxygen delivery in the presence of a decreased arterial oxygen. In a fully acclimatized individual, the hematocrit may reach 60, with hemoglobin concentration as high as 20 g/dl. The blood volume also increases by 20 to 30%, resulting in a total increase of around 50% in the circulating hemoglobin. This is a slow process and takes many months to complete. These changes increase arterial oxygen content and tissue oxygen delivery.

At high altitude, adaptations occur in the oxygen-hemoglobin dissociation curve that may help facilitate oxygen transfer. Increased 2,3-DPG concentrations have been reported that should result in a right shift in the curve. However, the persistent respiratory alkalosis more than counterbalances the 2,3-DPG effect, shifting the curve back to normal or even slightly to the left. At very high altitudes, a rightward shift of the oxygen-hemoglobin dissociation curve could be a disadvantage for oxygen transport. While favoring the unloading of oxygen from the tissues, the same would also hinder the loading of oxygen in the lungs. A left-shifted curve at extreme altitude would result in enhanced oxygen loading in the lungs and higher arterial oxygen content.

DEEP DIVING[42-56]

Deep diving is done for professional and occupational purposes and increasingly for recreation. The environment on diving changes and has effects on the body systems that can vary from trivial to profound and may sometimes be even fatal if the diver is not careful. In relation to respiration, physiological alterations occur in the breathing cycle and blood gases. There are indirect effects related to alterations in the pressure of blood gases. There occur direct pressure-related problems on descent (including effects on ears, sinuses, thorax, stomach and intestines), and on ascent (air embolism, pneumothorax, mediastinal and subcutaneous emphysema). The effects of the pressure occur especially on compressible fluids, i.e. gas compartments. Pressure has no direct effects on noncompressible tissues and fluids. In addition, there are effects of temperature stimuli. Immersion causes a central redistribution of blood volume, which is increased if cold water triggers vasoconstriction. This reduces Antidiuretic Hormone (ADH) release and results in a diuresis, increasing the risk of hypovolemia on surfacing. The high risk of dehydration is further increased by the breathing of dry gas. Dehydration increases the susceptibility to diving related illnesses. Another challenge is that of temperature regulation. Water has a high thermal conductivity and capacity and the cold water predisposes the diver to, the risk of hypothermia.

Physical Principles in Deep Diving

It would be useful to review some basic laws of physical sciences to understand the diving physiology and associated abnormalities. The effect of diving deep into the sea stems from the tremendous increase in the hydrostatic pressure on the body. The human body is normally exposed to a pressure of 1 Atmospheres Absolute (ATA) at sea level. Water being far denser than air, for every descent of 33 feet, an additional pressure of 1 ATA is added. This is equivalent to 1.013 bar, 760 mm Hg or 14.7 psi. Thus, at 33 feet, the body is exposed to a pressure of 2 ATA, 1 ATA of pressure caused by the weight of the air above the water and the second by the weight of the water itself.

The increase in pressure causes a decrease in the volume of body cavities containing gases in accordance with the Boyle's law, i.e. the volume of gas is inversely proportional to the pressure it is subjected to, with the temperature remaining constant. Thus, compression (i.e. increased pressure) on descent will decrease the volume. If volume of a compartment is expressed as 100% at 1 ATA, it would be 50% at 2 ATA and 33% at 3 ATA and so on. Thus, proportional reduction is greatest in shallow water, i.e. the volume halves at 33 feet. The compression of the air pockets can be extremely dangerous and the lungs are especially vulnerable. An actual volume of 1 liter at a depth of 300 feet is the same quantity of air at a sea-level volume of 10 liters. Deeper a subject goes under the sea, the greater is the compression. To keep the lungs from collapsing, air must be supplied at very high pressure to keep them inflated. This exposes the blood in the lungs also to extremely high alveolar gas pressure, a condition called "hyperbarism." Beyond certain limits, these high pressures can cause tremendous alterations in body physiology, and can be lethal.

The individual gases to which a diver is exposed when breathing air, are *nitrogen*, *oxygen*, and *carbon dioxide;* each of them at times can cause significant physiological effects at high pressures. Even gases, such as carbon monoxide that normally are in negligible concentrations, can pose hazards when their alveolar pressures are increased. Dalton's law states that the total pressure exerted by a mixture of gases is equal to the sum of the pressures of each of its constituent gases, i.e. partial pressures of each gas added up make the total pressure of the mixture. Thus, if the total pressure increases with descent, pressures of body gases in their compartments will also increase proportionately without any change in their concentrations. Henry's law states that at a constant temperature, the amount of gas that will dissolve in a liquid is directly proportional to the partial pressure of that gas at its surface. The amount also depends on the solubility coefficient of the gas. Thus, gases will increasingly dissolve in body fluids on descent depending on their solubility and on ascent, these will bubble out as the pressure decreases. This is the physical principle underlying Decompression Sickness (DCS), described later.

Increased pressure on descent, reduces the volume and increases the density of gases in the airways. This, combined with immersion, reduces pulmonary compliance, increases airways resistance and also results in increased $\dot{V}/\dot{Q}$ mismatch, and an increase in the work of breathing. This increase in the work of breathing is one of the factors, which limits maximum diving depth and along with breath-holding (apnea) is responsible for dyspnea. The combination of resistive and elastic loads is also responsible for the reduction in ventilation. Further, there is a density-related increase in dead space/tidal volume ratio (Vd/Vt), possibly due to the impairment of intrapulmonary gas phase diffusion and distribution of ventilation. The net result of relative hypoventilation and increased Vd/Vt is hypercapnia. Professional divers, therefore, breathe helium-oxygen mixtures that are much less dense and have reduced viscosity compared with air. The concentrations of oxygen and CO_2 do not change except when the breathing apparatus is faulty or of poor design causing CO_2 rebreathing.

Depth and Nitrogen Narcosis

About 80% of the air is nitrogen. At sea-level pressure, the nitrogen has no significant physiological effects. However, at high pressures it can affect the functioning of the central nervous system, an effect called "nitrogen narcosis." The relation of depth to narcosis is sometimes informally known as "Martini law" as the symptoms of nitrogen narcosis resemble those of alcohol intoxication, developing roughly after 66 feet at the rate of the effect of one martini after every 33 feet. When the diver remains beneath the sea for an hour or more and breathes compressed air, the depth at which the first symptoms of mild narcosis appear is about 100–120 feet. Rarely, the effects may be seen with shallow dives. Individuals vary in their susceptibility. However, the problem is universal and related to the depth reached. Tolerance does not develop. The condition is entirely reversible on careful ascent.

Physiological Basis of Oxygen Toxicity

Oxygen is transported in blood largely bound to the heme portion of hemoglobin and to a much smaller extent dissolved in the blood, 0.0031 ml per mm PaO_2. Normally, at a PaO_2 of 100 mm, only 0.3 ml oxygen is dissolved in the blood, physically. When the PaO_2 in the blood rises above 100 mm Hg, the amount of oxygen dissolved in the water of the blood increases several-folds. While the amount bound to hemoglobin is limited due to the saturation of the binding sites, the increase in oxygen content is largely due to an increase in the dissolved oxygen. At an alveolar PO_2 of 3000 mm Hg (4 ATA), each 100 ml of blood contains 29 ml oxygen, 20 ml bound with hemoglobin and 9 ml dissolved in the blood water. The tissues take up their normal requirement of 5 ml leaving 24 ml of oxygen still in the blood. At this point, the PO_2 is approximately 1200 mm Hg, which means that oxygen is delivered to the tissues at this extremely high pressure instead of at the normal value of 40 mm Hg. The normal, safe range is between 20 and 60 mm Hg.

Pathogenesis of Decompression Sickness (DCS) (Caisson Disease, Dysbarism)

An increase in the alveolar PN_2 increases the dissolved nitrogen in the capillary bed, resulting in the same level of tissue PN_2. As nitrogen is not metabolized by the body, it remains dissolved in all the body tissues. However, when the alveolar pressures return to normal, the excess nitrogen is removed by the reverse process from the tissues. This removal often takes hours to occur and is responsible for a constellation of symptoms called "decompression sickness." (Details in Chapter 105).

At the sea level, almost exactly 1 liter of nitrogen is dissolved in the entire body, slightly more than one half of this is dissolved in the body fat, and the remaining in water, nitrogen is five times as soluble in fat as in water. After complete saturation, there is an increase of 1 L equivalent of sea-level volume of nitrogen dissolved in the body for every 33 feet depth. Equilibration of the pressure of nitrogen in all the body tissues with that in the alveoli occurs slowly as several cycles of blood flow are required and the nitrogen diffuses slowly. The equilibrium is complete in less than one hour, but takes much longer in fat tissue because of poor blood supply. For this reason, longer stay will allow more nitrogen to enter tissues at the same depth than a shorter stay. However, if large amount is dissolved due to a long stay, and the diver ascends quickly to surface, due to sudden fall in the pressures to 1 ATA, nitrogen (and to a small extent, other gases) move out of the liquid phase quickly and these cannot be transported to lungs fast enough to be exhaled out. Significant quantities of nitrogen bubbles can develop in the body fluids either intracellularly or extracellularly and can cause minor or serious damage in almost any area of the body, depending on the number and sizes of bubbles formed; this is the mechanism for decompression sickness and follows the Henry's law described above.

Direct Effects of Pressure: Barotrauma

Sinuses and Middle Ear

Noncommunicating spaces are susceptible to the effects of pressure with damage occurring during compression ("squeeze") or due to gas expansion on ascent. In the paranasal sinuses with blocked ostia or middle ears with blocked eustachian tubes, descent of as little as 1–2 m is enough to cause pain, edema and even hemorrhage. Though common, middle ear barotrauma is usually minor and self limiting. More serious injuries such as tympanic membrane rupture can occur. Differential ear equalization can result in alternobaric vertigo that is usually transient.

Pulmonary Barotrauma and Arterial Gas Embolism

Pulmonary volumes remain nearly normal while diving with breathing apparatus, but during ascent, the compressed gas in the lungs expands with the falling ambient pressure. Excessive transpulmonary pressures result if intrapulmonary gas is prevented from escaping as a result of a closed glottis, bronchospasm or gas trapping. If the rate of gas efflux from the lungs is slower than the rate of gas volume change, it will precipitate pulmonary overexpansion, and can happen in uncontrolled ascent from scuba diving at the depth of 3 feet or more. Because of the heterogeneity of compliance, there are differences in the expansion of adjacent lung units causing focal shearing between vessels and airways, and rupture of small airways and/or alveoli. This may result in pneumothorax, mediastinum and subcutaneous emphysema and pneumopericardium. When the air enters pulmonary venules, it reaches the left heart resulting in arterial gas embolism.

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Mechanisms of Dyspnea in Respiratory Diseases

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INTRODUCTION

Respiration is an automatic process, that however can be modulated voluntarily. The respiratory drive originates in the respiratory center in the brainstem with inputs from the periphery, as well as the cerebral cortex. Normally, the sensation to breathe and the effort of breathing do not reach a person's consciousness. However, in certain physiological conditions and in pathological states, a person may become aware of his breathing activity.

The term "*Dyspnea*" is used to imply an uncomfortable and unpleasant awareness of an increased effort to breathe. It is a symptom, not a sign. Due to its subjective nature, dyspnea will only have a modest or no relationship with an objective measure of the functional disability of a patient. Therefore, there are no objective surrogates for dyspnea and the patient is the prime source of information. The symptom of exertional fatigue must be distinguished from dyspnea.

DEFINITIONS

The American Thoracic Society has defined dyspnea as "a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioral responses."[1]

Certain other terms used to describe alterations in respiratory rate, depth and rhythm may be associated with dyspnea. These have different clinical connotations and are not synonymous. *Tachypnea* is a rapid respiratory rate, greater than the normal frequency of 12–18/min. It may be present with or without dyspnea. Conversely, a dyspneic patient usually has tachypnea on physical examination. *Hyperventilation* is minute ventilation that is greater than what is required to maintain a normal arterial CO_2. Thus the subject will have hypocapnia, but may not be dyspneic. *Orthopnea* or shortness of breath on assuming the supine position, results from an increase in the venous return and pulmonary blood flow that in patients with heart failure causes an increase in the left atrial and left ventricular filling pressures, leading to pulmonary vascular congestion and interstitial or alveolar edema. This is also referred to as "cardiac dyspnea." *Platypnea* is the shortness of breath when the patient is in the upright position and is a rare symptom associated with orthodeoxia (hypoxemia on standing) occurring in pulmonary or intracardiac shunts. *Trepopnea* is the shortness of breath when the patient lies on his or her side and can be relieved by moving to the opposite lateral position. *Paroxysmal nocturnal dyspnea* is waking up from sleep due to dyspnea and is usually a symptom of heart failure. As with orthopnea, the recumbent position is important, but this symptom differs in that breathlessness does not occur soon after lying down. The mechanism and the clinical implications are however similar with the increase in intrathoracic intravascular volume occurring due to a slow mobilization of tissue fluid such as peripheral edema. Patients with asthma and even Chronic Obstructive Pulmonary Disease (COPD) may also have disruption of sleep due to dyspnea. However, the mechanisms are different from those in heart failure.

PERCEPTION: THE SUBJECTIVE ELEMENT IN DYSPNEA

Dyspnea being a sensation, areas in the cerebral cortex concerned with perception must come into play. Indeed, the definition of dyspnea translates into a perceived unpleasant difficulty with breathing. In contrast to the physical stimuli, such as touch, pressure or temperature that are sensed by the peripheral nervous system and perceived as such by the cerebral cortex, the sensation of dyspnea is a central translation in the cerebral cortex of inputs of different nature from several peripheral sites to the respiratory center. The central cortical processing of the information from the respiratory center is modulated by psychological, behavioral and cultural factors that determine a person's ability to sense the stimulus and respond to it. This ability to sense constitutes "perception," a complex behavioral phenomenon that imparts to dyspnea, its subjective quality.[1]

The appropriate qualitative and quantitative feeling or perception of breathlessness in response to a stimulus of a particular strength and nature is impossible to define. A patient of asthma with severe airways obstruction may be asymptomatic, failing to sense the stimulus arising out of severe bronchospasm while another patient with a milder degree of airways obstruction may be very dyspneic, responding to the milder stimulus in an exaggerated manner. The former situation carries the risk of undertreatment, and the latter, overtreatment. The standards of patient care today recognize that monitoring of patients using objective outcomes, such as lung function has limitations, and, patient-reported outcomes that reflect the impact of disease on the person and on daily activities are equally, and perhaps, more important. Dyspnea is a major determinant of the person's response to his ailment, activities of daily living, functional capacity, and hence, the quality of life.

Dyspnea may occur in a variety of respiratory and cardiac conditions, both acute and chronic, as well as in other pathological states, such as anemia, thyrotoxicosis and psychiatric illness, and also in certain physiological states. Differences are expected among patients with regards to the intensity of the stimulus that will cause dyspnea, the language used to describe the sensation, as well as the psychological and physiological response to it. It is necessary for the physicians to appreciate that there are qualitative and quantitative differences in dyspnea in patients with different diseases. The underlying pathophysiological factors responsible for the sensation of dyspnea differ. Therefore, a uniform approach to treating dyspnea cannot be adopted. Management based on an understanding of the underlying mechanisms is more scientific.

While animal studies can provide information about the ventilatory responses under experimental conditions simulating physiological abnormalities encountered in different disease states, such as increased resistive or elastic loads, altered hemodynamics and blood gases, the subjective nature of dyspnea can be studied only in humans. The mechanisms have been investigated in patients with different diseases, as well as in normal subjects under the conditions of mechanical loading or altered oxygenation and acid-base milieu. Instruments have been developed and validated for the quantification of dyspnea. In recent years, there has been a further refinement of methodologies for assessment and quantification of dyspnea and understanding the neurophysiologic mechanisms that may contribute to its genesis. The availability of techniques, such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (MRI) have provided a means to study the central neuronal activity. Yet, the complex nature of the sensation of dyspnea and interplay of several neural pathways in concert makes it extremely difficult to design studies and provide definitive proofs of the responsible mechanisms. The information in literature is therefore often contradictory, controversial and, sometimes, even speculative.

NEURAL PATHWAYS OF DYSPNEA

The neural pathways regulating respiratory activity have been studied extensively and a vast amount of literature is available in this area.[2] The respiratory drive originates from the neurons in the medulla, called the respiratory center. The motor output travels to the diaphragm and the inspiratory muscles leading to their contraction, and, inflation of the chest wall and the lungs. The gas exchange and transport of oxygen and carbon dioxide are intimately involved in the regulation of acid-base balance. Changes in oxygen and carbon dioxide tensions in blood are sensed by central chemoreceptors in the medulla and peripheral chemoreceptors in the carotid and aortic bodies. Signals from these chemoreceptors are transmitted back to the brainstem respiratory centers that adjust breathing to maintain blood-gas and acid-base homeostasis. Mechanoreceptors in the airways, lungs and chest wall provide sensory inputs to the respiratory center on the changes in lung volumes and tissue displacement. Muscle spindles are abundant in the intercostals muscles and the diaphragm contains tendon organs that signal muscle tension and exert inhibitory influences on central respiratory activity. These provide feedback information about changes in the length and force of contraction of the respiratory muscles in response to the motor output. Afferent impulses from vagal receptors in the airways and lungs convey information on several aspects of lung physiology. These include impulses from pulmonary stretch receptors (lung expansion), irritant receptors around the epithelial cells of the bronchial walls (activated by irritants, high rates of air flow, and increases in bronchial smooth muscle tone) and C fibers, found in the interstitium of the lung in proximity to the alveoli and pulmonary capillaries (stimulated by increases in pulmonary interstitial and capillary pressure).

Corollary Discharge to Sensory Cortex

Additionally, there is evidence that corollary signals or efferent copies of brainstem respiratory center motor output, i.e. similar parallel outputs, are also transmitted to higher brain centers in the sensory cortex and may play an important role in the perception of dyspnea. This creates a conscious awareness of the outgoing respiratory motor output to the ventilatory muscles.[3] So far, specific receptors and pathways for this parallel relay have not been identified. However, rostral projections from brainstem respiratory motor neurons to the midbrain and thalamus have recently been described in the cat.[4] Studies have shown that in conditions, such as decreasing muscle length, muscle fatigue or respiratory muscle weakness, where a greater motor command is required to achieve a given tension in the muscle, there is an increased appreciation or perception of respiratory effort.[5,6] Further, the perception of the respiratory effort increases with increase in central respiratory motor output and is proportional to the ratio of the pressures generated by the respiratory muscles to the maximum pressure-generating capacity of those muscles.[7]

Chest Wall Receptors

There is evidence that afferent signals from mechanoreceptors in the joints, tendons, and muscles of the chest may play a role in modulating respiratory sensations. In a study using evoked-potential techniques to determine whether low-threshold muscle afferents from the chest wall project to cortical levels in conscious human subjects, evidence for a short-latency projection was provided.[8] It has been suggested that an uncomfortable sensation of breathlessness may be induced by muscle spindles in the intercostal muscles being activated out-of-phase with the respiratory cycle.[9] On the other hand, in-phase chest wall vibration (inspiratory intercostal muscles vibrated during inspiration and expiratory intercostal muscles vibrated during expiration) has been shown to decrease pathologic dyspnea in patients with chronic respiratory disease at rest and on exercise.[10-12]

Dyspnea increases with the level of respiratory chemical drive during hypercapnia, but intensity of the sensation was found to be greater when the consequent increase in ventilation was constrained. Voluntary hypoventilation produces an intense sensation of breathlessness even when blood gases are maintained constant that correlates closely with the degree to which the tidal volume is reduced.[13] In conscious patients on mechanical ventilator receiving the low levels of ventilation, dyspnea may be troublesome requiring heavy sedation.

Lung Receptors

Studies have shown that vagal influences, independent of ventilatory and blood gas changes may modulate the sensation of dyspnea. Mechanically ventilated patients with high cervical spinal cord transaction who are thus unable to transmit impulses from chest wall receptors experience a sensation of air hunger when their ventilation is reduced.[14,15] Further, vagal blockade or vagotomy has been shown to reduce dyspnea during exercise, breath-holding and after pulmonary venous obstruction.[16-18]

The three types of sensory receptors in the lungs that have been considered as the site of origin of dyspnea are: (i) the bronchial C-fiber receptors (ii) the pulmonary stretch receptors, i.e. the Slowly Adapting (SARs) and Rapidly Adapting Receptors (RARs), (iii) and the Juxtapulmonary (J) receptors, also referred to as pulmonary C-fiber receptors.

The bronchial C-fiber receptors were first described by Coleridge and Coleridge.[19] These are located mainly in the wall of the large airways, both extrapulmonary and intrapulmonary, and are characteristically accessible to chemicals injected only into the bronchial circulation. Their exact anatomical location in the airway wall or in relation to the capillaries of the bronchial circulation is not known. While their natural stimulus is as yet unknown, it is hypothesized that these are likely to contribute to bronchoconstriction and mucous secretion as the chemicals that they are sensitive to, include various inflammatory mediators.[20] That they do not contribute to an acceleration of respiration was shown by Anand[21] in cats where an impressive activity produced in them by injecting phenylbiguanide into the bronchial circulation was accompanied by an inhibitory influence on respiration. Capsaicin, on the other hand injected by a similar route is accompanied by a marked stimulation of respiration that persists after bilateral vagotomy thereby showing that the increase in respiration did not originate by their stimulation.

Located in the mucosa and smooth muscle of the extrapulmonary and intrapulmonary airways, the slowly and rapidly adapting pulmonary stretch receptors sense lung volume and are stimulated by lung inflation, and the latter, also by lung deflation.[22] These conduct their impulses in myelinated vagal afferents. According to Widdicombe[23,24], who changed their name briefly to "irritant receptors" because these receptors could trigger cough and reactions to noxious agents, and as also reviewed recently by Ravi and Kappagoda,[25] the stimulation of RARs produces dyspnea. However, in man, a rapid voluntary hyperventilation, which would produce a high-frequency neural discharge in RARs does not give rise to dyspnea or to any kind of unpleasant sensations.[26-28] Further, these receptors produce relief from dyspnea or breathlessness under circumstances when they would be maximally stimulated.[29] After breath-holding at total lung capacity, there is immediate relief with rapid expiration, i.e. a physiological stimulus for maximizing neural output from RARs.[30] This relief is similar to the relief felt on breathing in, after holding the breath at functional residual capacity that would be attributed to the stimulation of the SARs.[29] There are no correlative studies available between humans and mammalian species on RARs and their likely role in generating dyspnea are an extrapolation of findings from the latter. So far, no human studies of dyspnegenic effects of RAR activation have been carried out. Their role in producing dyspnea on exercise is not clear. However, there is evidence in animals that RARs play a role in the respiratory responses in acute pulmonary congestion due to heart failure. Activation of RARs causes a reflex increase in respiratory rate, tracheal tone and mucus secretion in the airways. A rise in left atrial pressure (LAP) by 5 mm Hg in dogs, which is sufficient to stimulate RARs[31] may occur on exercise. This is not accompanied by dyspnea. However, sustained application of LAP of 10 mm Hg for 15 minutes produces a sustained activation of RARs along with some activity in bronchial C fibers and very little in pulmonary C fibers. At this level, the increase in extravascular compartment in the lung is largely in the proximal airways. Thus, it has been suggested that the RARs may come into play in the early stages of acute heart failure.[25] Pulmonary edema requires an elevation of LAP to 20 mm Hg. At this level, RARs, bronchial C fibers and pulmonary C fibers, all show strong activation and are likely to modulate respiratory responses in frank pulmonary edema. Interestingly, the response of the RARs to pulmonary congestion is nonadapting unlike the response to maintained inflation where rapid adaptation occurs.

The J capillary receptors, or type J-receptors, so named because they lie in close proximity to the pulmonary capillaries in the interstitium of the lung, were discovered by Paintal.[33] These are stimulated in animals by pulmonary congestion and by intravenously injected chemicals to give rise reflexly to tachypnea.[32-36] These are also called pulmonary C-fiber receptors. Majority (80%) of these are non-myelinated C-fiber endings and 20% are A-delta fiber endings. Their natural stimulus is an increase in pulmonary blood flow leading to a rise in Pulmonary Capillary Pressure (PCP). Doubling of pulmonary blood flow (i.e. doubling cardiac output), which will result in increasing the PCP, increases their activity from nearly zero to 0.7 impulses/sec,[35] a stimulation which in earlier studies has been shown to stimulate respiration.[33,34] A correlative study of animals and human subjects demonstrated that small doses of lobeline i.v. (10–15 μg/kg) gave rise to respiratory reflexes and distinct sensations in the throat or upper chest by stimulation of J (pulmonary C fiber) receptors.[36] The sensations felt on J-receptor stimulation resemble those reported in dyspnea,[36-40] including those perceived by patients in left ventricular failure,[40] patients of mitral stenosis on exercise,[39] and those reported by subjects with high altitude pulmonary edema[28], suggesting a common origin of these. Thus, dyspneic sensations are produced under conditions in which the J (pulmonary C fiber) receptors are stimulated, and, conversely no or reduced dyspnea is observed under circumstances when they are not being stimulated or their stimulation is reduced. Valvulotomy relieves dyspnea in mitral stenosis[39] even without changes in skeletal muscle peak exercise oxygen consumption[41] muscle structure or biochemistry[42] and lung-function abnormalities,[43] suggesting that J-receptors are involved in the sensation of breathlessness on exercise in these patients as surgery relieves pulmonary congestion. Paintal[26-28] has provided evidence that an increase in interstitial fluid volume resulting from elevated pulmonary arterial and capillary pressures contributes to the breathless sensation after moderate and severe exercise. In acute heart failure, their activation follows that of RARs.[25] That vagal afferents are involved in the origin of the sensation of dyspnea, is strongly supported by the observation that intravenous lobeline does not produce sensations described above in patients who have undergone bilateral lung transplantation.[44]

Chemoreceptors

Changes in arterial blood gases, hypoxia with/without hypercapnia, are commonly observed in respiratory conditions causing dyspnea and are sensed by central and peripheral chemoreceptors. Their contribution to the sensation of dyspnea becomes difficult to evaluate as changes in lung and chest wall mechanics are associated with, and usually precede the alterations in blood gases in the pathophysiology of these conditions. However, certain models and interventions allow the evaluation of dyspnea due to chemically-induced increases in respiratory motor activity, independent of changes in chest wall and lung mechanics. Both ventilator-dependent quadriplegics with high cervical spinal cord transection and normal subjects paralyzed with neuromuscular blocking agents experience the sensations of air hunger when $PaCO_2$ is increased.[45,46] Moreover, hypercapnia produces greater dyspnea than exercise and voluntary hyperventilation at similar levels of ventilation.[47] In normal subjects paralyzed with a neuromuscular blocker and receiving adequate mechanical ventilation, acute hypercapnia and hypoxia cause respiratory distress. Importantly, the changes in dyspnea ratings precede changes in ventilation.[48] It has also been shown that the administration of oxygen during exercise produces a small reduction in ventilation, but a larger and consistent decrease in dyspnea suggesting that hypoxemia itself may be a stimulus for dyspnea independent of ventilatory changes.[49]

PATHOPHYSIOLOGICAL MECHANISMS OF DYSPNEA

Dyspnea may be produced by diseases and disorders affecting the respiratory centre, the ventilatory apparatus, including the airways and the lung parenchyma, gas exchange and oxygenation, and cardiopulmonary hemodynamics. As the activity of the respiratory centre, the ventilatory response in the terms of changes in lung volumes, pressures and airflows, changes in blood gas tensions and alterations of cardiopulmonary hemodynamics in physiological states and diseases are integrated and influence each other. Dyspnea is likely to be precipitated and modulated by multiple factors and mechanisms in different diseases and disorders of the cardiorespiratory systems. It is also likely that dyspnea experienced by patients represents more than one sensation. The choice of phrases used by patients with a variety of conditions causing dyspnea are distinctly different.[50,51] The pathophysiological mechanisms that operate in the common causes of dyspnea are discussed in the following sections.

In obstructive airways diseases, such as COPD and asthma, the functional abnormalities that may underlie the origin of dyspnea include (Table 10.1):

- Increased work of breathing due to increased resistive loading and functional weakness of the ventilatory muscles.
- Hypoxia and hypercapnia leading to chemoreceptor activation.
- Restriction of lung expansion in a hyperinflated chest and functional abnormalities in lung mechanics worsening on exertion (dynamic hyperinflation).
- Airway inflammation altering vagal afferent activity.
- Afferent signals from mechanoreceptors in the joints, tendons and muscles of the chest.
- Altered pulmonary circulation hemodynamics
- Associated cardiac dysfunction
- Any combination of the above.

In Interstitial Lung Diseases (ILDs), the following abnormalities may contribute to dyspnea (Table 10.2):

- Increased work of breathing due to increased elastic loading and functional weakness of the ventilatory muscles
- Physical restriction of thoracic expansion and functional abnormalities in lung mechanics
- Hypoxia leading to chemoreceptor activation
- Lung interstitial inflammation and fluid changes altering vagal afferent activity
- Afferent signals from mechanoreceptors in the joints, tendons and muscles of the chest
- Altered pulmonary circulation hemodynamics
- Associated cardiac dysfunction
- Any combination of the above.

With such diverse pathophysiological alterations, clearly a single mechanism or pathway cannot explain the origin of the sensation of dyspnea at rest and on exercise in these conditions.

Among the several proposed mechanisms, a popular theory that has been put forth is that dyspnea results from a disassociation or a mismatch between central respiratory motor output and incoming afferent information from the receptors in the airways, lungs and chest wall structures, i.e. the motor response is sensed as being “not matched” with the afferent inputs. The afferent feedback from the peripheral sensory receptors informs the center that the mechanical response of the lungs and chest wall (changes in volumes, pressures and airflows) are not appropriate for outgoing motor output (tension of the inspiratory muscles) leading to the sensation of dyspnea. In simple terms, the ventilatory response of the lungs and the chest wall is inappropriate for the effort. This is the crux of Campbell and Howell hypothesis of "length-tension inappropriateness."[52-54] and is also termed as "neuro-mechanical"[55] or "efferent-reafferent dissociation."[46] In terms of this hypothesis, if the inspiratory muscles contract less than usual for the tension generated because of a noncompliant chest wall, or if the airflow generated is less than expected for a given inspiratory effort or if the volume of inspiration is less than expected for the degree of activation of the muscles, the intensity of respiratory discomfort gets intensified. This dissociation between the efferent and afferent information may occur in patients with a resistive (obstructive diseases) or elastic (restrictive diseases) mechanical load on the respiratory system, or respiratory muscle abnormalities. This mechanism may explain dyspnea associated with breath-holding, increased airways resistance, decreased lung and chest wall compliance, voluntary hypoventilation, as well as that experienced by patients on mechanical ventilation with small tidal volumes and low inspiratory flow rates. However, as discussed above, quadriplegics and normal subjects paralyzed with neuromuscular blocking agents also experience air hunger to a hypercapnic or hypoxaemic stimulus and dyspnea precedes changes in ventilation.[13-15,45-47] The hypothesis also does not explain the dyspnea occurring due to changes in pulmonary hemodynamics on exertion in pulmonary and cardiac diseases.

In the absence of a single hypothesis that integrates all mechanisms of dyspnea, it is convenient to discuss origin of dyspnea in the terms of major pathophysiological alterations that occur in different diseases.

Increased Ventilatory Demand and Activity

Increased output from the brain is the primary manifestation of dyspnea in which the respiratory center may play a role in certain disorders and conditions. While it is possible to voluntarily increase ventilation, it is subjectively not an unpleasant sensation. Patients with psychiatric morbidity may hyperventilate and the corollary discharge from the respiratory center to cortical areas may also bring the increased ventilatory drive to consciousness. The dyspnea commonly seen in the first trimester of pregnancy is likely due to the stimulatory effect of progesterone on the respiratory center in the medulla. However, in most of the diseases causing dyspnea, the increased output of the respiratory center is a response to the increased ventilatory requirements sensed and communicated by the afferent inputs to the center through the neural mechanisms discussed above, rather than a primary abnormality. Abnormalities in gas exchange along with the stimulation of pulmonary receptors, as evidenced by the hyperventilation seen in patients with asthma and pulmonary embolism, may contribute to heightened activity in the center. Patients with a non-compliant wall, increased airway resistance, weakened muscles, or thickened pleura have problems with the ventilatory pump in achieving normal ventilation and derangements of the gas exchange occurring in several diseases leading to hypoxemia, with or without hypercapnia, have increased ventilatory drive to meet the increased ventilatory demand.

The intensity of dyspnea increases progressively with increase in the workload during exercise. However, halving the intensity and doubling the duration of activity reduces the maximal intensity of dyspnea to less than a third.[56,57] This is likely to be due to the increase in respiratory motor output to meet the increased ventilatory demand and a corresponding increase in the sense of effort. The cortex also takes into account the context in which the ventilation has increased in its interpretation. Increased ventilation at rest is likely to cause more dyspnea compared to an activity that gives rise to similar levels of ventilation. This is because higher ventilation at rest is seen as excessive or out-of-proportion to normal requirements at rest while it is considered as more appropriate for the activity. This has been reported in COPD.[58]

Diseases of airways (COPD), lung parenchyma (ILDs) and pulmonary vasculature (pulmonary embolism) that increase dead space and other conditions causing wasted ventilation due to V/Q mismatch require an increase in the minute ventilation to achieve normal gas exchange. Hypoxemia at high altitude and in patients with respiratory disease, stimulates arterial chemoreceptors and increases respiratory motor activity. The increased ventilatory demand leads to an increased motor command under these conditions, contributing to dyspnea.

Another stimulus for excessive ventilation is a consequence of deconditioning because of prolonged inactivity imposed by cardiorespiratory diseases. Patients with COPD have an early and accelerated rise in blood lactate production by skeletal muscles during exercise and the consequent metabolic acidosis is an additional respiratory stimulus leading to excessive increase in the ventilation for a given level of exercise, and this increases dyspnea.[59] This would limit exercise capacity leading to a vicious cycle of greater inactivity and consequent deconditioning and greater dyspnea.

While the level of ventilation often correlates well with the intensity of dyspnea, increased motor output is unlikely to be solely responsible for dyspnea. Even with conditions causing increased ventilation, the subjective sensations experienced by subjects are different. As pointed out above, at similar level of ventilation, hypercapnia produces greater dyspnea than voluntary hyperventilation and exercise[47] and the relief in dyspnea with exercise in hypoxic subjects afforded by supplemental oxygen is out of proportion to the reduction in ventilation.[49] Increased ventilatory drive is unlikely to produce an uncomfortable awareness of breathing as long as the response of the chest wall and lungs is commensurate with the requirements and the effort expended in ventilation is sensed as "normal." This requires a normal lung mechanics and an efficient musculature. However, when the other alterations as discussed in the following sections occur, the increased ventilatory drive becomes the driving factor for dyspnea.

Mechanical Inefficiency of Ventilatory Pump

A weakness or mechanical inefficiency of the respiratory muscles results in a mismatch between the central respiratory motor output and achieved ventilation. Some conditions that predispose to ventilatory failure increase the work of breathing due to altered lung mechanics (COPD, asthma, ILDs, obesity, kyphoscoliosis), whereas others cause severe respiratory muscle weakness. Specific reasons for muscle weakness include critical illness (electrolyte imbalance, acidosis, shock, severe sepsis), chronic illness (poor nutrition, cachexia), and neuromuscular diseases and dysfunction (steroid myopathy). In order to generate the inspiratory pressures required to initiate inspiration, greater effort is required by the inefficient muscles and even then, the maximal inspiratory pressures may be decreased.[60] Thus, there is an increased gap in the pressures achieved and pressures required leading to an inefficient ventilatory pump and dyspnea progressively worsens.[61]

The abnormalities of lung mechanics at rest and on exercise have been studied extensively in COPD.[62] Besides a partially reversible airflow limitation, COPD is characterized by a redistribution of lung volumes at rest and on exercise. The airflow limitation results in a requirement of a longer expiratory time to exhale a given volume of air. Associated emphysema leads to a loss of elastic recoil and hence the driving pressure for expiratory airflow, causing further reduction in flow rates along with an increased size of the alveoli and larger volume to be exhaled. The increased airflow limitation (resistance) and loss of elastic recoil (reduced compliance) lead to reduced time constants of the lung units and this impedes emptying within the available expiratory time. The result is an incomplete emptying and hyperinflation at the end of expiration (increased end-expiratory lung volume, EELV). As the next inspiration begins before the previous expiration has been completed, the airways pressures are still positive relative to the atmosphere (auto PEEP). This increases the inspiratory threshold, i.e. inspiration can begin only after this pressure is overcome. The increased inspiratory threshold thus increases the work of breathing and is also the cause of inspiratory dyspnea. On exercise, the increase in ventilation further increases the volume to be exhaled while the increase in respiratory frequency further reduces the expiratory time resulting in a progressive increase in the EELV due to the stacking of incomplete expirations and worsening of dyspnea. This phenomenon is called "dynamic hyperinflation" and occurs on even mild exertion in patients with severe COPD. The hyperinflation also causes breathing to take place on the stiffer upper portion of the pressure-volume curve, resulting in an added elastic load that further increases the inspiratory threshold load. The hyperinflation also imposes a "restriction" on the extent to which the tidal volume can be increased on exercise thus compromising ventilation. The increased resistive and elastic loads lead to increased work of breathing. Further, the low and flattened diaphragm is an inefficient muscle of inspiration. Finally, inspiratory muscle shortening with hyperinflation reduces the mechanical efficiency. In the face of the added resistive and elastic loads and mechanical disadvantages of a hyperinflated chest, to achieve a given level of ventilation requires substantial additional effort and if the ventilatory pump is able to achieve the required level of ventilation, it does so at the cost of increased work of breathing and if it is not, respiratory failure occurs. Either way, a mismatch is sensed between the respiratory drive and the achieved ventilation.

Evidence for the above concepts has been provided. On exercise, patients with mild COPD were found to have higher dyspnea ratings for a given work rate and ventilation compared to normal subjects. Changes in EELV were greater and dyspnea intensity increased as inspiratory reserve volume decreased, indicating dynamic hyperinflation. Thus, dyspnea in COPD arises out of the combined deleterious effects of higher ventilatory demand and abnormal dynamic ventilatory mechanics.[63] Bronchodilators may relieve dyspnea partly by reducing hyperinflation and restoring the lungs and the chest wall to a more mechanically advantaged position. It has been shown that more patients with COPD respond to bronchodilators by increasing the forced vital capacity, reflecting a reduced residual volume, than by an increase in expiratory flow rates and the forced expiratory volume in the first second(FEV_1).[64] An increase in the inspiratory capacity following bronchodilators also captures the same effect.[65] This is a "pharmacological lung volume reduction." The beneficial effects of lung volume reduction surgery are also attributable to reduced volumes of the chest wall and restoration of the muscle length to a more favorable and efficient position. Reduction in hyperinflation due to the prolongation of expiration favoring lung emptying is also the likely mechanism by which breathing exercises, such as pursed lip breathing, that form part of pulmonary rehabilitation programs, reduce dyspnea and improve exercise capacity.[66] The strategy of smaller tidal volumes and slower frequency with greater inspiratory-to-expiratory time ratios during mechanical ventilation of these patients also has the same physiological basis.

Changes in lung mechanics in acute exacerbations of asthma are similar with the important difference that these are largely reversible. However, asthmatic airways that have undergone substantial remodeling have a largely irreversible airway narrowing, thus increasing the work of breathing persistently and suffer from the same consequences of hyperinflation as outlined above in patients with COPD.

In ILDs, inspiratory pressures are increased due to lower lung compliance, which also reduces the tidal volume. The increased work of breathing is related to the increased elastic load, the resistive load being largely normal or low. The demand for increased ventilation is met by increasing the respiratory rate particularly during exertion. Thus, such patients typically have a rapid and shallow breathing. Reduced tidal volume also increases the proportion of wasted ventilation due to increased dead space/alveolar vthe center. This drives ventilation further in order to have sufficient alveolar ventilation. Tachypnea reduces expiratory time more than the inspiratory time, thus increasing the inspiratory duty cycle. The result is an increased ventilatory effort in ILD. Again, as in patients with COPD, this requires an adequately responsive ventilatory apparatus that may achieve the required ventilation, but at the cost of increased work of breathing and if it cannot, respiratory failure will follow.

Thus, in both, COPD and ILDs, the level of central respiratory motor output required to achieve the desired ventilation increases. Given the functional abnormalities in lung mechanics in these diseases discussed above, the mechanical response of the lungs is achieved at the cost of increased effort of breathing that is likely sensed as uncomfortable. In both diseases, dyspnea intensity is increased at any given ventilation compared with age-matched healthy individuals.[67] Addition of external resistive and elastic loads leads to a progressive rise in the intensity of dyspnea as the applied load increases.[68]

Harty et al.[69] applied external thoracic restriction in healthy subjects and observed that during exercise, this produced a shallow and rapid breathing pattern and was associated with greater dyspnea, with descriptors of dyspnea used by subjects (inspiratory difficulty, tightness and increased effort) similar to those reported by ILD patients. A contribution of pulmonary and chest wall mechanoreceptors in the sensation of dyspnea was suggested. O'Donnell et al.[70,71] using a combination of external chest wall restriction and added dead space in normal subjects to create a closer approximation of the physiologic disturbances caused by ILD, and, on direct studies in patients with ILD has provided evidence that the inability to expand tidal volume appropriately in the face of an increased drive to breathe contributes to the intensity and quality of dyspnea in ILD.

As the natural history of COPD and most interstitial and diffuse parenchymal lung diseases is one of progressively worsening pathology and hence the load on breathing, progressively increasing dyspnea on exertion is the classical presentation of both the types of diseases.

While the above mechanisms operating in COPD and ILDs may support Campbell and Howarth's hypothesis of "length-tension inappropriateness"[52-54] or neuro-mechanical dissociation, it is also difficult to prove because comprehensive measurements of efferent and afferent signals are not currently possible. Further, the pathophysiology in these states that may be responsible for dyspnea extends beyond the alterations in lung mechanics (Tables 10.1 and 10.2). There are associated changes in cardiopulmonary hemodynamics on exertion along with alterations in arterial blood gases. These are sensed independent of the changes in ventilation by different pathways as described above. Thus, other mechanisms are likely to operate as well.

Afferent Pulmonary Vagal Receptors Stimulation

As discussed above, sensory receptors in the lungs are innervated by the vagus nerves and consist of three types: Pulmonary stretch receptors (SARs and RARs) and bronchial C-fiber endings in the large airways, and pulmonary C-fibers (type J-receptors).[72] While the irritant receptors appear to modify the intensity of dyspnea associated with induced bronchoconstriction,[73] and the airway stretch receptors appear to modify breathlessness

TABLE 10.1: Mechanisms of dyspnea in chronic obstructive pulmonary disease

Increased ventilatory demand
- Increased ventilation/perfusion inequality
- Increased physiological dead space
- Hypoxemia and hypercapnia
- Early lactic acidosis due to muscle deconditioning

Inefficient ventilatory pump
- Altered lung mechanics (increased airway resistance, hyperinflation, including dynamic, leading to increased resistive and elastic loads)
- Poor nutrition
- Muscle fatigue due to the sustained increased work of breathing, mechanical disadvantage and systemic inflammation

Stimulation of vagal afferents
- Airway Inflammation
- Increased pulmonary blood flow and congestion on exercise

Signals from mechanoreceptors in the joints, tendons and muscles of the chest

Coexistent cardiac failure (diastolic/systolic)

Psychiatric morbidity

TABLE 10.2: Mechanisms of dyspnea in interstitial lung diseases

Increased ventilatory demand
- Increased ventilation/perfusion inequality
- Increased physiological dead space
- Hypoxemia and hypercapnia (later stages)
- Early lactic acidosis due to muscle deconditioning

Inefficient ventilatory pump
- Altered lung mechanics (deflation and decreased lung compliance leading to increased elastic load)
- Poor nutrition
- Muscle fatigue due to sustained increase in work of breathing

Stimulation of vagal afferents
- Interstitial inflammation and edema
- Increased pulmonary blood flow and congestion on exercise

Signals from mechanoreceptors in the joints, tendons, and muscles of the chest

Coexistent cardiac failure (diastolic/systolic)

Psychiatric morbidity

by altering ventilatory pattern, neither of these receptors has been shown to be specifically dyspnegenic. On the other hand, in addition to being short of breath, the sensations felt by the subjects on the stimulation of type J-receptors were found similar to the manifestation of dyspnea[36-40] and also resemble the cluster of "breathlessness-indicating sensations" of left ventricular failure patients,[39] as well as those felt by the patients of high altitude pulmonary edema.[28]

In two recent investigations, a significant similarity was found between the nature of respiratory sensations evoked in response to intravenous lobeline and modest treadmill exercise in cardiac disease patients,[38] and with a six-minute walk in mitral stenosis patients.[39] The latter were found to have an increase in the dose of lobeline required to produce the threshold levels of respiratory sensations after valvulotomy reduced the pulmonary wedge pressure, thus suggesting a reduction in the intensity of the natural stimulus, i.e. pulmonary congestion. This was accompanied by an increase in the symptom-free six-minute walk distance further substantiating their role in subserving the sensation of dyspnea on the exertion and limitation of exercise. This mechanism of relief is supported by the fact that neither the skeletal muscle peak exercise oxygen consumption[41] nor muscle structure or biochemistry change[42] and lung-function abnormalities still persist.[43] The evidence points to a major role for the J-receptors in the origin of dyspnea in acute heart failure.

However, acute increases in extravascular fluid volume in the airways also activate the RARs and with larger increases, both the RAR and the C-fiber receptors in the airways and the alveoli are activated. Activation of RAR causes a reflex increase in respiratory rate, tracheal tone and mucus secretion in the airways. It has also been suggested that the RARs play a significant role mediating the respiratory reflexes associated with acute heart failure.[25] However, direct evidence in humans is lacking.

Thus, whereas the role of vagal afferents in the genesis of the sensation of dyspnea in acute heart failure is fairly well established, there is uncertainness on their contribution to dyspnea in COPD and ILDs. The level of exercise that can precipitate dyspnea in these conditions is much less than that required to alter cardiopulmonary hemodynamics and produce stimulation of these afferents and exercise limitation in normal subjects. However, these may play a facilitator role as pulmonary blood flow does increase on exercise and in addition, coexistent cardiac failure is common in these conditions. Further, inflammatory changes in the airways and the interstitium may lower the thresholds for their stimulation, as discussed later. The stimulation of J-receptors on experimental aortic occlusion in cats was more closely related to the fall in lung compliance than the increase in pulmonary artery pressure associated with congestion.[74] Interestingly, the rapid shallow breathing that is characteristic of ILDs resembles the reflex response to the stimulation of pulmonary J-receptors. Therefore, J-receptors may be responsible for the dyspnea related to interstitial edema. Direct observations on the role of J-receptors in ILDs are however limited and do not support the suggestion that vagal stimulation is the principle mechanism for dyspnea on exercise in ILD.[75]

Inflammation is the most prominent pathological feature of both COPD (and asthma) and ILDs. The responses of lung receptors may be altered in these conditions and may be different from those observed in normal animals, as well as human volunteers. Recent studies have revealed that the sensitivity of bronchopulmonary C-fibers can be markedly elevated in acute and chronic airway inflammatory diseases, probably caused by a sensitizing effect of certain endogenously released inflammatory mediators. Normal physiological actions, such as an increase in tidal volume (e.g. during mild exercise) can then activate these C-fiber afferents, and consequently may contribute, in part, to unpleasant breathing efforts in diseases with inflammation in the airways and parenchyma.[76] Inhaled PGE_2 is known to stimulate vagal afferent receptors in the lung in particular C-fiber endings, without a significant increase in airway resistance. It significantly increases the magnitude of the dyspneic sensation when compared with inhaled saline at the same levels of workload, ventilation, and oxygen consumption on exercise and thus may modulate receptor responsiveness by lowering the thresholds for stimulation.[77] Only a small percentage (< 10%) of the bronchopulmonary C-fibers exhibit CO_2 sensitivity under control conditions, but alveolar hypercapnia exerts a consistent and pronounced stimulatory effect on the C-fiber endings during airway inflammation produced by acute exposure to ozone, infusion of inflammatory mediators, such as adenosine or prostaglandin E_2 and airway exposure to poly-L-lysine, a cationic protein known to induce mucosal injury.[78] Several other autacoids (e.g. bradykinin, neurotrophic factors, certain lipoxygenase metabolites, etc.) can also sensitize pulmonary C-fibers. These mediators may also contribute to the heightened respiratory discomfort found in patients with airway inflammatory diseases.[79]

Increases in pulmonary arterial and capillary pressures occur due to pulmonary vasoconstriction in healthy individuals exposed to the hypoxic environment at high altitude. Dry cough and choking sensations felt in the throat and upper chest of subjects with high altitude pulmonary edema are likely caused by the activation of pulmonary C-fibers and the same may also be the mechanism for similar respiratory sensations that occur after moderate or severe exercise at sea level.[80]

More evidence for the involvement of vagal afferents in the sensation of dyspnea has been obtained in studies employing local nerve blocks with anesthetic agents in normal subjects, as well as observations in patients who underwent vagotomy for some indications. Exercise studies in a patient who developed severe exertional dyspnea after a failed surgery that resulted in unilateral pulmonary venous obstruction demonstrated a markedly abnormal ventilatory pattern consistent with excess vagal stimuli to the respiratory center. Temporary and then permanent vagal interruption markedly altered the respiratory pattern and improved her functional status.[18] In normal human subjects, bilateral local anesthetic block of the vagus nerves at the base of the skull was found to diminish breath-holding sensation, and prolong breathholding.[17] On the other hand, results of vagotomy in patients have been inconsistent in relieving dyspnea, although the pattern of breathing may be altered with deeper breathing.[16, 81] In normal subjects, alveolar deposition of lignocaine to block unmyelinated pulmonary afferent nerves did not reduce dyspnea on exercise.[82] However, anesthesia of central airways in normal subjects was shown to produce slower and deeper breathing and reduced breathlessness on exercise.[83] In contrast, in patients with interstitial lung disease, anesthesia of the central airways did not modify the perception of dyspnea.[75] Intravenous adenosine in normal subjects does not cause bronchospasm, yet causes dyspnea, most likely by an effect on vagal C-fibers in the lungs.[84] The same effect was also seen in asthmatics.[85]

Blood-gas Abnormalities

Blood-gas abnormalities occur frequently in acute emergencies in several respiratory diseases and also develop in due course in the natural history of several progressive chronic diseases, including COPD and ILDs. Intuitively, one may expect these to contribute to the sensation of dyspnea. However, these correlate poorly with the magnitude of dyspnea in individual patients. As both hypoxaemia and hypercapnia also increase the central respiratory motor output acting through peripheral and central chemoreceptors,[86] the increased ventilation confounds any independent effect these may have on the respiratory sensations. Increased ventilation is not necessarily "unpleasant" and therefore, the contribution of changes in blood gas abnormalities to the origin of the sensation of dyspnea is difficult to evaluate.

However, dyspnea is aggravated by hypercapnia at the similar levels of ventilation on exercise and voluntary hyperventilation suggesting a direct effect on the intensity of dyspnea.[47] The effect of $PaCO_2$ on ventilation is effected through changes in hydrogen ion concentration at the medullary chemoreceptors. While this may operate during acutely developing hypercapnia, in patients with chronic hypercapnia, metabolic compensation neutralizes changes in hydrogen ion concentration and consequently limits ventilatory responses and changes in respiratory sensation. Acute changes in hydrogen ion concentration may explain the dyspnea of diabetic ketoacidosis and renal insufficiency.

Yet, a complementary role of hypoxaemia in the sensation of dyspnea cannot be denied. Certainly, the administration of oxygen reduces dyspnea in both acute and chronic respiratory failure, even in the absence of any changes in ventilation.[49] Bye et al.[87] noted that exercise duration was increased with the addition of supplemental oxygen in patients with ILD. It also clearly lowered ventilation measured at a given time-point during exercise. Marciniuk et al.[88] observed that in patients with ILD, exercise was limited primarily by dyspnea in some and by leg fatigue in others. The former had greater ventilation and demonstrated the evidence of expiratory flow limitation during exercise. However, the average arterial oxygen saturation at peak exercise was equal in both groups. This suggests that hypoxia may not be the primary mechanism causing dyspnea in ILDs. Moreover, relief in dyspnea on oxygen therapy may result from other beneficial effects, including improved ventilatory and peripheral skeletal muscle performance, as well as improved cardiac performance. It may also modify central processing of other stimuli causing dyspnea and thus influence respiratory sensation. It is also like to have a strong psychological effect, as it is synonymous with life.

Psychological Origins of Dyspnea

Considering the inherent element of perception and the subjective nature of the sensation of dyspnea, psychological factors undoubtedly play an important role in its origin. Not only factors related to personality are important as the major determinants of perception, psychiatric morbidity complicates chronic disabling diseases and thus confounds the symptoms. The communications between cortical areas concerned with the perception of dyspnea and the respiratory control center are two-way pathways. Interpretation of incoming corollary discharge to the cortical centers as being “unpleasant” is modulated by psychological, behavioral and cultural factors. However, emotional upsets may themselves lead to an increase in ventilation and a worsening of dyspnea. This is classically observed in hyperventilation states, such as acute anxiety and also contributes to dyspnea in acute exacerbations of asthma, COPD and other acute emergencies.

Associations were found between respiratory symptoms, including dyspnea and psychological scales incorporating anxiety, anger, depression, and cognitive disturbance with the perception of respiratory symptoms increasing with a rise in psychological scores.[89] The prevalence of anxiety and depression among patients with COPD is significantly higher than that in the general population and has been linked to increased mortality, decreased functional status and decreased quality of life.[90] Sarcoidosis is associated with a high rate of psychiatric comorbidity, including major depressive disorders and may contribute to a poorer quality of life.[91] A more fundamental association between psychiatric morbidity and respiratory illness has also been proposed, suggesting that a subset of patients may be more prone to develop both. In anxiety states, such as panic disorders, the respiratory abnormality most often reported is increased CO_2 sensitivity.[92]

Psychiatric morbidity and respiratory diseases may be involved in a vicious cycle, the former leading to a greater perception of symptoms of the latter, and, the latter giving rise to the former as a complication. A psychotherapeutic approach, managing both may thus be more associated with improved outcomes.[93]

SUMMARY

Dyspnea is a complex symptom of several diseases and disorders of the respiratory, cardiovascular and other systems. The subjective and complex nature of the symptoms of dyspnea makes it difficult to develop an appropriate model to study its origin. All such models have limitations and hence there are large gaps in the state of knowledge about its underlying mechanisms. It is unlikely that a common mechanism and pathway may explain its genesis. The origin of dyspnea is likely to be multifactorial, and, qualitative and quantitative differences exist in the perceived sensation of breathlessness in these different conditions. Increased central ventilatory drive, inefficient ventilatory pump, stimulation of vagal afferents by inflammatory and cardiopulmonary hemodynamic changes, as well as alterations in lung mechanics, sensations from mechanoreceptors in joints, tendons and muscles of the thorax, abnormalities of arterial blood gases, and acid-base balance acting through peripheral and central chemoreceptors, and psychological factors are the multiple factors involved. Management of patients based on an understanding of the pathophysiological mechanisms of dyspnea will be more rewarding both for the patient and the physician.

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11

Surfactant

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INTRODUCTION

Pulmonary surfactant is a complex mixture of phospholipids and proteins that reduce surface tension at the air-liquid interface of the alveolus, thus preventing its collapse during end-exhalation. This chapter outlines the complexity of the surfactant system and describes its basic biophysics, physiology and biochemistry. The physiological basis for the pathology and the treatment of salient respiratory diseases due to altered surfactant metabolism in children and adults, are also reviewed briefly.

COMPOSITION OF LUNG SURFACTANT

Lung surfactant is produced by type II alveolar epithelial cells, also called pneumocytes and consists of a mixture of phospholipids (PLs) and proteins.[1] Lung surfactant recovered from Bronchoalveolar Lavage (BAL) fluid, is composed of approximately 80 to 85% PLs, mainly Dipalmitoylphosphatidylcholine (DPPC), 5% to 10% proteins, and 5% to 10% other lipids[2] (Table 11.1).

Phospholipid Composition

Phospholipids are the main components that confer surfactant its ability to lower surface tension. The most abundant form of alveolar phospholipid is the tubular myelin, which are large relatively dense aggregates (termed large aggregate surfactant) composed of phospholipids and surfactant proteins. Small less dense particles (small aggregates) are also present in the alveolar space, which represent the remnants or catabolic forms of surfactant. These are taken up, reutilized or catabolized by type II pneumocytes or alveolar macrophages.

TABLE 11.1: Composition of lung surfactant[3]

Phospholipids	**80%–85%**
Phosphatidylcholine (PC)	75% (50% DPPC)
Phosphatidylglycerol (PG)	12%
Others	
Proteins	**5%–10%**
SP-A	50%–70%
SP-B, SP-C and SP-D	30%–50%
Neutral lipids	**5%–10%**
Cholesterol	90%–95%

DPPC, dipalmitoyl-PC

Lung surfactant contains several major PL classes: Phosphatidylcholine (PC), Phosphatidylglycerol (PG), Phosphatidylethanolamine (PE), Phosphatidylinositol (PI), Phosphatidylserine (PS), Sphingomyelin (SPM) and Lysophospholipid (LPL) (Table 11.1). Dipalmitoyl-PC accounts for at least 50% of PC molecular species, which is a critically important component for achieving the maximum reduction of surface tension. Surfactant is secreted into the amniotic fluid, levels of certain PLs like total PL, DPPC and lecithin to sphingomyelin ratio are used to predict the pulmonary maturity prior to the birth of preterm infants. Phosphatidylethanolamine, phosphatidylserine and lysophosphatidylcholine are present in relatively low concentrations in lung surfactant, an increase in concentration can indicate ongoing inflammation and cellular injury.[2]

Protein Components

Four surfactant proteins, called SP-A, SP-B, SP-C and SP-D, named in the order of discovery, are unique to the lung and intimately associated with surfactant lipids, each playing specific roles in surfactant homeostasis or host defense. Two classes of proteins have been distinguished on the basis of their structures. The small hydrophobic surfactant proteins B and C enhance the spreading, adsorption and stability of surfactant lipids required for the reduction of surface tension in the alveolus. They are essential for lung function and pulmonary homeostasis after birth, and are important protein components of the animal-derived surfactant replacement preparations used for the treatment of infantile respiratory distress syndrome. The two collectins, SP-A and SP-D, are relatively abundant hydrophilic proteins. They contribute to innate immunity and perhaps to the extracellular trafficking of pulmonary surfactant rather than to its surface activity.

Surfactant protein-A (SP-A): SP-A is the major surfactant protein in regard to relative abundance in the surfactant complex. It is a 26 to 38 kDa oligomeric glycoprotein that is expressed by the Clara cells and alveolar type II cells of the distal respiratory epithelium. The deduced primary structure and amino terminal sequencing of rat SP-A reveal five discrete structural domains: (1) Amino terminal domain (Asn^{1}-Ala^{7}); (2) Collagen-like sequence of Gly-X-Y repeats (Gly^{8}-Pro^{80}); (3) Hydrophobic neck region (Gly^{78}-Val^{114}); (4) Carbohydrate recognition Domain (CRD) (Gly^{115}-Phe^{228}), especially Mannose Binding Protein (MBP); and (5) Two differentially occupied consensus sites for asparagine-linked glycosylation.[4] SP-A is composed of a series of discrete structural domains. Monomers of SP-A form trimers by triple-helix formation in the collagen-like domains. The fully assembled molecule is an octadecamer, stabilized by intertrimeric and intratrimeric disulfide bonds at the amino terminus. The human SP-A gene locus consists of two functional genes, SP-A1 and SP-A2, which have four coding exons located on the long arm of human chromosome 10.

Deletion of the SP-A gene in mice does not alter survival or lung function after birth. However, they are highly susceptible to lung infection by bacterial, viral and fungal pathogens, indicating the primary role of SP-A in innate host defense of the lung. SP-A has been shown to bind to the lipid A moiety of endotoxin and to a variety of pulmonary pathogens, including *Haemophilus influenza* type A, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Pneumocystis jiroveci* and influenza A virus. SP-A also binds to alveolar macrophages and stimulates chemotaxis and phagocytosis.[4] SP-A also function as an alveolar opsonin to defend hosts without specific antibody or for immediate protection against remotely encountered pathogens that require the clonal expansion of lymphocytes for adequate response. It also acts an anti-inflammatory agent by inhibiting certain cytokines like interleukin-1 and TNF-α. SP-A increases the association of lipids with type II cells, but does not appear to increase the internalization of lipid.

The expression of SP-A in amniotic fluid increases in late gestation, and is a marker for determining fetal lung maturity. The levels of SP-A in BAL fluid are elevated in many diseases like sarcoidosis,[5] hypersensitivity pneumonitis,[5] idiopathic pulmonary fibrosis,[6] alveolar proteinosis[7] and asbestosis.[8] Thus, elevated SP-A levels in BAL fluids are not specific or diagnostic of a specific disease, however, may reflect acute alveolar inflammation.

Surfactant protein-B (SP-B): SP-B is a relatively small, 79 amino acid, amphipathic peptide produced by type II epithelial cells lining the alveoli. It is encoded by a single gene located on chromosome 2, which is expressed in the lung by type II cells and Clara cells. SP-B is tightly associated with surfactant PLs, and forms tubular myelin in the presence of SP-A, phospholipids and calcium. It is then secreted into the alveoli, where it interacts at the surface of surfactant lipids, forming stable monolayers and bilayers that reduce surface tension. The dimeric structure of SP-B may account for its ability to cross-link different lipid membranes. It plays a critical role in surfactant homeostasis by promoting the adsorption of lipid molecules into the expanding surface film by a factor of >150;[2] and enhancing their stability during the compression and expansion that occur during the respiratory cycle. This effect is further accelerated by the presence of calcium ions such that mixtures of phospholipids and SP-B display almost the same biophysical properties as the whole lung surfactant.

SP-B is critical for lamellar body formation and its deficiency results in the abnormal processing of SP-C due to abnormal lamellar body formation. Its transcription is regulated by TTF-1.[9] The concentration of SP-B increases with advancing gestation, as does SP-A. SP-B is absolutely essential for breathing and SP-B(-/-) mice, and infants with mutations in SP-B gene die of respiratory distress after birth.[10] SP-B reconstitutes most of the surface activity of natural lung surfactant, in combination with lipids. The sequence region 64–79 of SP-B contains peptides with two or more basic residues that include arginine or lysine. This sequence has been shown to be most effective in lowering surface tension.[11]

Surfactant protein-C (SP-C): SP-C is the only surfactant protein, which is expressed exclusively by type II cells in the mature lung. The human gene is found on chromosome 8 and SP-C, too, is translated as a larger preprotein and processed intracellularly. SP-C precursor protein is routed with SP-B precursor protein to multivesicular bodies, where both are processed and packaged into lamellar bodies for secretion into the air space along with phospholipids. Insertion of the surfactant protein-C peptide into phospholipid membranes disrupts the packing of lipids, thereby enhancing the movement of lipid molecules between the sheets of membrane and vesicles. The main function of SP-C is to maintain the biophysical surface activity of the lipids. This occurs through an acceleration of the rate of adsorption at the air-water interface, as well as through an increase in the resistance of surfactant to inhibition by serum proteins or by edema fluid. SP-C stabilizes the surface activity of the surfactant film during the expansion and compression involved in breathing.

Its transcription is regulated by TTF-1. SP-C(-/-) Swiss black mice does not demonstrate abnormalities in lung structure at birth.[12] In a congenic 129/Sv strain, SP-C deficient mice developed severe, progressive pulmonary disease associated with emphysema, alpha-smooth muscle actin staining, monocytic infiltrates, and epithelial cell dysplasia in conducting and peripheral airways.[13] SP-C is also an active component of various mammalian surfactant preparations that are used to treat respiratory distress syndrome in preterm infants.

Surfactant protein-D (SP-D): SP-D is the second hydrophilic surfactant protein and also a collectin. The molecular weight of the SP-D monomer is approximately 43 kDa that is structurally similar to SP-A and other C-type lectins. The collagenous domain of SP-D is much larger than that of SP-A, is attached directly, without a connecting region to the CRD domain. About 12 SP-D monomers are present in the lungs, three of which join to form trimers. These four trimers form a crisscross-like structure that may bind to bacterial Lipopolysaccharide (LPS) and to cell surfaces, forming larger networks of cells or bacteria. The interaction of SP-D microbial pathogens is Ca^{++} and carbohydrate dependent. SP-D is produced in type II cells and in Clara cells, the gene being located on long arm of chromosome 10. The SP-D gene consists of 8 exons spanning >11 kb of DNA. The majority (70%) of SP-D is found dissolved in the watery surfactant residue, whereas SP-A, SP-B and SP-C are almost entirely found in an association with lipids. Levels of SP-D and SP-A are potential markers for lung maturation because the studies of amniotic fluid and lung tissue have demonstrated the increasing levels of SP-D with increasing gestational age.

For SP-D, there are no known functions that are related to the biophysical activity of surfactant. The molecule may be of great importance for the nonadaptive defense system of the lung. SP-D has specific binding sites on alveolar macrophages,[14] can induce a "respiratory burst," and stimulates their phagocytotic activity. SP-D also binds to polymorphonuclear granulocytes, LPS, *Escherichia coli*, *Pseudomonas aeruginosa*, Influenza A virus and *P. jiroveci*.[2]

Other Lipids

Surfactant contains a small percentage of neutral lipids that are generally comprised of cholesterol, cholesterol esters, diglycerides, triglycerides and free fatty acids (FA). The roles of these components for surfactant function have not been fully characterized.

FUNCTIONS OF LUNG SURFACTANT (TABLE 11.2)

The best documented function of surfactant is its ability to reduce surface tension. Surface tension arises from the difference between the attractive forces on molecules at an air-liquid interface. As a result of this, there is a force or tension in the surface film that resists expansion of the bubble and consequently acts to contract surface area. This force is surface tension and has a value of 70 mN/m or 70 dynes/cm of water at 37°C.[9] The amphipathic

TABLE 11.2: Functions of lung surfactant

Biophysical Functions

1. Reduces surface tension and prevents collapse of alveoli during expiration
2. Increases lung compliance and decreases work of breathing
3. Maintains gas exchange area of lung
4. Counteracts edema formation by balancing hydrostatic filtration forces
5. Improves mucociliary clearance
6. Reduces bronchoconstriction
7. Smooth muscle relaxant

Host Defense Functions

1. Opsonization of bacteria, viruses, fungi and allergens
2. Facilitate phagocytosis of pathogens
3. Modulate production of inflammatory mediators
4. Direct microbicidal activity
5. Promote phagocytosis of apoptotic cells

properties of lung surfactant allow its alignment at the air-liquid interface. Surfactant intermolecular repulsive forces act by opposing attractive forces between molecules at the liquid surface. The presence of lung surfactant in the alveoli, therefore, reduces surface tension preventing collapse of alveoli. Natural surfactant generally lowers surface tension to < 6 dynes/cm.[15]

The law of LaPlace states that the pressure difference (ΔP) across a spherical surface (e.g. alveoli) depends on the ratio between surface tension (σ) and the radius (r) of the sphere.[1,2]

$$\Delta P = \frac{2\sigma}{r}$$

A constant surface tension in conjunction with a small radius would lead to a high pressure difference across the sphere. So, there is an increased tendency for the collapse of smaller alveoli during expiration. The lowering of surface tension by the lung surfactant allows pressure differences across the alveolus to remain constant throughout the respiratory cycle; and thus, preventing collapse of alveoli and small airways. The surfactant also increases lung compliance, and reduces the work of breathing. It counteracts edema formation by balancing hydrostatic forces. Surfactant forms a nonspecific barrier against the adhesion and invasion of microorganisms into the lung.[16] Furthermore, airway surfactant was shown to improve mucociliary clearance,[17] and to reduce bronchoconstriction in response to inhaled allergens.[16] A recent study suggested the role of surfactant as a smooth muscle relaxant.[18]

Host defense functions of surfactant are primarily assured by SP-A and SP-D. Nevertheless, surfactant PLs also influences pulmonary immune function. SP-A and SP-D facilitate phagocytosis of pathogens by at least three different mechanisms: Opsonization of pathogens, ligand-activation of immune cells and upregulation of cell receptors involved in microbial recognition.[19] Collectins also have a direct microbicidal activity against bacteria or fungi without the presence of immune effector cells.[19,20] The mechanisms leading to microbial killing have not been fully characterized. SP-A and SP-D promote the uptake of apoptotic cells by alveolar macrophages.[21] It also slow the release of proinflammatory mediators and inhibit the activation of nuclear factor-κB and the L-selectin-induced signal transduction.[22] The phospholipid components in large abundance under normal conditions have been shown to suppress various lymphocyte and macrophage immune function. They suppress the proliferation, immunoglobulin production and cytotoxicity of lymphocytes; and also inhibit endotoxin-stimulated cytokine (TNF, IL-1, and IL-6) release from macrophages.[2]

SURFACTANT METABOLISM AND SURFACTANT FILM FORMATION (FIG. 11.1)

The size of the surfactant pool is tightly regulated by mechanisms controlling the synthesis, recycling and catabolism of surfactant.[23] Both during development and postnatally, the synthesis of pulmonary surfactant is subjected to precise regulatory controls. It increases markedly in late gestation and is enhanced by a variety of hormones, including the glucocorticoids. In fact, glucocorticoids are routinely used to induce lung maturity in infants at risk for preterm delivery. Thyroxine accelerates type II cell differentiation while acting synergistically with glucocorticoids to enhance the distensibility of the lung and DPPC synthesis. Beta-agonists and purines, such as adenosine triphosphate are also potent stimulators of surfactant secretion. Mechanical stretches, such as lung distension and hyperventilation have also been found to be involved in stimulating surfactant secretion. Certain cytokines like Tumor Necrosis Factor alpha (TNF-α) and Transforming Growth Factor Beta (TGF-β) and insulin inhibit surfactant production depending on experimental conditions.

Surfactant PLs and proteins are synthesized in the endoplasmic reticulum of type II alveolar cells. In addition, SP-A, SP-B and SP-D are produced by Clara cells and submucosal cells. PLs and surfactant proteins are processed through the Golgi apparatus and packaged into lamellar bodies (intracellular storage organelles). ABCA3 is present in the limiting membrane of the lamellar bodies, where it is likely to regulate lipid transport at the air-liquid interface. Surfactant is exocytosed from these structures into the alveolar hypophase (a liquid layer between air and lung epithelium) where it exists in the form of heterogeneous PL-rich aggregates, including tubular myelin. Tubular myelin is the most abundant form of alveolar phospholipid and consists of large dense aggregates. 'Large aggregates' have been demonstrated to have a strong ability to lower surface tension (highly active surface) and to contain the hydrophobic surfactant proteins along with SP-A and specialized PL structures (i.e. lamellar bodies and tubular myelin). Phospholipids from extracellular surfactant structures form continuous monolayers and multilayers of phospholipids that line the alveolar spaces and airways, with their polar heads oriented toward the liquid and their acyl chains toward the air.

During breathing the surfactant film at the air-liquid interface is subjected to "compression" and "expansion." The following concept has been proposed for surfactant film behavior: At the end of expiration, the surfactant

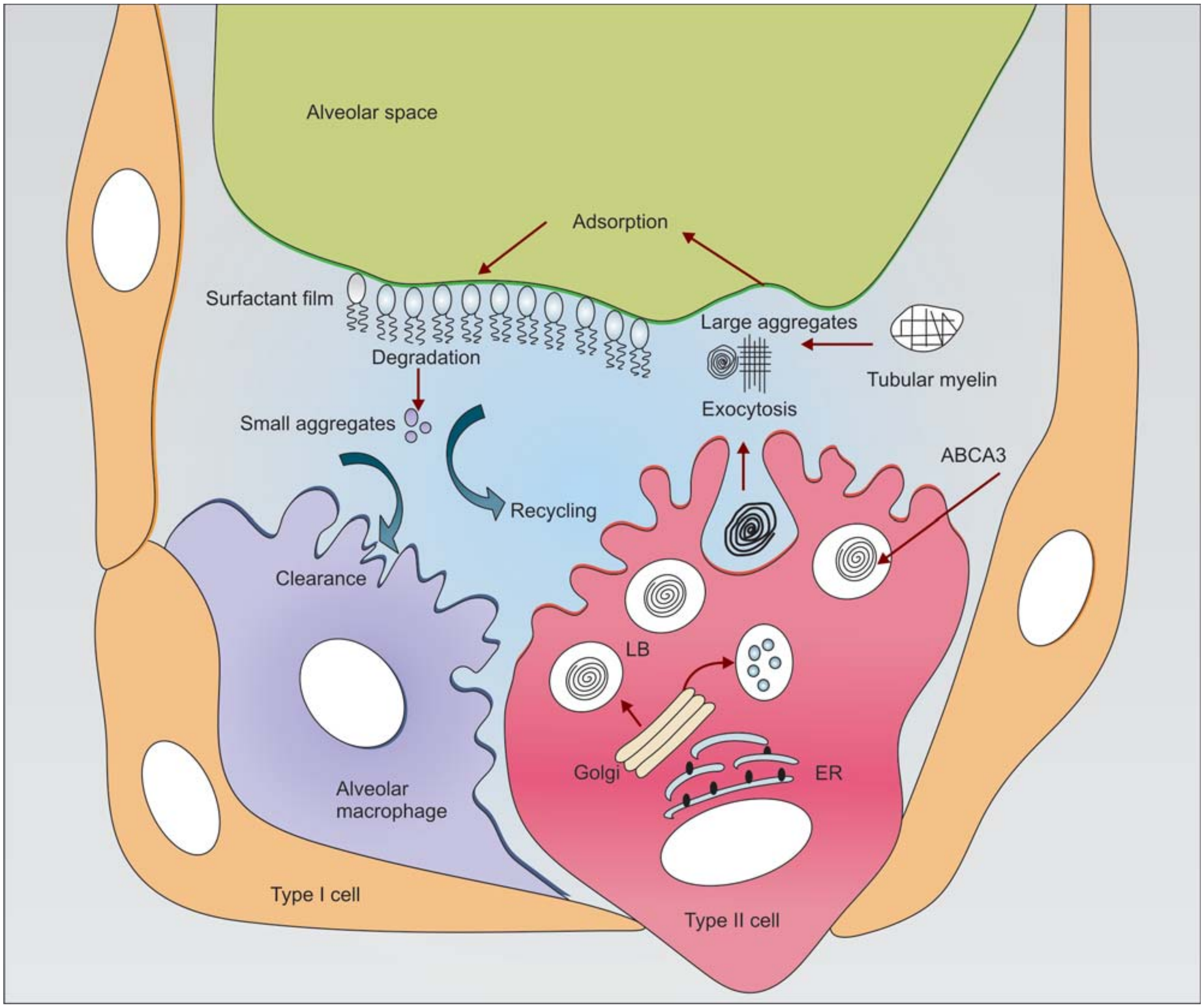
Alveolar space
Adsorption
Surfactant film
Large aggregates
Tubular myelin
Degradation
Exocytosis
Small aggregates
ABCA3
Recycling
Clearance
LB
Golgi
ER
Alveolar macrophage
Type I cell
Type II cell

Fig. 11.1: Schematic representation of surfactant metabolism and surfactant film formation. See text for details. ER, Endoplasmic reticulum; LB, Lamellar bodies

film is enriched in DPPC as the phospholipids with unsaturated fatty acid chains are squeezed out of the surfactant film (compression). DPPC films can be tightly compressed, which allows the achievement of very low-surface tensions at the end of expiration and thus prevents alveolar collapse. Although the ability to maximally lower surface tension is attributable to the presence of DPPC in surfactant films, proper surfactant function, which is highly dynamic *in vivo*, could not be achieved without the action of other lipids and surfactant proteins. The surfactant components, which are expelled during expiration, are reincorporated into the surface-active film during inspiration (expansion). This leads to enhanced surfactant spreading. PLs with unsaturated or shorter FA chains introduce fluidity into surfactant films, and allow fast surfactant adsorption and respreading at the air-liquid interface. Anionic PLs (PG and PI) enhance surfactant film adsorption and film stabilization during the respiratory cycle.[24] Surfactant proteins (SP-B, SP-C and SP-A) are essential for the packaging of surfactant PL in lamellar bodies, organization of tubular myelin, and ultimately formation of an efficient surfactant film at the air-liquid interface.

Normally, surfactant is inactivated by mechanical and biologic processes and converted into small, surface-inactive aggregates. "Small aggregates" typically represent surfactant, which is being removed from the air-liquid interface for recycling, or has been injured during inflammation. Approximately, 70 to 80% of the "small aggregates" are taken up by alveolar type II cells, transported to phagolysosomes, and reused or catabolized. Alveolar macrophages internalize and catabolize the remaining surfactant pool, a process critically dependent on GM-CSF.[25] Although less than 10% to 15% of surfactant is cleared by catabolism by the alveolar macrophages, this pathway is critical in controlling steady state surfactant concentrations *in vivo*. GM-CSF acts within the lung by stimulating the terminal differentiation of alveolar macrophages, principally by raising the levels of transcription factor PU.1.[7] It has been shown in experimental studies that GM-CSF(-/-) and GM-CSF receptor-deficient mice are not capable of clearing surfactant proteins and phospholipids, causing alveolar proteinosis.[26] GM-CSF signaling also enhances the function of peroxisome-proliferator–activated receptor γ (PPARγ), another transcription factor that regulates many cellular functions, including intracellular lipid metabolism.[26] These findings explain how inhibiting the binding of GM-CSF to its receptor causes the decreased clearance of surfactant from the alveolar spaces.

DISORDERS OF SURFACTANT METABOLISM

Surfactant alterations have been implicated in the pathophysiology of a number of alveolar and airway diseases. This occurs either due to decreased production or due to accelerated breakdown by oxidation, proteolytic degradation, inhibition or inherited defects of surfactant metabolism (Table 11.3). Decreased clearance of surfactant by alveolar cells, causing the excess deposition of surfactant in the lungs can also cause respiratory failure. Surfactant alterations have been described in a much larger number of respiratory diseases (Table 11.4).[2] It is beyond the scope of this chapter to address all of these. Some of the important diseases linked to the altered surfactant metabolism have been briefly discussed as under.

TABLE 11.3: Mechanisms of lung surfactant abnormalities[3]

- **Deficient surfactant formation (synthesis/storage/release)**
  - Immaturity of type II pneumocytes
  - Injury to type II pneumocytes
- **Inhibition of surfactant function (surfactant inhibitors)**
  - Meconium
  - Plasma proteins
  - Cellular lipids
  - Hemoglobin
- **Degradation of surfactant**
  - Free radical injury
  - Proteases
  - Phospholipases

TABLE 11.4: Disorders of surfactant metabolism

- **Decreased surfactant**
  - Quantitative defect
    - Infantile respiratory distress syndrome
  - Qualitative defect
    - Hereditary SP-B deficiency
    - Hereditary SP-C deficiency
    - ABCA3 transporter gene mutation
  - Both (Decreased production and inhibition of surfactant activity)
    - ARDS
    - Meconium aspiration syndrome
    - Pulmonary hemorrhage
- **Excess surfactant**
    - Alveolar proteinosis

Infantile Respiratory Distress Syndrome

Respiratory Distress Syndrome (RDS) is one of the most common causes of morbidity in preterm neonates, the risk increases as the gestational age decreases. The preterm infant who has RDS has low amount of surfactant that contains a lower percent of disaturated phosphatidylcholine species, less phosphatidylglycerol, and less of all the surfactant proteins than surfactant from a mature lung. Minimal surface tensions are also higher for surfactant from preterm than term infants. Decreased alveolar surfactant activity associated with pulmonary immaturity causes atelectasis, alveolar collapse and hypoxemia. Radiological findings include a diffuse reticulogranular "ground glass" appearance (resulting from alveolar atelectasis) with superimposed air bronchograms. Oxygen support and mechanical ventilation are typically required.

Surfactant Replacement Therapy (SRT) significantly reduces the incidence, severity and mortality associated with RDS, and it has become the standard of care in the management of preterm infants with RDS.[27] SRT reduces the incidence of death, air leak syndromes and intraventricular hemorrhage in premature infants. Surfactant treatments are effective because of complex metabolic interactions between surfactant and the preterm lung. The large treatment dose functions as substrate; it is taken up by the preterm lung and is reprocessed and secreted with improved function. The components of the treatment surfactant remain in the preterm lung for days. If lung injury is avoided, then surfactant inhibition is minimized.[27] Prenatal corticosteroids complement surfactant to further enhance lung function.

Exogenous surfactant preparations, both natural and synthetic, are approved for the treatment and prevention of RDS in infants. Synthetic surfactants differ most notably from natural surfactants in their protein composition. Surfactant preparations containing surfactant proteins B and C act rapidly, increasing lung volumes and compliance, and thereby decreasing the requirements for positive pressure ventilation and oxygen supplementation. Synthetic surfactant preparations lacking surfactant proteins, e.g. colfosceril palmitate, improve lung functions in a delayed manner. However, the overall efficacy of both the type of preparations does not differ much, and are now the standard treatment for RDS. Prophylactic SRT in patients who are at risk for RDS, particularly those infants born at <30 weeks gestation, improves neonatal survival and reduces morbidity. For infants in whom RDS develop, SRT early in the course of RDS, before surfactant inactivation plays a prominent role in lung pathophysiology, is superior to later SRT when lung disease is more advanced.[28]

Inherited Defects of Surfactant Metabolism

A variety of inherited defects of surfactant metabolism includes:

Hereditary SP-B Deficiency

Homozygous SP-B gene (SFTPB) mutations lead to surfactant dysfunction and lethal respiratory distress. Most infants with SP-B deficiency are present with progressive respiratory failure in the first 24 to 48 hours of life. Pulmonary function studies and radiographic findings in these infants are consistent with surfactant deficiency. Radiographic findings include alveolar infiltrates and collapse, reticular-granular infiltrates and air bronchograms in term infants. The disorder is usually inherited as an autosomal recessive condition due to mutation in the SFTPB gene located on chromosome 2. SFTPB mutations are detected in approximately 10% of full-term infants with unexplained respiratory failure.[23] The carrier rate for SFTPB mutation is estimated to be ~1 in 1000.[29] SFTPB mutations include nonsense mutations, point mutations, frameshift mutations, splice-site mutations, deletions and insertions in the SFTPB gene. A single mutation, termed 121 ins 2 (a net insertion of two nucleotides in codon 121 that causes a frame shift, unstable surfactant protein B messenger RNA, and a failure to synthesize surfactant protein B precursor protein), accounts for approximately the two thirds of mutant SFTPB alleles.[23] However, heterozygous relatives of surfactant protein B–deficient infants do not have clinically apparent lung disease.[30]

SP-B deficiency disrupts the formation of lamellar bodies and tubular myelin. The normal packaging and routing of SP-C is also disturbed by SP-B deficiency. Misprocessed surfactant protein C precursor protein (proSP-C) accumulates in amniotic fluid and intracellularly in the airway lumen, causing a proteinosis-like syndrome. Detection of this surfactant protein-C precursor protein fragment in BAL fluid of affected patients, by immunohistochemistry, is useful in the diagnosis of hereditary surfactant protein B deficiency. The definitive diagnosis is made by the identification of both mutations in alleles of the SFTPB gene by nucleotide sequence analysis. The disorder is refractory to surfactant replacement therapy and most infants die within the first month of life, despite maximal medical therapy. The only known treatment is lung transplantation; it has been found that long-term outcomes after lung transplantation for SP-B deficient infants are similar to those of infants transplanted for other indications.[31]

Some other uncommon forms of mutations in SP-B gene that cause partial deficiency of surfactant protein B have been associated with chronic interstitial lung disease in childhood. Most of these children often require intermittent oxygen therapy.

Hereditary SP-C Deficiency

Mutations in the human SP-C gene (SFTPC) resulting in the lack of SP-C represent a rare cause of acute and Chronic Lung Disease (CLD) in infants and adults.[23] SP-C deficiency is inherited as an autosomal dominant disorder; and the mutation could be familial or de novo. This is associated with various forms of interstitial lung disease, including Nonspecific Interstitial Pneumonitis (NSIP), Chronic Pneumonitis of Infancy (CPI), and Idiopathic Pulmonary Fibrosis (IPF); and susceptibility to ARDS following lung injury and infection. Both direct toxicity of abnormal proSP-C, and deficiency of mature SP-C are involved in the pathophysiology of the lung disease caused by SFTPC mutations. Since surfactant protein C may have other functions, including reuptake and catabolism of surfactant particles and surfactant function in the alveolus, it is unclear whether all or some of these activities contribute to the pathogenesis of lung disease caused by mutations in SFTPC.[23] Considerable allelic heterogeneity exists, but there is no obvious correlation between genotype and disease severity. Severe cases resulting in death in early infancy and some requiring lung transplantation have been reported.[9]

ABCA3 Transporter Gene Mutation

Mutations in the ABCA3 transporter gene have been frequently implicated in severe neonatal lung disease and chronic lung disease in older individuals.[32] The genes for ATP-Binding Cassette (ABC) transporters encode membrane proteins involved in the transport of compounds across biologic membranes, and 14 ABC genes have been associated with distinct genetic diseases in humans till now.[33] Mutations in the gene encoding ABCA3 have been found in children with severe neonatal respiratory disease and older children with some forms of interstitial lung disease.[34] ABCA3 mutations are not confined to a single group, and infants from several major racial or ethnic groups can be affected. Generally, this disease presents within first few days of life in full-term infants, with clinical and radiographic features suggestive of surfactant deficiency. Newborn infants are present with grunting, chest retractions and cyanosis followed by rapidly progressive respiratory failure. Diffuse air space consolidation, air bronchograms and reticular–granular infiltrates are seen on chest radiographs.

Most of these patients are refractory to conventional therapies like lung-protective ventilation and ECMO, resulting in respiratory failure and death in the first months of life. Respiratory failure does not respond to the surfactant replacement therapy, and lung transplantation is the only known treatment for this disease. Some infants can also present with persistent pulmonary hypertension of the newborn.[35] Alveolar proteinosis, interstitial thickening, hyperplasia of alveolar type II cells, loss of normal alveolar structure, and features of Desquamating Interstitial Pneumonia (DIP) are certain ultrastructural findings associated with ABCA3 mutations.

ABCA3 gene mutation related lung diseases are inherited in an autosomal recessive manner with phenotypic heterogeneity ranging from fatal to milder forms. Certain forms of Pediatric ILD (pILD) particularly DIP, chronic pneumonitis of infancy, and nonspecific interstitial pneumonitis have been related to the ABCA3 mutations.[34] Some of these children may have a family history of neonatal lung disease. The mechanism for decreased severity of lung disease in these children remains unclear, but it is speculated that it may be related to reduced function rather than complete absence of the ABCA3 protein. It has also been suggested that ABCA3 can be a candidate gene for other pulmonary disorders involving surfactant dysfunction, including the neonatal respiratory distress syndrome and disorders with a later onset such as asthma and the acute respiratory distress syndrome.[32]

Nucleotide sequencing of the gene in infants and children with refractory pulmonary disease may confirm the diagnosis of ABCA3-related lung disease. Nonsense and frameshift mutations, as well as mutations in highly conserved residues and in splice sites of the ABCA3 gene can be identified in the affected group.[32] The E292V mutation in particular is responsible for the genetic etiology of pILD related to abnormal surfactant function.[34] Electron microscopy of lung tissue from affected patients demonstrates the presence of small, atypical lamellar bodies in alveolar type II epithelial cells and the absence of tubular myelin in the airways, indicating an abnormality in intracellular and extracellular lipid homeostasis.

Acute Respiratory Distress Syndrome (ARDS)

ARDS is characterized by sudden onset, impaired gas exchange, decreased static compliance, and by a non-hydrostatic pulmonary edema.[36] Surfactant production decreases due to diffuse lung injury in ARDS, presumably because the alveolar epithelium becomes damaged. Damage to the alveolar Type I cells lead to an influx of protein-rich edema fluid into the alveoli, as well as decreased fluid clearance from the alveolar space. Neutrophils are attracted into the airways by host bacterial and chemotactic factors and express enzymes and cytokines, which further damage the alveolar epithelial cells. Type II epithelial cell injury leads to a decrease in surfactant production, with resultant alveolar collapse. In ARDS, lavage phospholipid, SP-A and SP-B are decreased, and the ratio of small to large aggregates is significantly increased compared with that in non-ARDS patients. Thus, ARDS leads to both deficiency in pulmonary surfactant constituents and inhibition of the activity of the remaining surfactant. This secondary surfactant deficiency may contribute to the disordered mechanical behavior of the lung in ARDS.

Despite the introduction of novel treatments, the mortality from ARDS still remains high. In a single study, the use of surfactant in younger children with ALI was effective in reducing ventilator days and increasing survival.[37] However, most other clinical studies of Surfactant Replacement Therapy (SRT) in adults and children have not shown significant improvement in lung functions; perhaps due to the complex nature of the lung injury in ARDS.[38-40] Therefore, routine SRT for adult patients with ARDS cannot be recommended based on the current data.

Meconium Aspiration Syndrome (MAS)

Meconium aspiration syndrome is also a significant cause of respiratory insufficiency in neonates. When aspirated into fetal lungs, meconium particles mechanically obstruct the small airways. Meconium or the chemical pneumonitis it causes inhibits surfactant function, and inflammation of lung tissue contributes further to small-airway obstruction. Acute intrapulmonary meconium contamination induces a concentration-dependent pulmonary hypertensive response, with 15% to 20% of infants with the meconium aspiration syndrome demonstrating persistent pulmonary hypertension.

Meconium causes surfactant inactivation by multiple mechanisms. It is now known that the fibrillary structure of surfactant is destroyed by the meconium and its surface adsorption rate also decreases.[41] The presence of elevated cell count and proinflammatory cytokines IL-1β, IL-6 and IL-8 as early as in the first six hours suggests that MAS is associated with an inflammatory response. Phospholipase-A_2 (PLA_2) present in meconium, has been found to inhibit the activity of surfactant *in vitro* in a dose-dependent manner, through the competitive displacement of surfactant from the alveolar film. PLA_2 is also known to induce hydrolysis of DPPC, releasing free fatty acids and lyso-PC, which damage the alveolar-capillary membrane and induce intrapulmonary sequestration of neutrophils.[42]

Exogenous surfactant replacement either as bolus therapy or with a diluted surfactant lung lavage have been shown to reverse the hypoxemia and reduce pneumothoraces caused by meconium aspiration, decrease requirement for Extracorporeal Membrane Oxygenation (ECMO), decrease duration of oxygen therapy and mechanical ventilation, and reduce the duration of hospital stays.[43] There is no difference in the different surfactant treatment regimens and it may be related to the heterogeneous nature of this form of lung injury.[44]

Pulmonary Hemorrhage

Pulmonary hemorrhage occurs due to the rise in lung capillary pressure, which could be multifactorial, such as due to the effects of hypoxia, volume overload, congestive heart failure, or trauma induced by mechanical suctioning of the airways. There is a build up of the capillary filtrate in the interstitial space, which can then burst through into the airspaces through the pulmonary epithelium. In addition to the plasma proteins, neutrophils are released, which in turn express proteases, oxygen free-radicals and cytokines. The free oxygen radicals damage type II cells, which decreases surfactant production. Serum albumin, globulin and fibrinogen reduce the rate of adsorption, and increase the minimum surface tension of the surfactant film. The probable mechanism for the increase in surface tension is the competition of plasma proteins with the surfactant, for the interface. Elastase, one of the proteases, damages and degrades SP-A, thereby inhibiting SP-A mediated surfactant lipid aggregation and adsorption *in vitro*.[45] Surfactant replacement therapy may be partially effective in such cases.

Pulmonary Alveolar Proteinosis

Pulmonary Alveolar Proteinosis (PAP) is a rare disorder caused by abundant accumulation of surfactant-derived components in the lungs. The characteristic pathological feature is the filling of alveoli and distal bronchioles with surfactant-derived material that is granular, acidophilic, acellular and amorphous. The substrate stains for periodic acid Schiff and is nearly identical to surfactant. The material consists of approximately 90% lipid (primarily phospholipids), 10% protein, and 1% carbohydrate and is usually sterile.[26] It has been demonstrated that the interruption of GM-CSF signaling in the lung results in pulmonary alveolar proteinosis. (See Chapter 166 for clinical details).

GM-CSF initiated signaling plays unique role in alveolar macrophage function and pulmonary homeostasis, including terminal differentiation and the survival of macrophages, intracellular lipid metabolism, surfactant catabolism and recycling, expression of pathogen receptors, and phagocytosis and killing.[26] Interruption of GM-CSF signaling in the alveolar macrophage either by the absence of the gene encoding GM-CSF or its receptor in mice or, by neutralizing anti-GM-CSF autoantibodies in humans, impairs the catabolism of surfactant by alveolar macrophages. These results in the intracellular build up of membrane-bound concentrically laminated surfactant aggregates. Progressive expansion of the extracellular surfactant pool and accumulation of cellular debris due to the impaired catabolism eventually cause filling of the alveoli, thus reducing the size of the available gas-exchange surface and eventually leading to the clinical syndrome.[7] Current standard of therapy for acquired PAP is whole lung lavage and GM-CSF therapy in selected group of patients.

CONCLUSION

Clinical investigations, research in transgenic mice, and translation of findings from the bench to the bedside have considerably improved our concepts of the pathogenesis and treatment of the diseases linked to the altered surfactant metabolism. Besides, their role in regulating surface activity, the surfactant components may also play in the local immune regulation of the lungs. Except for respiratory distress syndrome in the premature infant, where surfactant deficiency has been unequivocally demonstrated and exogenous surfactant substitution is now part of the routine clinical management, the contribution of surfactant therapy is currently under investigation in a variety of disease states.

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12

Respiratory Defenses and Immunology

Padmavathi Ramaswamy, Padma Srikanth, Vijayalakshmi Thanasekaraan

INTRODUCTION

A moderately active person inhales about 20,000 liters (15 kg) of air every 24 hours, while his food and water consumption for the same period are only about 1.5 kg and 2 kg respectively. Very little selectivity can be exercised over the inhaled materials as compared to the control one has over what is ingested. So, the respiratory tract is constantly exposed to the external ambient environment. The respiratory tract is exposed to environmental toxic substances, such as the smoke, soot, dust and chemicals in the atmosphere, and also to a wide range of organisms such as viruses, bacteria, fungi and parasites. It has been calculated that the average individual inhales about 8 microorganisms per minute or about 10,000 per day. The magnitude of this atmospheric insult on the respiratory tract is much greater in the developing countries. The vulnerability of individuals to these inhaled substances varies widely depending on age, atopic status, nutrition and coexisting conditions. In India, the Acute Lower Respiratory Infection (ALRI) is thought to be responsible for about 490,000 deaths annually, responsible for nearly 1.5% of the entire global burden of disease among children under five years of age.[1] It is, therefore, vital for respiratory clinicians to have a clear understanding of the normal defenses of the respiratory tract.

The defense against foreign material within the lungs is a critical physiological function. This is accomplished by passive mechanisms, such as the branching nature of the respiratory tract and the regulation of airway lining fluid composition. The first line of respiratory defense consists of mechanisms, such as the physical barrier; reflexes, including sneezing and coughing; production of mucus; mucociliary clearance; transport of IgA and antimicrobial mediators (defensins, lysozyme, lactoferrin, lectins). The second-line of defense mechanisms include the innate immunity and the acquired immunity (Table 12.1). These defenses can be overcome by a large number of organisms and inhibitory factors of pathogens, by compromised effectiveness resulting from air pollutants (e.g. cigarette smoke, ozone) or interference with protective mechanisms (e.g. endotracheal intubation or tracheostomy) or genetic defects (e.g. cystic fibrosis). Following exposure to airborne microorganisms (bioaerosols) in air, the defense mechanisms are able to eliminate most of the larger microorganisms; however,

TABLE 12.1: Defense mechanisms of respiratory tract

Anatomical site	*Defense mechanism*
Conducting zone of respiratory tract (Nose, Nasopharynx, Larynx, Tracheobronchial region excluding the respiratory bronchioles)	Mechanical barrier Lymphoid tissue: adenoids, tonsils, Waldeyer's ring NALT, BALT Mucociliary clearance mechanism Secretory IgA Sneeze and cough reflex
Gas exchange region (Terminal or respiratory bronchioles and alveoli)	Alveolar macrophages Immunoglobulins (humoral immunity) Cell-mediated immunity Polymorphonuclear granulocytes

NALT: Nasopharynx-Associated Lymphoid Tissue
BALT: Bronchus-Associated Lymphoid Tissue

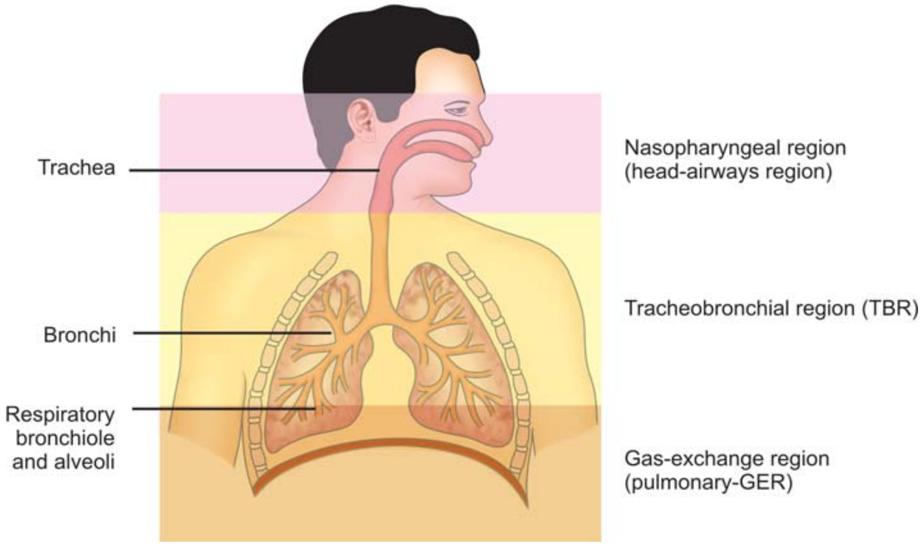

Trachea
Bronchi
Respiratory bronchiole and alveoli
Nasopharyngeal region (head-airways region)
Tracheobronchial region (TBR)
Gas-exchange region (pulmonary-GER)

Fig. 12.1: Regions of respiratory tract

smaller particles and spores may be trapped within the lung tissue, which pose health risks. The impact on health depends on the interaction between genetic differences in the host, agent and environments (duration and exposure dose).

PARTICLE DEPOSITION IN THE RESPIRATORY TRACT

Three regions of respiratory tract have been described based on the deposition of the particles (Fig. 12.1): The nasopharyngeal region or Head Airways Region (HAR) {anterior nares to larynx}, the Trachea-Bronchial Region (TBR) {trachea, ciliated bronchial airways till terminal bronchioles}, and the pulmonary region or Gas Exchange Region (GER) {respiratory bronchioles, alveolar sacs and alveoli}. The particle deposition in HAR is primarily limited to large sized particles that are 10 µm or above. Particles that are 1–10 µm are deposited throughout the respiratory tract, but as the size decreases to 1 µm, these particles can reach the trachea-bronchial region and GER. As the size diminishes below 0.5 µm, the probability of deposition again increases particularly in pulmonary region and to a lesser extent in the trachea-bronchial region.[2,3]

The deposition probability of particles based on the size, in each region can sometimes be used to relate to the anatomical locations of various diseases, e.g. nasal cancer in woodworkers where the airborne particle size is above 10 µm in aerodynamic diameter. The three principal mechanisms for particle deposition are sedimentation, impaction and diffusion. There are several mechanism of clearance, such as dissolution of relatively soluble material with absorption into the systemic circulation, direct passage of particles into the blood, phagocytosis of particles by macrophages, transfer of particle to lymphatic channels and lymph nodes. A proportion of insoluble particles depositing in GER becomes sequestrated either in immotile macrophages or in fixed tissue over a long period of time contributing to cumulative lung burden.

THE DEFENSE MECHANISMS OF CONDUCTING ZONE OF THE AIRWAYS

The upper respiratory tract performs several essential physiological functions, such as filtration, olfaction, phonation, microbial defense and conditioning the air that is inhaled, to maintain a suitable temperature and humidity. The mucosal surfaces of the nasal passages are important for conditioning air before it reaches the more delicate alveolar tissue. Many mucosal glands provide moisture for humidification and mucus to adhere the inhaled dust.

Anatomical Defenses

The anatomy of the upper respiratory tract is composed of many features that help to get rid of particles and pathogens. The inside of the nose is lined with hairs, which filters larger particles that are inhaled. The turbinate bones are covered with mucus that collects particles, which are not filtered by nasal hair. Usually, particles 5–10 μm in diameter are either trapped by nasal hair or adhere to the nasal mucosal surfaces. The anatomy of the upper airway is such that it causes many of the larger airborne particles to impinge on the back of the throat.

Most of the surfaces of the upper respiratory tract are colonized by normal flora. These organisms are regular inhabitants of these surfaces and rarely cause disease. The regular inhabitants of the nose, nasopharynx and oropharynx include *Staphylococcus aureus*, *S. epidermidis* and *nonencapsulated H. influenza.* The normal flora of these areas play a role in maintaining the healthy state of the host by competing with pathogenic organisms for potential attachment sites and often produce substances (toxins or acids), which are bactericidal. There are no resident bacteria in the lower respiratory tract.

Lymphoid Tissue

The adenoids and tonsils are lymphoid organs in the upper respiratory tract that are important in developing an immune response to pathogens and are located in an area where many of these airborne particles are in contact with the mucosal surface. Tonsils consist of localized lymphoid tissue located in the mucosa of the pharynx. Each tonsil consists of an epithelial crypt surrounded by the dense clusters of lymph nodules. At the center of each lymph nodule is a "germinal center" where the lymphocytes proliferate. Pharyngeal tonsils (also called "adenoids") provide sites where immune surveillance cells (lymphocytes) can encounter foreign antigens, which enter the body through inspired air.

The Nasal-Associated Lymphoid Tissue (NALT) consists of the lingual, palatine and nasopharyngeal tonsils, the Waldeyer's ring (Fig. 12.2). Inhaled allergens first encounter the NALT, which is more developed than the bronchus-associated lymphoid tissue. The NALT drains into the cervical lymph nodes. The respiratory tract contains lymph nodes in the mediastinum, hilar areas of the lung and submucosal aggregates present along the airways at branching points. The lymphoid aggregate with a specialized epithelium in the bronchial lamina propria is called Bronchus-Associated Lymphoid Tissue (BALT) (Fig. 12.3), similar to the organized lymphoid tissue of the gut (GALT), e.g. Peyer's patches. The BALT at branching points of the airway is likely to contribute to local immunity. BALT formation following pulmonary infections is coordinated by mediators such as macrophages, dendritic cells, lymphocytes, fibroblasts and endothelial cells.[4] There are dendritic cells present in the airways, which are the antigen-presenting cells that constitutively express a high level of MHC (class II) antigen.[5,6] Dendritic cells become more numerous in response to inhaled antigens and rapidly decrease in number after treatment with glucocorticoids. Dendritic cells after binding with antigens in peripheral airways, migrate via lymphatics to the T-cell-dependant areas of regional lymph nodes, such as BALT and Lung-Associated Lymph Node (LALN), where they encounter naive lymphocytes and initiate a primary immune response. While BALT performs an essential immunologic function such as sustaining the immunity in airways, hyperplasia of this structure may contribute to bronchial pathology. In the overall immune response, BALT plays a minor role.

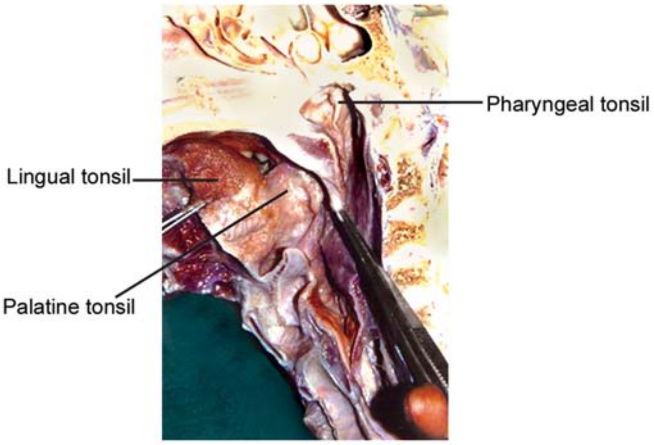


Fig. 12.2: Lymphoid tissue (Waldeyer's ring) (*Courtesy:* Dr Melani Rajendran, Department of Anatomy, SRU)

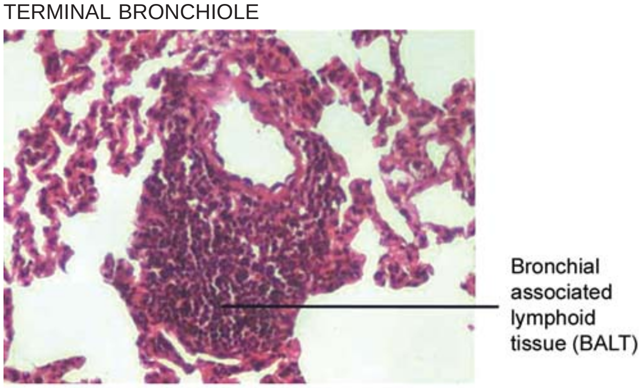


Fig. 12.3: Lymphoid tissue (BALT) (*Courtesy:* Dr Melani Rajendran, Department of Anatomy, SRU)

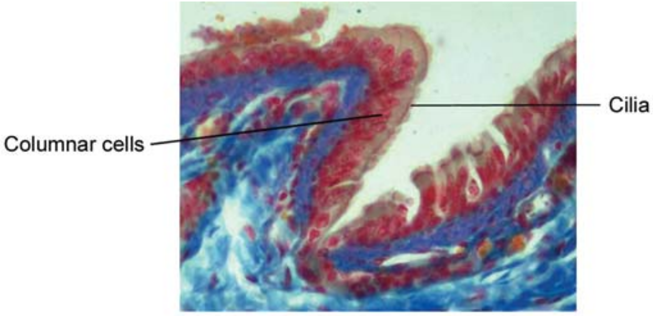


Fig. 12.4: Pseudostratified ciliated columnar epithelium (*Courtesy:* Dr Melani Rajendran, Department of Anatomy, SRU)

Mucociliary Clearance Mechanism

The respiratory tract, from the nasal cavity through the bronchi, is lined by ciliated, pseudostratified columnar epithelium with goblet cells. Bronchioles are lined by simple cuboidal epithelium and the lung alveoli are lined by very thin simple squamous epithelium. Pseudostratified respiratory epithelium consists primarily of columnar ciliated cells (Fig. 12.4). Subepithelial cells secrete mucus. The respiratory tract lined with ciliated epithelium is surrounded by thick connective tissue and smooth muscle. Scattered among the ciliated cells are occasional goblet cells. Basal cells are the source of replacement of ciliated and goblet cells.

Respiratory pathogens that reach the respiratory tract are trapped in the mucus layer and are driven upwards by ciliary action (the mucociliary elevator or mucociliary escalator) to the back of the throat.[7] The mucus gel acts as a barrier for bacteria wherein these organisms adhere. The mucus may then be swallowed or coughed out. The sneeze and cough reflexes are important mechanisms for clearing material that accumulates in or irritates the respiratory tract.

i. *Cilia:* The two human lungs contain approximately 0.5 m^2 of ciliated epithelia, with a total number of cilia in the order of 3×10^{12}. Nasal cavity, paranasal sinuses, pharynx, layrnx, trachea are lined by ciliated epithelium. Immediately below the larynx, the tracheobronchial tree is formed by a pseudostratified ciliated columnar epithelium, up to the sixteenth bronchial division of Weibel.[8] The ciliated cells, characterized by their cytoplasmic projections and numerous microvilli, have about 200 cilia.[1] Each cilium has length of 5–7 µm in the trachea and 2–3 µm in the seventh airway generation and a diameter of 0.25–0.33 µm. Cilia beat 600–1,000 times a minute. Cilia are structurally analogous to flagella, where the motion is dependent on the ATPase dynein. As ATP is metabolized, the structural proteins of the cilium change their configuration so that the cilium moves. Cilia move in a characteristic fashion that makes the overlying mucus to move in one direction only towards the pharynx.[9]

ii. *Airway Mucus:* The airway epithelium is covered by a thin layer of Airway Surface Fluid (ASF). The airway surface fluid consists of both a periciliary aqueous layer and an overlying mucus layer. ASF from healthy airways contains approximately 45% Na^+ and Cl^- and 600% more K^+ than plasma. ASF in normal subjects is hypotonic than plasma.[10] The ionic composition of the ASL is assumed to be important for airway function and may be altered in diseases such as cystic fibrosis and exercise-induced asthma.[11] In patients with sustained airway irritation, infection or cystic fibrosis, the ASF composition becomes more isotonic than that of plasma.[12]

The mucus layer is primarily produced by mucus glands in the larger airways and goblet cells in the more peripheral airways. Another type of secretory cell, Clara cell is present in small ciliated bronchioles, which changes to goblet cell in certain disease states.[13,14] Over 125 ml of mucus is secreted each day and forms a continuous sheet like a mucus blanket that covers respiratory tract. The respiratory mucus contains products from several sources, such as the alveolar liquid and secretory products from a variety of cells along the surface of conducting airways. Mucus is composed of $\geq$ 95% of water and approximately 1% of salts and other dialyzable components, 0.5 to 1% free protein and a similar proportion of carbohydrate-rich glycoproteins or mucins.[15] The physical properties of mucus are provided mainly by mucins, which are mucoglycoproteins and proteoglycans secreted from the surface of epithelial cells and from the glands. Phospholipids are also secreted by the epithelial cells and submucosal glands of the airways weakening the adhesion of the mucus and thereby altering its physical properties. Spinability, non-Newtonian viscosity, elasticity, shear thinning (thixotrophy) are some of the rheological properties of the viscoelastic mucus gel of respiratory tract.[16,17] In addition it also possesses properties, such as adhesivity and wettability that determine the capacity of the mucus to protect, hydrate and lubricate the underlying airway epithelium.[18]

Mucus also carries some important bactericidal substances, which contribute to lung defenses such as the secretory IgA, lysozyme, lactoferrin and peroxidases.[19] Lysozyme is a muramidase that degrades a glycosidic linkage of bacterial membrane peptidoglycans. The role of lysozyme as an antibacterial substance is well-known. Besides lysozyme, bronchial secretions contain other antimicrobial substances, such as N-AcetylMuramyl-L-Alanine Amidase (NAMLAA) and β-defensins such as Human Beta Defensins-1 (hBD-1) and hBD-2, and pulmonary lectins and surfactant collections. At a cellular level, lung epithelial cells express S100a, antileucoprotease and large amounts of Major Vault Protein (MVP). In cells infected with *Pseudomonas aeruginosa*, MVP-1 localizes in lipid raft sections of cell membranes and helps to mediate bacterial clearance. The iron binding proteins, such as lactoferrin may reduce the availability of elemental iron that is a cofactor for bacterial replication. However, in addition, lactoferrin may also be bactericidal by binding to endotoxin. The secretory peroxidases (lactoperoxidases) or those from leukocytes (myeloperoxidases) act on thiocyanate ions or produce oxygen radicals, which are bacteriostatic or bactericidal. Epithelial cells are important sources of compounds, such as glutathione that act as antioxidants. They also produce nitric oxide, which has antimicrobial properties. Epithelial cells also actively participate in host defense against inflammation. These cells are capable of producing and responding to a variety of eicosanoids, cytokines and growth factors, which form a complex network regulating inflammatory responses. They also express cell surface receptors that can interact directly with inflammatory cells.

iii. *Mast Cells:* Mast cells store or generate a number of substances, such as histamine, leukotrienes, specific chemotactic factors and proteases, which have potent inflammatory effects. Mast cells are present in mammalian lung in the bronchial wall, in the epithelium itself, and in airway lumen. Evidence implicating mast cells in the induction of airway muscle constriction and mucosal inflammation includes direct studies of mast cell secretion, measurement of histamine release and inhibition of asthmatic reactions with antihistamines and with the inhibitor of mast cell degranulation, sodium cromoglycate. Definitive evaluation of the role of the mast cell in asthma remains unknown, in part because of the general hyperactivity of airway smooth muscle in asthmatics.

iv. *Mucociliary Transport:* Approximately, 90% of inhaled particles with a diameter larger than 2–3 μm are deposited on the mucus overlying the ciliated epithelium. Mucus is propelled by ciliary movement. The particles are transported from the terminal bronchioles to the trachea by the ciliary beats with the mucus. This motion called mucociliary transport occurs at a speed varying between 100 and 300 μm s^{-1}. Mucus acts as a physical and chemical barrier onto which particles and organisms adhere. It is further propelled to the oropharynx where it is either swallowed or expectorated. Cilia start moving from the resting position by bending sideways and backwards. This is called recovery stroke.[20,21] This is followed by an effective stroke during which the cilia move in a plane perpendicular to the cell surface. During this active phase, the tip of the cilia engages in the overlying mucus and sweep it in a cephalic direction. The cilium moves in a layer of periciliary fluid whose depth is a little less than the ciliary length. The overlying mucus is only penetrated by the ciliary tips in the effective stroke and not in the recovery stroke, thereby optimizing the propulsive force of the ciliary beating on mucociliary transport. The thickness of the periciliary layer is critical for effective propulsion of mucus. A wide range of Ciliary Beating Frequencies (CBF) is observed in the central airways.[22] Differences in CBF may be attributed to changes in temperature and humidity. The presence or absence of mucus and the load of mucus may also play a role in determining the CBF. CBF decreases with increasing age.

v. *Factors Affecting Mucociliary Clearance:* Physiological factors such as age, posture, sleep and exercise affect mucociliary clearance. Number of cilia, their structure, activity and coordinated movement are required for normal functioning of the mucociliary clearance.[23,24] Temperature of 37°C and an absolute humidity of 44 mg/dm^3 corresponding to a relative humidity of 100% is required for optimum functioning of cilia. High humidity enhances the functionality of the mucociliary clearance. Mucociliary clearance is also affected by certain risk factors such as malnutrition, exposure to air pollution and smoking. Malnutrition affects the integrity of mucosal epithelial cells. Air pollutants, such as sulfur dioxide, nitrogen dioxide and ozone are known to affect the functioning of the mucociliary mechanism.[25-27] Hair spray exposure is known to depress the tracheal mucous velocity. Cigarette smoke causes excess mucus production, paralyses the cilia and allows mucus to accumulate so that smokers have to cough to clear the secretions. Chronic smoking induces an increased number of abnormal cilia, which causes impairment of tracheobronchial clearance. The ultrastructural ciliary damage seems to be nonreversible, even after a long period of smoking cessation.[28]

Mucociliary clearance is altered in several airway diseases where structural damage to the epithelium or alteration of the mucus composition increases bacterial adhesiveness. Bacterial products, some of which are ciliotoxic may, furthermore, alter the mucociliary clearance. This is true for the *Pseudomonas aeruginosa*-derived elastase.[29] Mucociliary clearance is altered in asthma, chronic bronchitis and cystic fibrosis.[30,31] An abnormal structure of the cilia has been observed in airway diseases, such as chronic bronchitis and in congenital diseases, such as the primary ciliary dyskinesia syndrome ciliary immobility and interciliary discoordination with virtually absent mucociliary clearance. In cystic fibrosis, the most common mutation results in a defective transmembrane receptor protein, which is responsible for mediating cyclic AMP-induced increase in chloride secretion. The resulting alterations in the epithelial overlying fluid composition are believed to lead to poor bacterial clearance.[32]

Cough Clearance Mechanism

Cough is an important defense mechanism. Cough is classically described as a very deep breath, followed by a forced expiration against a closed glottis, which opens suddenly to produce the expulsive phase (Fig. 12.5). This

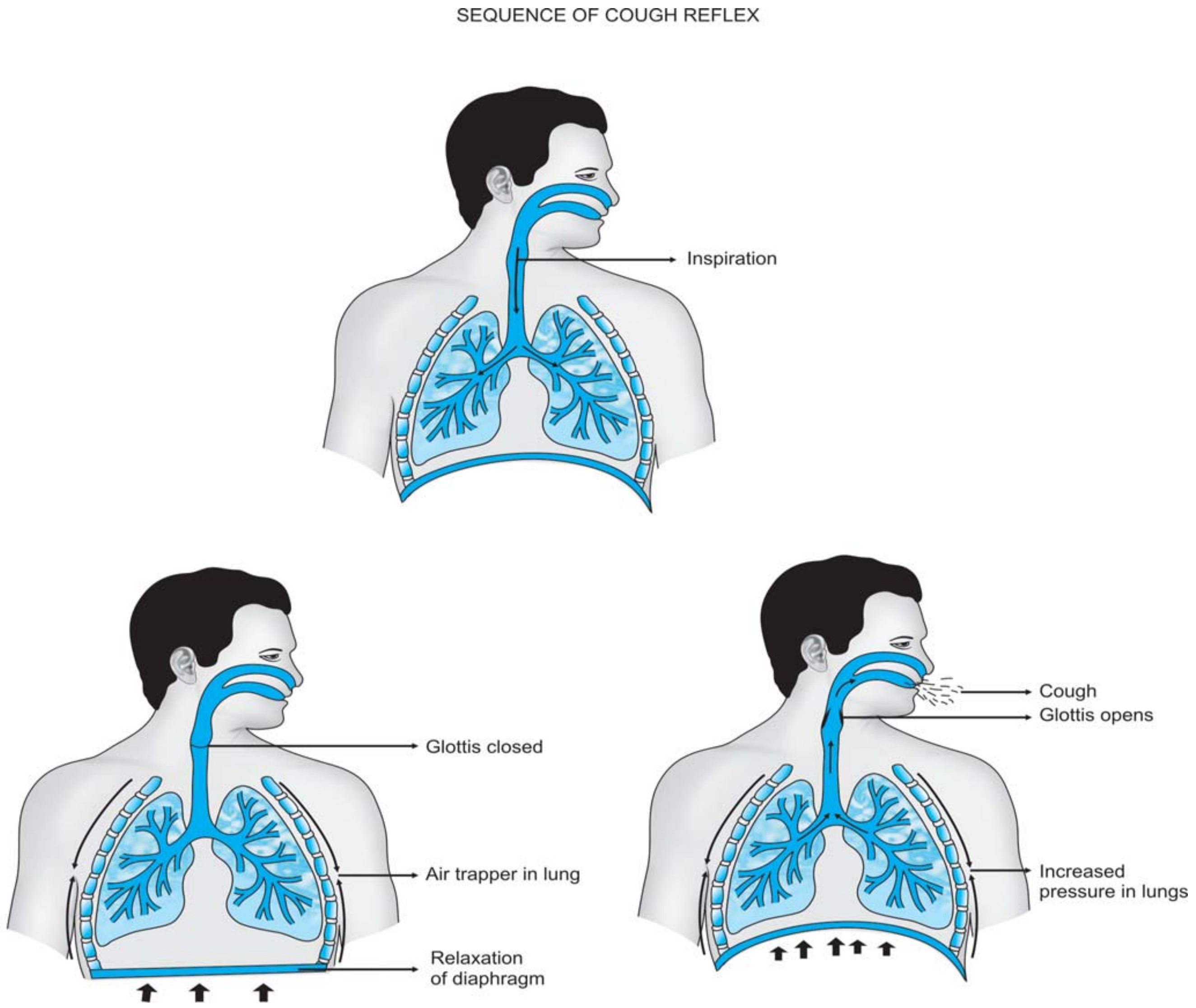
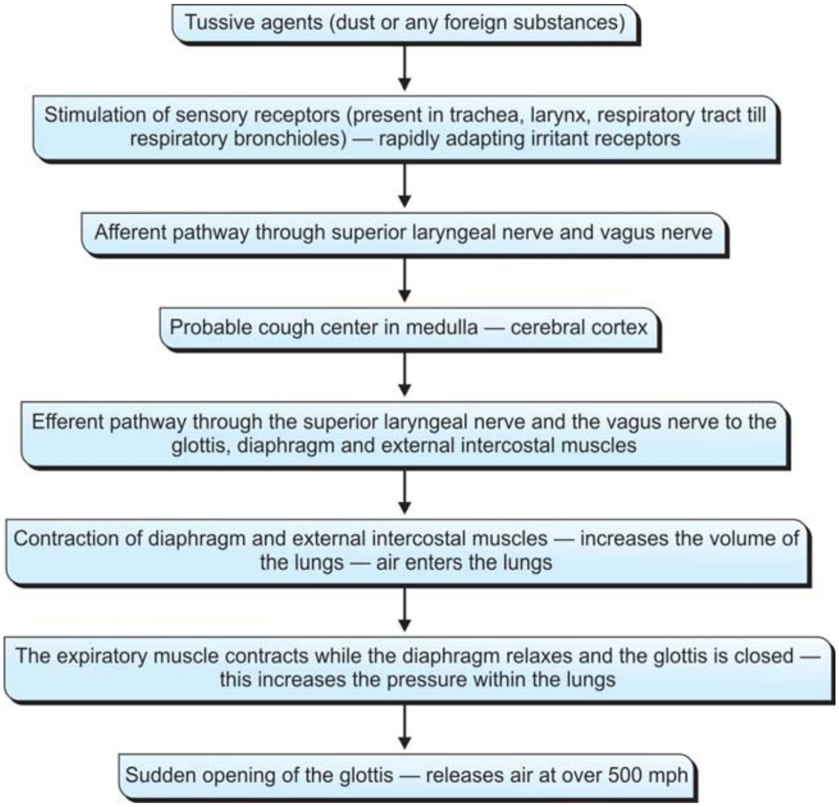


Fig. 12.5: Mechanism of cough reflex

Flow chart 12.1: Mechanism of cough reflex



Tussive agents (dust or any foreign substances)

Stimulation of sensory receptors (present in trachea, larynx, respiratory tract till respiratory bronchioles) — rapidly adapting irritant receptors

Afferent pathway through superior laryngeal nerve and vagus nerve

Probable cough center in medulla — cerebral cortex

Efferent pathway through the superior laryngeal nerve and the vagus nerve to the glottis, diaphragm and external intercostal muscles

Contraction of diaphragm and external intercostal muscles — increases the volume of the lungs — air enters the lungs

The expiratory muscle contracts while the diaphragm relaxes and the glottis is closed — this increases the pressure within the lungs

Sudden opening of the glottis — releases air at over 500 mph

allows enough turbulence and shearing forces in the major bronchi and trachea to extrude material such as debris, infected mucus or products of epithelial damage. The cough is triggered by a very wide variety of stimuli: Mechanical, chemical or inflammatory. It is triggered by irritant receptors in the airways is mediated by the vagus nerve. The cough receptors or rapidly adapting irritant receptors are located mainly on the posterior wall of the trachea, pharynx, at the main carina and at branching points of the large airways. Cough promotes clearance by establishing high shear rates at the epithelial surface. Air forced over the mucosal surface at a sufficiently high velocity, generates lateral force that moves large particles in the direction of air flow. Within certain limits, this process is facilitated by the pliable nature of the walls of peripheral airways. During the forced expiration phase of a cough, the airways are narrowed by the rise in intra-thoracic pressure. The medulla regulates the special breathing pattern that characterizes coughing.

Mechanism of cough reflex is also shown in Flow chart 12.1.

Cough serves as a protective mechanism when mucociliary clearance fails especially in patients with Primary Ciliary Dyskinesia (PCD), also known as immotile ciliary syndrome or Kartagener Syndrome (KS).[13,33] Sneezing is also a protective reflex stimulated when the nasal mucosa is irritated. A series of short inspirations is followed by an explosive expiration, through the mouth, the nose or both. This explosive force carries droplets for long distances, a common means of spreading disease.

THE DEFENSE MECHANISMS OF RESPIRATORY ZONE OF THE AIRWAYS

Most of the respiratory passageways, from the nasal cavity through the bronchi, are lined by ciliated, pseudo-stratified columnar epithelium with goblet cells. Bronchioles are lined by simple cuboidal epithelium and the alveoli by very thin simple squamous epithelium (Fig. 12.6). The squamous epithelial cells of the alveolar walls are sometimes called Type I pneumocytes. This epithelium is exceedingly thin to facilitate diffusion of

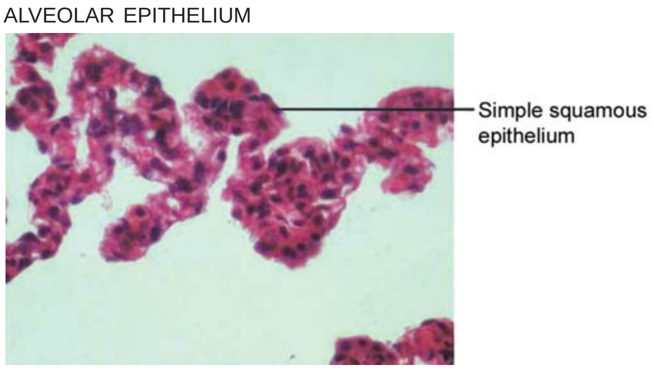


Fig. 12.6: Simple squamous epithelium
(*Courtesy:* Dr Melani Rajendran, Department of Anatomy, SRU)

oxygen and CO_2. The alveolar walls also contain cuboidal surfactant-secreting cells. The surfactant overcomes the tendency of alveolar walls to adhere to one another (which would obliterate the air space). As the epithelium of the respiratory or terminal bronchioles and alveoli are not ciliated, immune effector cells, primarily macrophages, are the dominant mechanism for clearance.

Allergens, toxic particles, microorganisms that have escaped the mucociliary transport system are cleared by the alveolar macrophages by phagocytosis. These alveolar macrophages are sometimes called "dust cells" (Fig. 12.7). Alveolar macrophages provide the defense by phagocytosis, and ingestion of foreign material (Fig. 12.8). Once they have engulfed the material, they may remain in the alveoli, may be cleared along the mucociliary clearance mechanism or may be cleared by lymphatics.[34,35] Alveolar macrophages promote both nonspecific immune responses, such as the production of cytokines (including IL-1, IL-6, tumor necrosis factor, interferon-γ) that mediate an acute-phase response that develops regardless of the inciting microorganism and specific immune response by participating in the production of a variety of antibodies, complex glycoproteins known as immunoglobulins that bind to specific microbial antigenic targets.[36,37] Antibodies can help eradicate the infecting organism by attracting the host's WBCs and activating the complement system. Alveolar macrophages are a phagocyte as well as an effector cell, which initiate immune response. The role of alveolar macrophages in lung immunology is discussed subsequently.

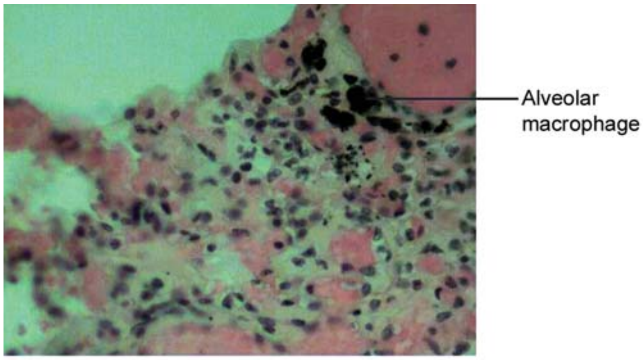


Fig. 12.7: Alveolar macrophages
(*Courtesy:* Dr Melani Rajendran, Department of Anatomy, SRU)

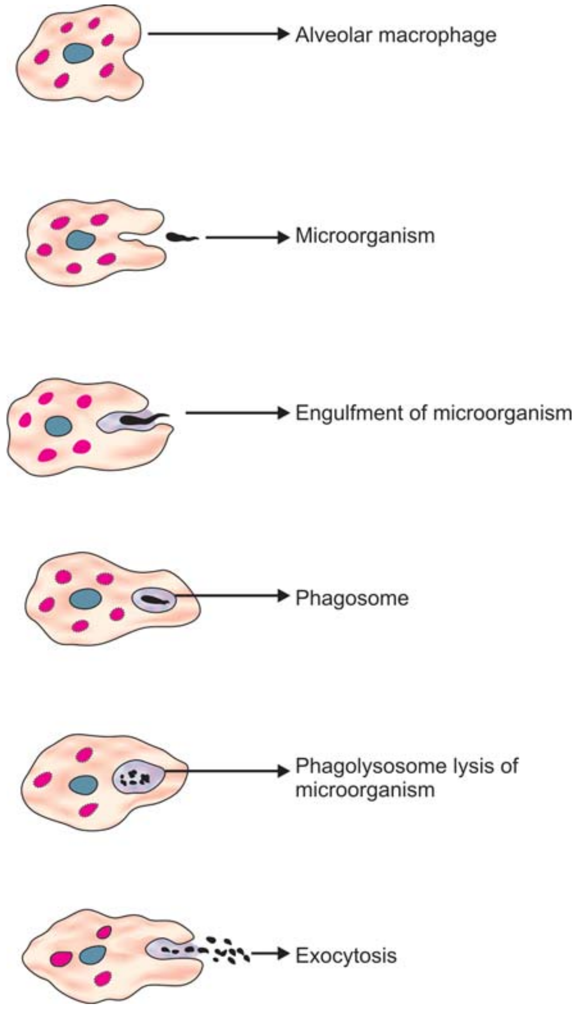

Alveolar macrophage
Microorganism
Engulfment of microorganism
Phagosome
Phagolysosome lysis of microorganism
Exocytosis

Fig. 12.8: Stages of phagocytosis

SURFACTANT AND SURFACTANT PROTEIN A (SP-A)

Pulmonary surfactant is a surface-active lipoprotein complex formed by type II pneumocytes. Pulmonary surfactant is critical for maintaining the alveolar stability and gas exchange. Surfactant protein A was the first surfactant protein identified by its association with surfactant lipid. Surfactant protein, B, C and D have also been identified. Surfactant protein A binds to a variety of microorganisms, including viruses, bacteria, mycobacteria, fungi and pneumocystis. Among viruses, SP-A binds influenza, herpes simplex and respiratory syncytial viruses.[38,39] SP-A also binds to and increases phagocytosis of *Streptococcus pneumoniae*, group A *Streptococcus* and *S. aureus*, may bind to peptidoglycan (an important component of the cell wall of gram-positive bacteria). It may not bind to peptidoglycan directly, but inhibits the effect of peptidoglycan by binding to toll like receptor 2.[40] SP-A binds to rough Lipopolysaccharide (LPS), aggregates these gram-negative bacteria and increases phagocytosis, however, it poorly binds to the smooth variants of *Escherichia coli*.[41]

SP-A enhances the adherence and phagocytosis of mycobacteria and fungi, such as *Aspergillus*, by binding the conidia, enhancing their phagocytosis and killing, by human neutrophils and alveolar macrophages.[42] SP-A also binds to and inhibits the growth of mycoplasma, but does not clear the infections, even if it binds to *Pneumocystis jeroveci*.[43]

RESPIRATORY IMMUNE MECHANISMS

The human host is armed with a wide variety of sensors to detect an invading pathogen. The successful clearance of airborne microorganisms follow Pathogen-Associated Molecular Patterns (PAMPs) that bind specific recognition molecules and activate innate immune pathways.

Innate Immunity

The most frequently detected PAMPs in bioaerosols are endotoxins (present in gram-negative bacteria), peptidoglycan (present in gram-positive bacteria) and glucans[44] another PAMP recognition molecule, TLR4 (toll like receptors), allow for endotoxin signaling to be achieved. Microbes that penetrate an epithelial barrier and enter a tissue site encounter three types of sentinel immune cells in the tissues: Tissue macrophages, mast cells and immature dendritic cells. These cells act like guards to differentiate between apoptotic particles generated by normal tissue turnover and particles that are indicative of infection.

The molecules mainly responsible for making this important distinction are those of the family of TLRs.[45] TLR proteins are pattern recognition proteins that obtain their name from the Drosophila Protein Toll with which they share sequence similarity.[46] Although Toll was originally shown to be of importance for dorsal-ventral patterning in fly embryos, generation of adult flies expressing mutant toll revealed that this transmembrane receptor also served as a critical component of host immunity against fungal infection. Toll was shown to be important for host defense against pathogens, because engagement of this receptor induced the production of several antimicrobial peptides (e.g. defensins). Ten distinct mammalian TLRs have been identified and agonists have been identified for some (TLR2, TLR3, TLR4, TLR5, TLR7, TLR8, and TLR9), but not for all of these TLR proteins.

Immune cells develop tolerance to repeated increased expression of TLR4 on the cell surface which leads to inflammatory response to lipopolysaccharide. Respiratory syncytial virus (RSV) present in bioaerosols in domestic day care settings increases TLR-4 expression and sensitizes the respiratory epithelial cells to endotoxin.[47] This may be one of the reasons why secondary bacterial infection occurs following viral infections. A protein called CD14, a mannose receptor specific to LPS and found on surfaces of mature macrophages is present in higher levels in patients with asthma. CD14 levels are also raised in patients exposed to endotoxin. Exposure to endotoxins is associated with increased severity of asthma.

There are a number of cellular receptor families that recognize PAMPs. These PRR families include nucleotide binding and oligomerization domain like receptors (nod like receptors, NLR), C-Type Lectin Like Promoters (CLR) and intracellular receptors to detect double stranded RNA helicase-like receptors. Through various signaling cascades activated TLRs lead to the activation of the nuclear transcription factor, Nuclear Factor Kappa B (NF-κB), this (in turn) leads to the regulation of many host cytokine and cytokine receptor genes, including those for IL-1, Tumor Necrosis Factor-alpha (TNF-α), IL-6, IL-8, IL-10 and IL-12, which have multifactorial effects. Depending on the TLRs activated, cytokine production can result in the full clinical presentation of the acute-phase response, including fever. Whether the acute inflammation results from infection or trauma, it is triggered along the same pathway. Adjuvants used for all current vaccines function through the activation of the TLR pathway. The most potent adjuvant, Freund's complete adjuvant is a water-in-oil emulsion containing mycobacterial cell wall components that activate TLR-1MTLR-2 and TLR-4. The simplest adjuvant, alum (aluminium hydroxide) includes molecules involved in antigen presentation in monocytes, MHC class II, CD40, CD54, CD58, CD83 and CD86; drives monocyte differentiation toward a dendritic cell like morphology;

and induces secretions of IL-4, a cytokine with potent antibody production enhancing properties.

ALVEOLAR MACROPHAGES

Alveolar Macrophages (AM) are bone marrow-derived cells that can be differentiated from blood monocytes after they have emigrated into the tissues. Alveolar macrophages are located at the air-tissue interface in the lung, and are the first cells, which interact with inhaled organisms and antigens. These cells inhabit the various compartments of the lung, differentiating into mature macrophages, surrounding themselves in phagolysosomes once they engulf ingested material into the alveoli. Alveolar macrophages produce lysozyme and defensins, which have bactericidal properties that are capable of destroying gram-positive and gram-negative bacteria and fungi. Reactive oxygen intermediates (superoxide anion, hydrogen peroxide, hydroxyl radicals) or reactive nitrogen intermediates [nitric oxide (NO), nitrites or nitrates] are also involved in destroying microorganisms and tumor cells.

Macrophages also produce macrophage metalloelastases, collagenase, metalloproteases (MMP1, MMP9) fibroblast growth factors, such as transforming growth factor (TGF) or platelet-derived growth factor that help in lung repair and remodeling. Intercellular adhesion molecule-1 ICAM-1, CD54) and vascular cell adhesion molecule (VCAM-1, CD106) are adhesion molecules of the immunoglobulin super-family. Adhesion to the vascular endothelium mediated through ICAM-1/VCAM-1-integrin interactions is a key step in the emigration of white blood cells to the sites of inflammation. It has also been shown that they play an important role in the adherence of effector cells, such as AM to the respiratory epithelium. All these inflammatory mediators together play a crucial role in the orchestration of an inflammatory response, particularly in neutrophil recruitment. Recent studies suggest that cytokines and chemokines originate from AM, and from other cells such as epithelial cells.[48]

The ability of macrophages to interact with microbes is mediated by the surface receptors capable of binding specific ligands, including toxins, polysaccharides, lipopolysaccharides, complement proteins and immunoglobulins. Pulmonary macrophages release the cytokines TNF-α and interleukin-1β (IL-1β), as well as the chemokines, Monocyte Chemoattractant Protein-1 (MCP-1), macrophage inflammatory protein -1β (MIP-1β), and growth factors.[49] Inflammatory cytokines will favor the activation of the neighboring cells and attract several inflammatory elements from the blood. Stimulation of macrophages or mast cells through their Toll-like receptors leads to the synthesis and the secretion of proinflammatory cytokines and lipid mediators, thereby initiating the inflammatory response that recruits both soluble immune components and immune cells from the blood. TLR stimulation of dendritic cells induces the initiation of an adaptive immune response.

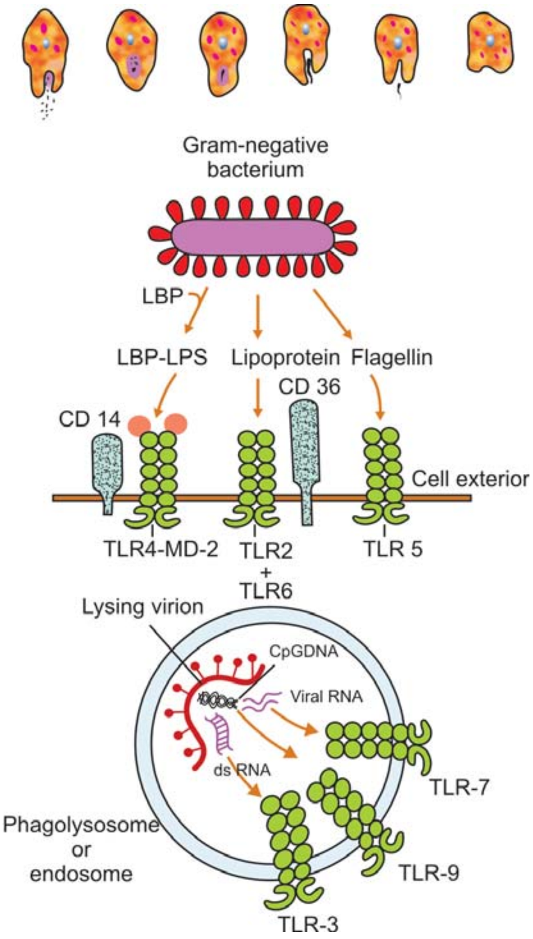


Fig. 12.9: Toll like receptors in phagocytosis

TLR's are involved in the uptake of pathogens such as bacteria or viruses by alveolar and airway macrophages (Fig. 12.9). TLRs also play a vital role in the maturation of Dendritic Cells (DCs) and hence play a key role in the adaptive protection of the lung against bacteria and viruses. TLR2 plays an important role in mediating inflammatory responses to gram-positive microorganisms and mycobacterial products such as peptidoglycan, lipoteichoic acid, lipoproteins and lipoarabinomannan.

Interstitial macrophages are located within the interstitial tissue surrounding the bronchioles and vessels. The ability of the interstitial macrophages to ingest materials appears variable and the phagocytic activity of interstitial macrophages is reduced compared to that of alveolar macrophages. Interstitial macrophages express the higher levels of major histocompatibility complex class II and CD54 and exhibit increased antigen presenting activity compared to both alveolar macrophages and blood monocytes.

Adaptive Immunity

Following inhalation, the lung is continuously bombarded with inhaled antigens, pathogenic and nonpathogenic particulate matter that have the potential to activate the adaptive immune system. Similar to the development of oral tolerance against commonly encountered antigens and microorganisms in the gut, the lung has developed a mechanism to functionally discriminate between material that can be disposed off through the innate immune system and that necessitates the activation of the adaptive immune system. A state of tolerance to commonly inhaled antigens is induced in the normal lung in which T-cell responses are actively suppressed both at the levels of the T cell itself and by the down regulation of antigen presenting functions of pulmonary DCs by resident alveolar macrophages. After the initiation of an inflammatory event or after disruption of the barrier function of the airway or alveolar epithelium, T-cell-mediated responses are rapidly activated to protect the lung. Alveolar macrophages suppress T-cell activation in the normal lung and this fine control against commonly encountered nonpathogenic organisms can be down-regulated during lung infections. The mechanisms underlying the induction of macrophage immunosuppressive activity depends on (1) NO, (2) Prostaglandin E2 (PGE2), and (3) immunosuppressive cytokines, especially TGF-β and IL-10. However, the relative contribution of each of these molecules is not completely clear.

Th1 or Th2 RESPONSES (Type1 Type2 Response)

The helper T-cells produce enormous amount of two types of cytokines: Th1 and Th2 (Fig. 12.10). Th1 and Th2 responses are polarized responses by the body's T-helper cells when faced by pathogens. T-lymphocytes recognize foreign antigens and produce cytokines that are responsible for the biological effects on the immune system. The Th1 cytokines produced by the helper T-cells produce a proinflammatory response. The Th2 cytokines produce an anti-inflammatory response, but promote allergic responses. The original observation that mouse CD4+ T-cell clones could be divided into two different sets based on their pattern of cytokine expression has

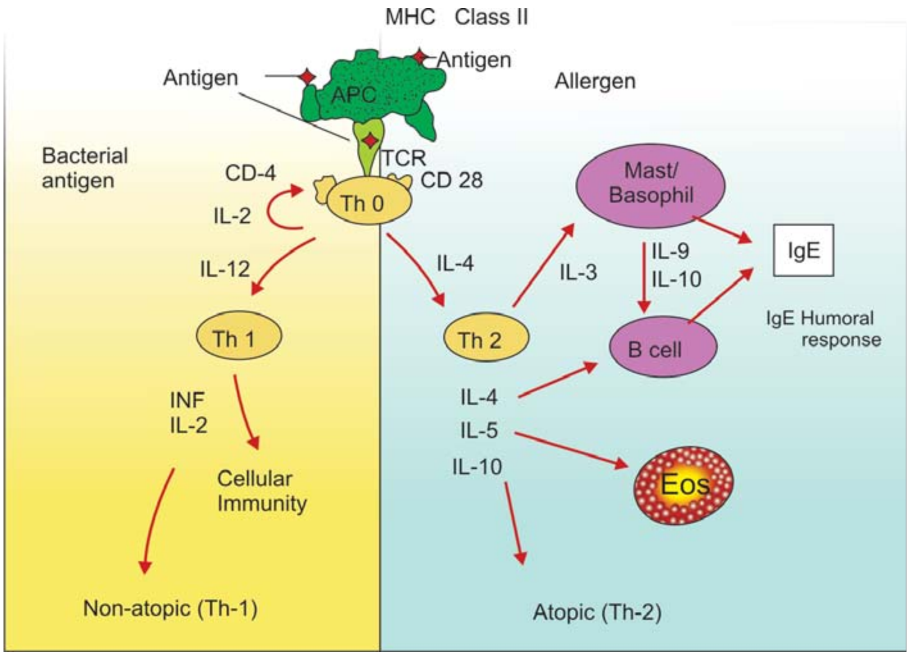


Fig. 12.10: Production of cytokines by T cells

become the paradigm for heterogeneity within the T-cell response *in vitro* and *in vivo*.[50] Th1 and Th2 cells are thought to be derived from a nonpolarized, naive Th0 precursor that produced a wide range of cytokines, that can differentiate after activation in the presence of IL-12 and IL-18 (from DCs) into Th1 cells that secrete IL-2, IFN-g and Lymphotoxin (LT) or in the presence of IL-4 (from B cells or lymphoid DCs) into Th2 cells that secrete IL-4, IL-5 and IL-10. This initial polarization of the response towards Th1 or Th2 is then self-perpetuating as Th1 cytokines enhance further Th1 responses and down regulate Th2 cytokines, and vice versa.

The Th1-type cytokines produce inflammation to kill intracellular organisms (viruses and certain bacteria such as *Listeria* and *Mycobacterium tuberculosis)*. These cytokines also perpetuate any form of autoimmune response, and can cause cell-mediated allergies. The Th2 cytokines counteract the effects of the Th1 cytokines – they have an anti-inflammatory action, but they also help to kill extracellular pathogens (which live outside the body's cells and are exposed to antibodies in blood and other body fluids). The Th2 cytokines induce a pronounced allergic response (e.g.) IgE-mediated allergies or asthma (Fig. 12.10).[51]

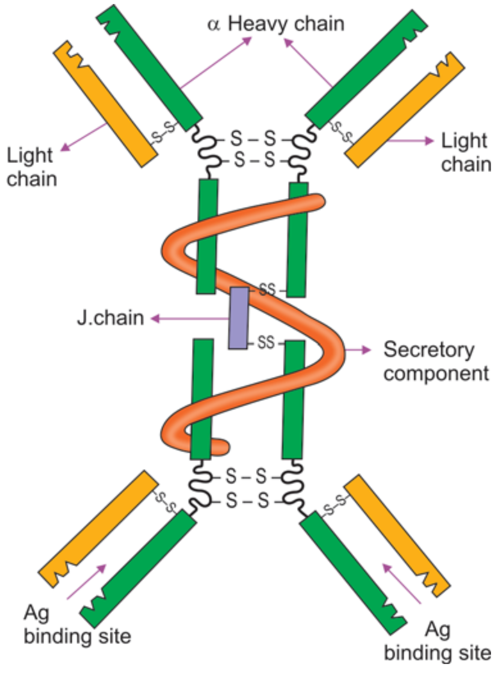


Fig. 12.11: Structure of immunoglobulin (IgA) with secretory component

Role of Immunoglobulins

The respiratory tract immunoglobulins are produced by passive diffusion from the vascular compartment across the lung tissue, and locally in the respiratory tract by the B cells within lung tissue. The bronchial mucosa is the most active site for production. The immunoglobulin reaches the airways lumina either by passive diffusion or by active transport through epithelial cells.

Experiments in animal models indicate that exposure to low doses of antigens usually does not evoke a primary antibody response. The low doses of antigens are cleared by the nonspecific defense mechanisms such as by mucociliary blanket and nonspecific phagocytosis. The dose of antigen required to elicit an antibody response has to be large to overcome the nonspecific defense mechanisms and induce pulmonary inflammation leading to the translocation of the antigen from the lung to the draining LALN.[52] Dendritic cells play an important role in antigen uptake, transport and presentation to the LALN. The nonspecific pulmonary inflammation allows for the recruitment of Antibody Forming Cells (AFC's), which are generated in the LALN and are released into efferent lymphatics and blood and subsequently reside in the lung parenchyma. It has been demonstrated in a dog model that B cells recruited to and/or produced in the lung interstitium are able to produce antibody for years after local immunization and challenge because of production of immune memory cells only in the immunized lung lobe.

i. *IgA:* Local production and active secretion of total IgA into human respiratory tract can be assessed by Bronchoalveolar Lavage (BAL) specimen analysis. The IgA producing plasma cells are found in large numbers in glands and lamina propria of the major bronchi, small bronchi, bronchioles and alveolar septa. Majority of the BAL IgA is polymeric sIgA. Subclass of IgA, IgA2 constitutes 10% to 20% of total IgA in blood and about 30% of total IgA in BAL. Free Secretory Component (SC) (Fig. 12.11) can also be recovered, however, the recovery of SC is markedly reduced in smokers. IgA deficiency, defined as IgA level less than 5 mg/dl, is a relatively common disorder (prevalence estimated as 1/300 to 1/2,000). It may be associated with IgG subclass deficiency, the infections commonly noted include recurrent pneumonia, bronchiectasis, COPD and chronic bronchitis. IgE-mediated allergy is strongly associated with IgA deficiency and allergic asthma frequently occurs in these patients.
ii. *IgG:* Respiratory tract IgG is mostly serum derived. All IgG subclasses have been identified in human

BAL. Increased levels of IgG1 (in both serum and lavage) and of IgG3 has been documented in smokers. IgG subclass deficiency is associated with a variety of infections, the clinical manifestation depends on the subclass or subclasses involved. For example, deficiency of IgG1 is associated with a lifelong increased susceptibility to pyogenic infection and progressive deteriorating lung disease. IgG1 deficiency is most often linked with IgG2 and IgG3 deficiency. IgG2 deficiency results in decreased antibody production to polysaccharide antigen. Such patients frequently have infections with capsulated microorganisms, develop sinusitis, otitis media, and pneumonias leading to chronic lung disease or recurrent meningitis. IgG2 subclass deficiency is associated with IgA deficiency. IgG3 subclass deficiency also results in recurrent respiratory tract infections and chronic lung disease.

It is difficult to demonstrate IgG4 subclass deficiency, since 30% of the general population may have undetectable levels using standard methods. Use of extremely sensitive techniques, that can detect IgG4 levels as low as 0.005 mg/dl, have shown that patients develop recurrent lung infections and/or bronchiectasis. Some individuals with IgG subclass deficiency may be completely normal and healthy in whom a complete evaluation of the patient's ability to make antibody to tetanus toxoid and pneumococcal vaccine must be undertaken.[53]

iii. *IgE:* IgE appears to be locally produced in the respiratory tract. IgE bound to histamine-containing cells can also be identified in the human lung by BAL. Elevated BAL Ig levels have been noted in hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, sarcoidosis and Acquired Immunodeficiency Syndrome (AIDS). However, it is unclear whether increased IgE levels are of pathogenic importance or simply a marker of some other underlying disease process.

iv. *Humoral B cell deficiency:* Sinopulmonary infections (such as otitis media, sinusitis bronchitis and pneumonia and bacteremia resulting in sepsis or meningitis) can occur in individuals with humoral (B-cell) deficiency. Encapsulated organisms, such as *S. pneumoniae*, *H influenzae* and *Neisseria meningitides* or gram-negative organisms are usually the etiologic agents. Recurrent infection leads to chronic diseases such as bronchiectasis and/or respiratory dysfunction. There may be a complete failure of B-cell development as characterized by Bruton's agammaglobulinemia to selective IgG subclass deficiency. A number of molecular defects with B-cell deficiency have been described. Usually B-cell deficiencies are found in children and recently there are reports in older individuals with primary immunodeficiency diseases.

Common variable immune deficiency presents as a hypogammaglobulinemia, decreased antigen-specific antibody function and increased recurrent infections.[54]

IMPACT OF BACTERIA AND VIRUSES ON LUNG IMMUNOLOGY

In healthy individuals, the lower airways are sterile and contain very few goblet cells. In patients with mucus hypersecretory diseases, the lower airways are often infected with bacteria or viruses and contain many goblet cells. The importance of bacteria and viruses in the pathogenesis of asthma, chronic bronchitis, cystic fibrosis, and in exacerbations of these diseases has become clear.[55] An important mechanism appears to involve the recruitment of neutrophil chemokines produced by epithelial cells infected with bacteria and viruses. Infection with rhinovirus (RV), the most common respiratory virus, associated with asthma exacerbations induces mucus hypersecretion in airway epithelial cells.[56] RV infection was associated with IL-8 levels and with increased neutrophils in lavage fluid. Virus replication also induces IL8 synthesis by airway epithelial cells.[57,58]

In COPD and cystic fibrosis patients, gram-negative bacteria, such as *P. aeruginosa* and *Chlamydia pneumonia* colonize the lower airways and cause acute exacerbations of disease. These exacerbations are associated with excessive mucus formation. The elevated sputum levels of IL-8 neutrophils, neutrophil elastase and DNA, suggest the role of bacteria in neutrophil recruitment and destruction in the airway lumen.[59] *P. aeruginosa* and *C. pneumoniae* induce IL-8 production by airway epithelial cells. In addition to its role in neutrophil recruitment, IL-8 inhibits neutrophil apoptosis, (self-death) resulting in increased neutrophils within the airways. Infection of mucus plugs in the lower airways where cough is ineffective, further leads to neutrophil-dependent mucin production.[60,61] *P. aeruginosa* deposited on mucus surfaces penetrate into hypoxic zones within mucus plugs, where they evade phagocytosis, multiply and secrete substances that promote neutrophil recruitment. The mucus plugs promote neutrophil necrosis via the entrapment of neutrophils in a microenvironment characterized by large numbers of bacteria, extracellular acidosis and very low oxygen tension causing the release of neutrophil products, such as reactive oxygen species that can induce further mucin production.

Double stranded RNA, a product of single stranded RNA virus replication has been shown to induce mucin in airway epithelial cells.[62] This occurs more frequently in chronic bronchitis and also in cystic fibrosis, in which hydration of submucosal gland mucins can result in the retrograde movement of mucus. Retrograde aspiration of bacteria and mucus into the peripheral airways may lead to bacterial infection, goblet cell formation, goblet cell degranulation and mucus plugging in the periphery.

HLA AND MYCOBACTERIAL DISEASES

There is a possible genetic predisposition to particular bacterial/mycobacterial diseases. Early studies on HLA variation established its relevance in susceptibility to TB and leprosy, especially in Asian population.[63] Children who are homozygous for mutations in the IFN-α receptor gene have been found to be susceptible to weakly pathogenic mycobacteria, including the Calmette-Guérin bacillus vaccine, and have a poor prognosis. The role of genetic factors in various lung defenses is a subject of further investigations.

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Section

3

PHARMACOLOGICAL AGENTS

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13

Antibacterial Drugs

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INTRODUCTION

Antibacterials are commonly, many times inappropriately, used for upper and lower respiratory tract infections. Therapeutic concentrations in respiratory secretions, in excess of the Minimum Inhibitory Concentration (MIC) for that pathogen are necessary for the successful treatment of pulmonary infections. Concept of blood-lung barrier on the lines of blood-brain barrier has been also proposed. Ability of drugs to penetrate respiratory secretions depends on factors such as molecular size of the antibacterial, lipid solubility and degree of ionization. In order to achieve higher local concentrations, especially those of polymyxins and aminoglycosides, some investigators in the past have administered them through the endotracheal route. However, the use of antibiotic aerosols continues to remain controversial.

Pharmacokinetic properties of the antibiotics, their ability to reach the site of infection, their half-lives (how many times per day) and presence of comorbid conditions (impaired renal or hepatic functions) may also determine the choice of drugs. For instance, the doses of drugs eliminated by kidneys (aminoglycosides, vancomycin, others) or metabolized by liver (chloramphenicol) must be adjusted in the presence of impaired renal or hepatic function, respectively.

Moreover, side effect profiles and drug interactions would need further consideration. Some side effects like gastrointestinal (nausea, vomiting, diarrhea) and drug rash can occur with the majority of the antibiotics. Hypersensitivity reactions can occur with most antimicrobials especially, but not exclusively, with parenteral use. Bone marrow suppression has also been reported with most of the antimicrobials. However, some may be typical for a class, e.g. nephrotoxicity for aminoglycosides, and QT prolongation for quinolones like moxifloxacin and sparfloxacin.

Cost factors are important especially in countries with sparse cover of health insurance. Most of the novel antimicrobials must be used sparingly, not only due to cost factors, but also to save the drugs from misuse and development of resistance.

The following chapter focuses on the pharmacological aspects of antibacterials used for the empiric management of respiratory tract infections.

BETA-LACTAMS

Beta-lactam group includes penicillins, cephalosporins, carbapenems and monobactams. The name of this group of agents derives from basic structure of thiazolidine ring connected to a beta-lactam ring to which a side chain is attached. They inhibit the synthesis of peptidoglycan, an important component of cell walls of the bacteria. Specifically, the final step of transpeptidation is inhibited by penicillins. Additionally, penicillins and cephalosporins bind to Penicillin-Binding Proteins (PBPs) bringing about lytic, as well as nonlytic killing. Alteration in PBPs and production of beta-lactamases are the important mechanisms of resistance, which is not inherently present in some bacteria. At least four types of betalactamases are known. Class A -beta-lactamases, also called extended spectrum beta-lactamases, inhibit penicillins, cephalosporins and carbapenems. Class B beta-lactamases destroy all beta-lactams except aztreonam. Class C beta-lactamases are against cephalosporins while Class D beta-lactamases degrade cloxacillin.

1. Penicillins

Penicillin G (benzylpenicillin) is the only naturally obtained penicillin used clinically; several semisynthetic penicillins with desired properties are derived from modification of 6-aminopenicillanic acid. Various classes of penicillin are:

a. Highly active against sensitive strains of gram-positive cocci, but ineffective against *Staphylococcus aureus*, which produces penicillinase: Penicillin G, Benzathine penicillin, Procaine penicillin, Penicillin V.

b. Penicillinase-resistant penicillins, effective against *S. aureus* and *Staphylococcus epidermidis* that are methicillin susceptible: Methicillin, Nafcillin, Oxacillin, Cloxacillin, Dicloxacillin, Flucloxacillin.

c. Penicillins effective against gram-negative organisms, such as *Haemophilus influenzae, Escherichia coli* and *P. mirabilis:* Ampicillin, Amoxicillin, Bacampicillin, Metampicillin, Pivampicillin.

   The last three are prodrugs and are hydrolyzed to ampicillin *in vivo.*

   Penicillins with activity against *Pseudomonas*, *Enterobacteriaceae* and *Proteus* species (carboxypenicillins): Carbenicillin, Ticarcillin. These penicillins are inferior to ampicillin against gram-positive cocci.

d. Penicillins with activity against *Pseudomonas*, *Klebsiella* (ureidopenicillins): Mezlocillin, Azlocillin.

e. Penicillins with activity against *Pseudomonas*, *Klebsiella* and gram-positive cocci: Piperacillin.

Individual Penicillins

i. *Penicillin G (Crystalline penicillin, benzylpenicillin):* Susceptible organisms include *Corynebacterium diphtheriae*, *Peptostreptococcus spp.*, non-beta-lactamase-producing staphylococci and streptococci, including *Streptococcus agalactiae* (group B), *Streptococcus pneumoniae* (pneumococci), *Streptococcus pyogenes* (group A), and some viridans streptococci; of these Group A Streptococci are an occasional cause of pneumonia in previously healthy adults. These organisms are responsible for 20% to 40% cases of exudative pharyngitis in children. Group B streptococci are the most common cause of pneumonia in neonates. Enterococci are relatively insensitive to penicillins. *Pasteurella multocida*, *Streptobacillus moniliformis* and *Spirillum minus* (or *minor*) are also susceptible to penicillins. *Actinomyces* show good susceptibility to penicillins. Most strains of *S. aureus* are resistant to penicillin. *Bacillus anthracis* and *C. diphtheriae* are other susceptible pathogens, which may cause respiratory tract infections. Resistance to staphylococcus, *S. pneumoniae*, pneumococci and *H. influenzae* are common.

Pharmacokinetics: Given intramuscularly, peak plasma concentration is reached in 15–20 minutes. It is widely distributed in the body and excreted mainly through renal tubular secretion. Renal tubular secretion may be inhibited by adding probenecid. Doses of 600 mg of benzylpenicillin sodium or potassium are considered equivalent to 1 MU. Dose reduction (25–50%) may be required if creatinine clearance decreases.

Indications and dosage: Str. pneumoniae has usually been considered to be sensitive to penicillins, but there is increasing prevalence of resistance although there are marked geographical differences. A survey conducted across 25 countries from 1999 to 2000 reported prevalence of resistance from 7.8% to 71.5%.[1] However, penicillin G remains agent of choice for serious infections like bacteremia, empyema, severe pneumonia, pericarditis, endocarditis, meningitis, and others caused by sensitive strains of the gram-positive species mentioned above. It may also be considered for sensitive strains of pneumococci.

The Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group (DRSP) argued that penicillin susceptibility categories should be shifted upward for pneumococcal pneumonia so that the susceptible category includes all isolates with MIC of no greater than 1 μg ml^{-1}, the intermediate category includes isolates with MIC of 2 μg ml^{-1} and the resistant category includes isolates with MIC of no less than 4 μg ml^{-1}. The group suggested the aforementioned classification in order to parallel penicillin resistance categories with clinical outcomes.[2] The dose of 20–24 MU of penicillin G should be administered daily by constant intravenous infusion (IV) or 1–2 million units intramuscularly (IM) every 2 hours. Therapy should be continued for three to five days after the patient becomes afebrile. Each million units contains approximately 6.8 mg (0.3 mEq) of sodium and 65.6 mg (1.68 mEq) of potassium.

In splenectomised patients with compromised immunity status, phenoxymethylpenicillin

(penicillin V) may be offered for lifelong prophylaxis against pneumococcal and *H. influenzae* infections. Penicillin G is the drug of choice for actinomycosis, 12–20 MU of penicillin G are given IV. Combination with aminoglycosides is synergistic and is usually employed for enterococcal infections. However, with bacteriostatic drugs like chloramphenicol and tetracyclines, antagonism may be seen.

ii. *Methicillin:* The antimicrobial spectrum is largely similar to benzylpenicillin. It is active against both penicillinase-producing and nonpenicillinase-producing staphylococci. This may be due to the fact that resistance to methicillin is due to alteration in penicillin-binding protein and not due to penicillinase production. Methicillin is also effective against *S. pyogenes* (group A beta-hemolytic streptococci), *Str. pneumoniae*, and some viridans streptococci. Its activity against penicillin-sensitive staphylococci and streptococci is less than that of benzylpenicillin.

It is inactivated by gastric acid and should be administered parenterally. Distribution is wide and nearly 80% of the drug is excreted unchanged in the urine. Since the drug is inactivated by gastric acid, it must be given by injection. Peak plasma concentrations are attained within 0.5 to 1 hour of an intramuscular injection. The half-life of methicillin in patients with normal creatinine clearance is 0.5 to 1 hour, but may increase to 3 to 6 hours in renal impairment. The majority is rapidly excreted by tubular secretion and glomerular filtration; up to 80% of an injected dose has been detected unchanged in the urine. Plasma concentrations are enhanced by probenecid.

It is not commonly used in clinical practice, but may be used to treat infections caused by susceptible gram-positive bacteria. The usual adult dose is 250 mg four times daily intramuscularly or 0.25 to 1 g four times daily by slow intravenous injection (over three to four minutes). The dose may be doubled in severe infections. Interstitial nephritis is an important adverse effect.

iii. *Oxacillin:* It is an orally active oxazolyl penicillin. Though it is active against sensitive strains of penicillinase producing staphylococci, it is not considered for the treatment of serious infections caused by penicillinase-producing staphylococci.

It is incompletely absorbed from the Gastrointestinal Tract (GIT) and the absorption is affected by the presence of food which is why a gap of one to two hours between food and drug intake is recommended. Peak plasma concentration is achieved in one hour after oral administration. Oxacillin is excreted both in the urine and bile.

Its indications are similar to flucloxacillin. It is administered orally in a dose of 1 g twice a day. Hepatitis may occasionally occur.

iv. *Flucloxacillin:* Penicillinase and non-penicillinase producing staphylococci and Strep pneumoniae are susceptible to flucloxacillin though the activity of benzylpenicillin is more against these organisms as compared to flucloxacillin. In some centers it continues to remain a good choice for the empirical treatment of staphylococcal infections in intensive care units.[3]

Absorption through gastrointestinal tract is good and peak plasma concentration is achieved in one hour. It may also be given by intramuscular injection. The oral and parenteral dose is 250 mg four times daily. Unchanged drug and the metabolite is excreted in the urine and bile. A spacing of 30 minutes from meals is recommended.

Susceptible gram-positive infections, including the recently important infection due to Panton-Valentine Leukocidin (PVL-) producing *S. aureus,* which is emerging as a serious problem worldwide. There has been an increase in the incidence of necrotizing lung infections in otherwise healthy young people with a very high mortality associated with these strains. Flucloxacillin (4 g tid) and rifampicin may be given empirically.[4] The usual dose is 250 mg four times daily orally or intramuscularly. Its IV dose is 0.25 to 1 g four times daily by slow injection over 3 to 4 minutes or by IV infusion. The dose may be doubled in severe infections.

Hepatitis and cholestatic jaundice may occur occasionally. The side effect may be delayed for more than two months after stopping the drug. Flucloxacillin is a pregnane X receptor (PXR) agonist at pharmacologically relevant concentrations, and a functionally significant upstream PXR polymorphism is a risk factor for flucloxacillin-induced liver injury.[5] It should be used with caution in patients with hepatic dysfunction.

v. *Cloxacillin:* Its spectrum and other features are similar to those of flucloxacillin. It is incompletely absorbed from the gastrointestinal tract. Peak plasma concentration after oral administration is achieved in one to two hours. Food affects its absorption and an interval of half an hour is required between the administration of the drug and food intake. Indications and dosage are similar to flucloxacillin. It is administered in a dose of 250–500 mg six hourly.

vi. *Dicloxacillin:* Absorption from the gastrointestinal tract is better than that of cloxacillin. Rest of the profile is similar to cloxacillin.

vii. *Ampicillin:* Ampicillin has a broader spectrum of activity than benzyl penicillin. In addition to gram-positive bacteria, some gram-negative bacteria such as *H. Influenzae* are susceptible to ampicillin. It is well absorbed after oral administration. Food hampers its absorption and hence it should preferably be taken 30 minutes before meals. Peak plasma concentrations are reached in one to two hours after oral administration. It undergoes enterohepatic circulation. Dose adjustment is required in renal impairment.

It is indicated for the initial treatment of acute tracheobronchitis of I, II and III Class. As a therapy for acute exacerbation of tracheobronchitis, it offers modest benefit at best.[6] Ampicillin in a dose of 1–2 g daily in 3–4 divided doses for 7–10 days orally or IV, either alone or in combination with beta-lactamase inhibitor (sulbactam) is indicated for the empirical therapy of pneumonia in adults—pneumonia with chronic bronchitis and for suspected pneumococcal pneumonia if resistance to ampicillin is not common.

Ampicillin-sulbactam is also indicated for empirical antimicrobial therapy for pneumonia in pediatric patients of less than one month of age when Group B streptococcus, *H. influenzae* and *S. aureus* are the usual pathogens. The combination is also indicated for the empirical therapy of pneumonia in pediatric patients of three months to six years of age in whom the suspected organisms include pneumococcus or *H. influenzae.* Ampicillin-resistant *H. influenzae* may be susceptible to ampicillin-sulbactam combination. Ampicillin for three months has been successfully used in patients with actinomycosis or a follow-up therapy to ceftriaxone. Benzylpenicillin, however, continues to remain the treatment of choice for this condition. Recently, aerosolized ampicillin was reported for the treatment of *S. aureus* lung infection in a 14-year-old patient of cystic fibrosis.[7]

Salient adverse effects: Urticarial and maculopapular rash are known to occur with ampicillin, the former represents hypersensitivity. Maculopapular rash may occur seven days after the drug administration. Appearance of rash is not necessarily an indication for stopping the use of penicillins. However, sensitivity testing should be undertaken before use. Patients with infectious mononucleosis, lymphatic leukemia and HIV infection are particularly susceptible to ampicillin induced rash. Caution should be exercised with the subsequent use of penicillin. Studies in adults indicate that ampicillin, in a dose-dependent manner, impairs platelet function and moderately prolongs the bleeding time (generally by 60 to 90 seconds). A similar increase in bleeding time is also noted in pediatric patients.[8] Diarrhea, hepatitis, cholestatic jaundice, erythema multiforme, Stevens-Johnson syndrome and toxic epidermolytic necrosis have all been reported with its use.

viii. *Amoxicillin:* Amoxicillin is a 4-hydroxy analog of ampicillin. The antimicrobial spectrum of amoxicillin is similar to that of ampicillin. It is not inactivated by gastric acid. Compared to ampicillin, it is absorbed more rapidly and completely. Half-life may increase to nearly 20 hours in severe renal impairment. It crosses the placenta and small amount may be secreted in breast milk. It is largely excreted by tubular secretion and glomerular filtration.

The indications for amoxicillin are similar to those of ampicillin. Addition of beta-lactamase inhibitor, clavulanic acid extends the spectrum of amoxicillin to include *H. influenzae* and *Moraxella catarrhalis*. In a recent Cochrane review done to evaluate effective antibiotics for ambulatory pediatric patients with community acquired pneumonia, amoxicillin had similar failure rates as those of co-trimoxazole.[9] The authors concluded that for severe pneumonia without hypoxia, oral amoxicillin may be an alternative to injectable penicillin in hospitalized children; however, for ambulatory treatment of such patients with oral antibiotics, more studies in community settings are required.[9] Its dose is 250–500 mg three times a day orally. An extended release preparation of amoxicillin is available in some countries. It is generally used for pharyngitis due to *S. pyogenes* and it is given as a single daily dose for 10 days.

The incidence of diarrhea is less than that of ampicillin. Hepatitis and cholestatic jaundice have been reported with the use of amoxicillin. These have largely been seen when it is used in combination with clavulanic acid.

ix. *Carbenicillin:* The antimicrobial spectrum is similar to that of benzylpenicillin and is penicillinase susceptible. However, it is not effective against most strains of *S. aureus* , *Enterococcus* and *Klebsiella*. In addition, it is also effective against *P. aeruginosa*. It has largely been superseded by piperacillin and ticarcillin for most of its indications.

It is not absorbed through gastrointestinal tract and needs to be given either intramuscularly or intravenously. However, carbenicillin indanyl is a prodrug, designed for oral administration. The carbenicillin, which is released from this prodrug does not achieve sufficient concentrations in the blood and is used only for the treatment of urinary tract infections. The half-life of carbenicillin is increased in renal impairment.

Indications and dosage are similar as for ticarcillin. Dose-dependent coagulation defect may occur. Congestive heart failure may result due to the sodium ions present in carbenicillin sodium. Carbenicillin sodium contains about 5 mEq Na^+ per gram of drug, and this will result in the administration of more than 100 mEq Na^+ when patients are treated for *P. aeruginosa* infections. Carbenicillin constitutes large amount of nonreabsorbable anion and may cause hypokalemia.

x. *Ticarcillin:* It is two to four times more active against *P. aeruginosa* than carbenicillin. It is given by intravenous route. The drug is eliminated renally and caution should be exercised in patients with reduced creatinine clearance. The maintenance dose needs to be modified from 2 g every 12 hours to 2 g every 24 hours for creatinine clearance of 10 ml min to 30 ml/min respectively. Half-life of the drug may be shortened in patients with cystic fibrosis.

   When given with clavulanic acid, the activity of ticarcillin is extended to beta-lactamase producing organisms such as staphylococci, enterococci and *H. influenzae*. It needs to be noted that addition of clavulanic acid does not increase its activity against *P. aeruginosa*. Ticarcillin-clavulanate is considered for the empirical antimicrobial therapy for pneumonia in adults with a history of alcoholism. The suspected organisms in these cases are Pneumococcus, *Klebsiella pneumoniae*, *S. aureus*, *H. influenzae* and possibly mouth anaerobes. More than 70% of pseudomonas isolates obtained from patients of cystic fibrosis may be susceptible to ticarcillin.[10] It is given by injection as the sodium salt in the doses of 200 to 300 mg/kg daily by intravenous infusion in four or six divided doses. The adverse effects of cholestatic jaundice and hepatitis seen with ticarcillin/clavulanic acid are mainly due to the clavulanic acid component. The defects of platelet aggregation are known to occur.

xi. *Piperacillin:* Its spectrum includes most strains of *P. aeruginosa,* Enterobacteriaceae (non-beta-lactamase producing), many *Bacteroides spp.,* and *Enterococcus faecalis*. In combination with a beta-lactamase inhibitor (*piperacillin-tazobactam),* it has the broadest antibacterial spectrum out of all penicillins. Peak plasma concentrations are achieved in half to one hour. High biliary concentrations are also achieved. Recently, it has been suggested that the plasma concentrations of piperacillin should be monitored to achieve better outcomes.[11] The combination with tazobactam is indicated for the empiric therapy of pneumonia in adults who have a history of alcoholism and those with nosocomial pneumonia. It is also indicated in patients with community-acquired pneumonia in whom pseudomonas infection is suspected. In life-threatening infections, particularly those caused by *Pseudomonas* or *Klebsiella spp*., it should be given in a dose of not less than 16 g/day up to a maximum dose of 24 g/day. The combination is also indicated for use in *Acinetobacter baumannii* infection, a causative organism of ventilator associated pneumonia.

xii. *Mezlocillin and azlocillin:* These penicillins do not find recommendations in most guidelines for the treatment of respiratory tract infections. They have good activity against pseudomonas.

Adverse Effects of Penicillins

Hypersensitivity reactions are not only the most common adverse reactions (up to 10%) associated with penicillins, but can also be fatal. The manifestations include the occurrence of maculopapular rash, urticarial rash, fever, bronchospasm, vasculitis, serum sickness, exfoliative dermatitis, Stevens-Johnson syndrome and anaphylaxis. There is a wide variation in their presentation; any history of hypersensitivity reaction to penicillin precludes its use in future.

All types of skin rashes are known to occur with their use. Rarely thrombocytopenic purpura and Henoch-Schonlein purpura may occur. Exfoliative dermatitis are erythema multiforme may also occur. Serum sickness characterized by fever, leukopenia, splenomegaly, arthralgia , arthritis, purpura, electrocardiographic changes may sometimes occur after one week of treatment with penicillin. Skin vasculitis, positive Coomb's reaction and reversible neutropenia may also occur. The latter is more commonly seen with the use of nafcillin. Fever, eosinophilia, reversible interstitial nephritis (mainly with methicillin) are sometimes observed.

Angioedema and anaphylaxis constitute the most serious adverse reactions associated with the use of penicillins. These can occur with any route of administration although more commonly with the parenteral routes. Anaphylactic and anaphylactoid reaction constitute medical emergency and occur with an incidence of 0.004% to 0.04%. It presents with severe bronchoconstriction, drop in blood pressure, nausea, vomiting, abdominal pain and diarrhea. Prior skin testing with a small amount of penicillin (a few units) is mandatory before the use of penicillins.

Oral penicillins are likely to cause GI adverse effects (diarrhea, nausea) in a significant proportion of patients. Pseudomembranous colitis can occur with almost all antibiotics, including penicillins (especially ampicillin and amoxicillin). Hematological adverse effects (like hemolytic anemia, neutropenia, abnormal platelet function leading to prolongation of bleeding time), convulsions, encephalopathy (intrathecal administration), and electrolyte imbalance can occur. Hepatitis and cholestatic jaundice are rare (especially with flucloxacillin, oxacillin, and amoxicillin/ticarcillin-clavulanic acid combination). Nephropathy and interstitial nephritis (mainly with methicillin) can occur.

2. Cephalosporins

The cephalosporins or cephem antibacterials are semi-synthetic antibacterials derived from cephalosporin C, a natural antibacterial produced by the mould *Cephalosporium acremonium*. The hydrolysis product of cephalosporin, 7-aminocephalosporanic acid, has been modified to give various classes of this drug. As a consequence, four generations of cephalosporins are available with differences in their antibacterial and other pharmacological properties.

a. First-Generation Cephalosporins

Included in this group are cefazolin, cephalexin, cephalothin, cephradine, and cephadroxil. They are active against gram-positive cocci like *S. aureus* (including beta-lactamase-producing strains), *S. epidermidis*, *S.pyogenes*, *S. agalactiae*, and *S. pneumoniae,* but not against enterococci, methicillin-resistant *S. aureus,* and *S. epidermidis*), anaerobes (except *Bacteroides fragilis),* and, to a lesser extent, against gram-negative microorganisms. Activity against *M. catarrhalis, E. coli, K. pneumoniae,* and *P. mirabilis* is quite good.

i. *Cefalexin:* It is well-absorbed from the GIT, absorption may be delayed by food, but extent of absorption is not affected. Most of it is excreted unchanged in urine. It is useful in respiratory tract infections and otitis media caused by susceptible organisms, especially if penicillin cannot be used. The usual dose is 1 to 4 g daily in divided doses.

ii. *Cefazolin:* Its gastrointestinal absorption is poor, thus used parenterally (IM, IV). It is excreted unchanged in the urine. It is used for respiratory tract infections and septicemia (caused by *S. pneumoniae*, *S. aureus* (including beta-lactamase producing strains), *P. mirabilis, E. coli.* It is used in doses of 0.5 to 1 g every 6 to 12 hours (up to a maximum of 12 g) by deep IM injection or by intravenous infusion.

iii. *Cefalothin:* It is used only parenterally as it is poorly absorbed from the GIT. About two thirds is excreted in the urine and the rest is metabolized by the liver.

b. Second-Generation Cephalosporins

The antimicrobial spectrum of second generation cephalosporins (cefamandole, cefoxitin, cefaclor, loracarbef, cefuroxime, cefotetan and cefprozil) extends to include enterobacter, proteus and *Klebsiella* species. *H. inluenzae* are also susceptible to this generation.

i. *Cefamandole:* It has similar or slightly less activity than cefalothin against gram-positive bacteria, but greater stability to hydrolysis by beta-lactamases produced by gram-negative bacteria. Due to its erratic absorption, it is given as an intravenous or intramuscular preparation. It is primarily excreted by the kidneys.

   It is effective against infections caused by susceptible organisms and also for surgical prophylaxis. Prophylaxis with cefamandole (3g/day) for six months, followed by amoxicillin/clavulanate for the next 12 months has shown to decrease the incidence of postoperative pneumonia following lung resection.[12]

ii. *Cefoxitin:* It demonstrates some resistance to beta-lactamases produced by some gram-negative rods. The hallmark of cefoxitin is its activity against *B. fragilis*. It is used parenterally and almost all of it is excreted unchanged by the kidneys. It does not cross the blood-brain barrier even in the presence of inflammation. Cefoxitin is an alternative for pulmonary disease with rapidly growing opportunistic mycobacteria such as *Mycobacterium abscessus*, *Mycobacterium chelonae*, *Mycobacterium fortuitum* and *Mycobacterium gordonae*. It is also a useful antimicrobial for anaerobic and mixed infections.

iii. *Cefaclor:* It has good activity against gram-negative bacteria such as *Klebsiella* and *H. influenzae*. It may be active against some beta-lactamase producing strains of *H. influenzae*. It is used in upper and lower respiratory-tract infections and otitis media in doses of 250 to 500 mg three times a day up to a maximum of 4 g/day. It is indicated for empirical therapy of pneumococcal pneumonia in children less than five years of age an alternative to amoxicillin. It is considered as an alternative drug for acute exacerbation of bronchitis in otherwise healthy individuals.

Serum sickness like illness with the repeated use of cefaclor in children has been reported. It may increase the prothrombin time when given concomitantly with warfarin.

iv. *Loracarbef:* It is actually a carbacephem, which is slightly different structurally from cephalosporin, but has antimicrobial activity similar to that of cefaclor. It is well-absorbed orally. The indications are also same as cefaclor.

v. *Cefuroxime:* The antimicrobial spectrum of cefuroxime is similar to that of cefamandole. Cefuroxime is considered for empirical therapy of pneumonia in elderly when the likely pathogens are *Pneumococcus, Klebsiella*, *H.influenzae* or *M. catarrhalis*. Cefuroxime axetil is a prodrug of cefuroxime, after absorption it is hydrolyzed in the intestinal mucosa to cefuroxime. Cefuroxime is also used parenterally.

The major indications are bronchitis, other lower respiratory-tract infections, meningitis, otitis media and sinusitis. It is also commonly used for surgical infection prophylaxis. It may also be used for the empirical antimicrobial therapy for pneumonia in children. It may rarely cause Stevens-Johnson syndrome and toxic epidermal necrolysis.

vi. *Cefprozil:* The indications for cefprozil are similar to that of cefaclor. It has a good oral bioavailability in a single daily dose. It may also be used for the treatment of pharyngitis caused by *S. pyogenes*.

vii. *Cefotetan:* It is another second-generation antibiotic, which is seldom used in respiratory tract infections. The antimicrobial spectrum is similar to that of cefoxitin. The N-methylthiotetrazole side chain has the potential to cause hypoprothrombinemia and bleeding.

c. Third-Generation Cephalosporins

These cephalosporins, also called extended spectrum cephalosporins, have good activity against many gram-positive and gram-negative bacteria. They are more resistant to hydrolysis by beta-lactamases than the second-generation cephalosporins. Some of these agents have activity against pseudomonas.

i. *Ceftriaxone:* Among gram-negative bacteria, *in vitro* activity is seen against Enterobacteriaceae and *Klebsiella* besides *H. influenzae* and *M. catarrhalis*. There is only moderate susceptibility towards *Pseudomonas*. Among gram-positive bacteria, it is active against staphylococci and streptococci except methicillin-resistant *S. aureus*. It is not absorbed orally, about two thirds is excreted by the kidneys and the rest by liver. It crosses the blood-brain barrier even in the absence of inflammation.

It is indicated for the presumptive therapy of pneumonia in elderly patients. It is also indicated in the management of pneumococcal pneumonia in immunocompetent adults for strains with reduced susceptibility to penicillins. In adult patients with community-acquired pneumonia who are admitted in the wards, ceftriaxone or cefotaxime may be combined with a macrolide (or doxycycline). Calcium salt may rarely cause biliary sludge and pseudolithiasis. Administration of calcium salts within 48 hours of ceftriaxone administration should be avoided. Isolated fatal cases have been reported in the neonates due to the deposition of calcium ceftriaxone in the lungs. Hyperbilirubinemia may occur due to the high protein binding associated with its use. Methylthiotriazine side chain may aggravate the action of anticoagulants and disulfiram-like reaction may occur when used concomitantly with alcohol.

ii. *Cefotaxime:*. It is highly resistant to most beta-lactamases, has more activity than first- or second-generation cephalosporins against gram-negative bacteria. It is active against gram-negative bacteria like Enterobacteriaceae, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, *H. influenzae*, *M. catarrhalis,* and *Neisseria meningitidis*. It is also active against gram-positive bacteria, including *Staphylococcus aureus (except* methicillin-resistant), *S. epidermidis, Streptococcus agalactiae, S pneumoniae, S. pyogenes, and* anaerobic bacteria (like some strains of *B. fragilis and Clostridium difficile*).

It is not orally absorbed. The main route of elimination is renal although there is some hepatic metabolism as well that leads to the formation of active metabolite desacetylcefotaxime.

It is commonly used in intensive-care settings to treat serious infections like brain abscess, endocarditis, sepsis, meningitis, peritonitis, pneumonia and typhoid. It is also used for surgical prophylaxis. Cefotaxime/sulbactam combination may be as effective as amoxicillin-clavulanic acid in children with lower respiratory tract infections.

iii. *Ceftazidime:* Its spectrum is similar to that of cefotaxime, but the activity against *Pseudomonas* is greater. It is given parenterally, the predominant route of elimination is renal.

iv. *Ceftizoxime:* It is similar to cefotaxime, administered either by intramuscular or slow intravenous injection. It is mainly eliminated by the kidneys.

v. *Cefixime:* It is active against Enterobacteriaceae, *H. influenzae*, *M. catarrhalis* and streptococci. It is slowly and partially absorbed from the gastrointestinal tract and eliminated by the kidneys and liver. It is used for the treatment of otitis media, pharyngitis, and lower respiratory tract infections caused by susceptible organisms.

vi. *Others:* Cefpodoxime, Cefditoren and Cefdinir have spectrum similar to that of cefixime, but more active against *Staphylococcus aureus*.

d. Fourth-Generation Cephalosporins

The fourth-generation cephalosporins have an extended antibacterial spectrum. This group of cephalosporins is largely resistant to beta-lactamases. They are active against many enterobacteriacae, which are resistant to type-1 beta-lactamases. These may, however, be hydrolyzed by extended spectrum beta-lactamases. The activity against *H. influenzae* is comparable to that of cefotaxime. These agents are also active against streptococci, including penicillin-resistant streptococci and methicillin-sensitive *S. aureus*. In combination with aminoglycosides, they are indicated for the empiric therapy of nosocomial pneumonia with suspected gram-negative bacilli (*K. pneumonia*, enterobacter, *P. aeruginosa*).

i. *Cefepime:* It is used in respiratory tract and other serious infections, including in patients with febrile neutropenia caused by susceptible. It has also been used successfully in the treatment of ventilator associated pneumonia.[13] Cases of neurotoxicity manifesting as nonepileptic convulsion have been reported.[14]

ii. *Cefpirome:* Used in serious infections like pneumonia and sepsis, especially in immunocompromised patients, it is given in the doses of 1 to 2 g twice a day by IV infusion.

The adverse effects of cephalosporins are similar to those of penicillins. The gastrointestinal (diarrhea, nausea), dermatologic (rash), rash, and electrolyte disturbances (most of them are administered as sodium salts) are seen in ≥1% of patients. Less common are headache, dizziness, antibiotic associated diarrhea, superinfection and fever. Hypersensitivity reactions as seen with penicillins can occur with cephalosporins, but less commonly compared to penicillins. Cross-reactivity with penicillins is seen in about 10% of patients.[15]

3. Carbapenems

Drugs such as imipenem, meropenem, doripenem and ertapenem of this group structurally resemble penicillins and have similar mechanism of action. Carbapenems are particularly useful for the initial empirical therapy for hospitalized patients with suspected bacterial community-acquired pneumonia, patients with pneumonia in medical wards with or without previous recent history of antibiotic therapy and for patients with pneumonia in intensive care unit with suspected pseudomonas infection. For the latter, ciprofloxacin is usually combined with carbapenems. Further, meropenem may be superior to ceftazidime/aminoglycoside for the empirical treatment of ventilator-associated pneumonia.[16]

i. *Imipenem:* It is a broad spectrum antimicrobial with activity against gram-positive, gram-negative (including the beta-lactamase producing), many aerobic and anaerobic bacteria. The sensitive gram-positive organisms include most streptococci, staphylococci (penicillinase and non-penicillinase producing), *E. faecalis*, *Nocardia*, *Rhodococcus*, and *Listeria.* It is not universally active against methicillin-resistant *Staphylococcus aureus.* The gram-negative bacteria susceptible to imipenem include Enterobacteriaceae, including the *Citrobacter, Enterobacter*, *E. coli, Klebsiella, Proteus, Providencia, Salmonella, Serratia, Shigella* and *Yersinia*. It is also active against *P. aeruginosa, Acinetobacter*, *Campylobacter jejuni*, *Haemophilus influenzae* and *Neisseria.* It is also active against anaerobes like *Bacteroides* and *Clostridium difficile.* Although it is stable to most beta-lactamases, it is hydrolyzed by metallo-beta-lactamases, which could be an important cause of resistance to carbapenem treatment in ventilator-associated pneumonia.[17] *Acinetobacter baumannii* is also increasingly showing resistance to carbapenems.[18] Carbapenem-resistant *A. baumannii* (CRAB) is often associated with ventilator-associated pneumonia. Cilastatin, commonly coadministered with imipenem (see below), does not have any antimicrobial action.

Imipenem not absorbed from the GIT, needs to be administered parenterally. It is partly metabolized to toxic metabolites in the kidneys by tubular brush border enzyme (dehydropeptidase-I) and it is given along with cilastatin (inhibitor of dehydropeptidase) to increase imipenem concentrations in urine (but not serum). It is eliminated by the kidneys with a half-life of one hour.

The major indications are for infections in febrile neutropenia and other immunocompromised states, for hospital-acquired pneumonia, and sepsis. In anthrax, it is combined with other agents. Combination with cilastatin reduces the nephrotoxicity of imipenem. Seizures may be precipitated with its use in up to 1.5% of patients, especially in those with compromised renal function and prior CNS disease. Mental disturbances and confusion may also occur. It can cause reddish discoloration of urine, which may be alarming, but not dangerous.

ii. *Meropenem:* The antimicrobial spectrum of meropenem is similar to that of imipenem, but it may have activity against some imipenem-resistant *P. aeruginosa*, may be more active than imipenem against Enterobacteriaceae and less active against gram-positive organisms. Meropenem may be particularly useful in aspiration pneumonia.[19] It is similar to imipenem in most aspects, but not metabolized to a significant extent by renal enzymes and not given with cilastatin. It has less potential to cause seizures and is less nephrotoxic than imipenem.

iii. *Ertapenem:* It is similar to meropenem in most aspects except that it is not active against *P. aeruginosa* and *Acinetobacter*. Its in vitro activity against Enterobacteriaceae carrying plasmid- or chromosomal-mediated beta-lactamases, including AmpC- and extended-spectrum beta-lactamases, is especially clinically significant.

iv. *Doripenem:* The supposed advantage of doripenem over other carbapenems is its potent activity against pseudomonas. Data from 6 phase 3 multinational doripenem clinical trials on Ciprofloxacin-Resistant Enterobacteriaceae (CIPRE) and Extended-Spectrum Beta-Lactamases (ESBL) were evaluated.[20] Doripenem and meropenem were more potent than other drugs.

4. Monobactams

Aztreonam: Its mechanism is similar to that of penicillins. The important feature of aztreonam is its resistance to most beta-lactamases. It has activity only against aerobic gram-negative bacteria like *E. coli*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella* and *Yersinia spp.* It has some activity against *P. aeruginosa* and *H. influenzae.*

Its major indications are serious infections caused by gram-negative organisms and is a useful alternative to aminoglycosides and third-generation cephalosporins. It is used in lower respiratory tract infections, including the pseudomonal infections in patients with cystic fibrosis, meningitis and sepsis. Use with an aminoglycoside is of benefit in serious *P. aeruginosa* infections.

It shows little cross-reactivity with penicillins and cephalosporins, with the exception of ceftazidime. Caution should be exercised in patients receiving anticoagulants as prothrombin time may be increased.

5. Beta-lactamase Inhibitors

Clavulanate, sulbactam and tazobactam are beta-lactamase inhibitors. When given in combination with beta-lactams, they inhibit plasmid-mediated beta-lactamases. Clavulanate is a suicide inhibitor of beta-lactamases produced by both gram-positive and gram-negative organisms. Since it is available as both oral and parenteral preparations, it has been combined with amoxicillin and ticarcillin to improve their antimicrobial spectra. Amoxicillin-clavulanic acid combination extends the spectrum of amoxicillin to beta-lactamase-producing strains of staphylococci and *H. influenzae.* Similarly, the antimicrobial spectrum of ticarcillin-clavulanic acid includes gram-negative bacilli and *S. aureus*.

Sulbactam is another beta-lactamase inhibitor available both as oral and parenteral preparation. Used with ampicillin, it improves the antimicrobial spectrum of ampicillin akin to that of amoxicillin. Tazobactam is available only for pareneteral administration. It is not effective against chromosomally mediated beta-lactamases. Though it is coadministered with piperacillin, the effectiveness of the combination against *P. aeruginosa* is doubtful. When given in combination, the dose of piperacillin gets reduced.

6. Macrolides

Erythromycin, the prototype of macrolides is obtained from *Streptomyces erythreus*. Clarithromycin and azithromycin are semisynthetic derivatives of erythromycin. These agents are largely bacteriostatic (may be bactericidal at high concentrations) and inhibit the growth of microorganisms by binding to the 50 S ribosomal subunit of sensitive microorganisms. They inhibit the translocation step in the peptide synthesis process wherein the newly formed peptidyl t-RNA moves from donor to acceptor site. Agents in this class also demonstrate postantibiotic effect where the effect persists after the antibiotic is removed from the system.

i. *Erythromycin:* The antimicrobial spectrum of erythromycin includes both gram-positive and certain gram-negative organisms. It is effective against pneumococci, streptococci, staphylococci and corynebacteria. Certain atypical microorganisms such as mycoplasma, legionella, *Chlamydia trachomatis, Chlamydophila psittaci, Chlamydophila* *pneumoniae, M. kansasii* and *Mycobacterium scrofulaceum* are also susceptible. Resistance has been seen in penicillin resistant *S. pneumoniae and* mycoplasma. Cross resistance is seen with other groups of these agents.

Erythromycin without an enteric coating is destroyed in the stomach. Erythromycin stearate, ethylsuccinate and estolate provide the requisite enteric coating and the latter is best able to resist destruction in the stomach. Absorption of erythromycin ethylsuccinate and estolate is not affected by the presence of food. Erythromycin gluceptate and lactobionate are available for intravenous administration. Only about 5% of the orally administered drug is excreted in the urine and dose adjustment is not required if the renal functions are compromised.

For pulmonary infections, the indications of erythromycin include acute tracheobronchitis, acute exacerbations of chronic bronchitis with or without complications, and for empirical antimicrobial therapy for pneumonia in previously healthy, ambulatory patients (pneumococcus, *Mycoplasma pneumoniae* being the usual causative organisms). It is also used for the elderly (*Pneumococcus, Klebsiella, S. aureus*, *H. influenzae* being the most likely causative organisms), empirical therapy of pneumonia in pediatric patients of one to three months of age (Chlamydia, ureaplasma, *Pneumocystis carinii* being potentially causative) and also for empirical therapy of pneumonia in children of more than 6 years of age (in whom pneumococcus and mycoplasma may be causative). Erythromycin is used in *Legionella* infections, and respiratory-tract infections such as bronchitis and pneumonia (mycoplasmal and other atypical pneumonias as well as streptococcal). It may be used as part of a multi-drug regimen for the treatment of inhalational anthrax. It is also used in the prevention of diphtheria in non-immune patients and of pertussis in non- or partially immune patients. It may be used as an alternative for actinomycosis for patients who are allergic to penicillin. It is also used as an alternative to the tetracyclines in patients with C*hlamydia pneumoni*a.

The adverse effects include gastrointestinal disturbances such as nausea, vomiting and diarrhea. Acute cholestatic hepatitis occurs most commonly with the estolate salt. This is a hypersensitivity reaction, which usually occurs 10 to 20 days after treatment and is characterized by nausea, vomiting, diarrhea and abdominal cramps. The condition recurs on the readministration of the drug. Reversible sensorineural deafness has been reported with its use. Prolongation of QT interval is known to occur with its administration. Erythromycin may aggravate myasthenia gravis. It inhibits cytochrome P450 enzyme and can lead to the elevated levels of theophylline, oral anticoagulants, cyclosporine and methylprednisolone. It may lead to the elevation of digoxin levels by the inhibition of gastrointestinal and renal P-glycoproteins.

ii. *Clarithromycin:* Clarithromycin is slightly more potent than erythromycin against the sensitive strains of streptococci and staphylococci, and has modest activity against *H. influenzae* and *Neisseria gonorrhoeae.* Clarithromycin has good activity against *M. catarrhalis, Chlamydia spp., Legionella pneumophila, Borrelia burgdorferi, Mycoplasma pneumoniae* and *Helicobacter pylori.* It is more active than erythromycin for Mycobacterium Avium Complex.

The oral absorption of clarithromycin is good. However, it undergoes extensive first pass metabolism. The extended release form is usually given with food to improve its bioavailability. The drug is metabolized in the liver to an active metabolite, 20% to 40% of the drug is excreted unchanged in the urine. Dosage adjustment is not needed in hepatic or renal impairment. Clarithromycin exhibits non-linear pharmacokinetics.

The gastrointestinal symptoms are lesser than that of erythromycin. Prolongation of QT interval has been reported rarely with its use. Isolated cases of corneal opacities, progressive cholestatic jaundice have been reported with its use. It inhibits CYP3A4 and has drug interactions similar to that seen with erythromycin. Concomitant use with theophylline, zidovudine, digoxin, statins, colchicine and carbamazepine may lead to the increase of serum levels and toxicity of these drugs. With verapamil, it may lead to hypotension, bradyarrhythmias and lactic acidosis, it may potentiate the effects of the oral anticoagulants. Inducers of the CYP3A4 (efavirenz, nevirapine, rifampicin, rifabutin and rifapentine) may increase clarithromycin metabolism and thus lower its plasma levels. Both clarithromycin and itraconazole (and also saquinavir) are CYP substrates and increase the plasma levels of each other if used together. QT prolongation leading to torsades de pointes has been reported with its concurrent use with other QT prolonging drugs.

iii. *Azithromycin:* Azithromycin generally is less active than erythromycin against gram-positive organisms and slightly more active than either erythromycin or clarithromycin against *H. influenzae* and *Campylobacter spp*. Azithromycin is very active against *Moraxella catarrhalis, Chlamydia spp.*, *M. pneumonia and L. pneumophila.* It is also active against some atypical mycobacteria. Its adverse effects and drug interactions are similar to clarithromycin.

iv. *Roxithromycin:* It is similar to azithromycin in the terms of spectrum and indications. The dose may need to be reduced in patients with hepatic or renal impairment. Gastrointestinal side effects are less as compared to erythromycin.

v. *Telithromycin:* It is actually a ketolide, obtained from the structural modification of macrolide structure. Addition of keto group confers its properties, which make it less prone to resistance. It is indicated for mild to moderate community-acquired pneumonia due to *S. pneumoniae*, including multi-drug resistant, *H. influenzae*, *M. catarrhalis*, *C. pneumoniae* or *M. pneumoniae*.

Mild gastrointestinal disturbances occur commonly. Severe liver injury leading to acute hepatic failure and even death has been reported. Visual disturbances (such as blurred vision, difficulty in focusing and diplopia) and transient loss of consciousness have been reported because of which patients should be advised to be careful while driving or operating machinery. It should not be given to patients with myasthenia gravis as it may lead to disease exacerbation. It may cause clinically significant QT prolongation. *Clostridium difficile* Associated Diarrhea (CDAD), which may range in severity from mild diarrhea to fatal colitis, has been reported.

7. Quinolones and Fluoroquinolones

Quinolones are derivatives of nalidixic acid. A major disadvantage with nalidixic acid and other quinolones (cinoxacin and oxolinic acid—no longer used) was the fact that they did not achieve sufficient concentration in the blood and tissues and were only suitable for very few conditions, like urinary tract infections. Fluorination of nalidixic acid has led to the development of compounds, which can achieve sufficient concentrations in the blood and tissues and have wider antibacterial spectrum.

Mechanism of action: Fluoroquinolones inhibit two enzymes, Topoisomerase II (DNA gyrase) and Topoisomerase IV. DNA gyrase condenses the large DNA strands into the cell by introducing supercoils into the DNA. During this supercoiling process, both DNA strands are cleaved by DNA gyrase, forming a "quinolone binding pocket."[21] Two quinolone molecules enter this pocket and inhibit further supercoiling. This creates gaps in the DNA strands activating exonucleases (DNA repair enzymes) leading to irreversible DNA damage and cell death. The function of Topoisomerase IV is not well-understood, but appears to be involved in the separation of the DNA daughter chains. Quinolones inhibit DNA gyrase in gram-negative organisms and Topoisomerase IV in gram-positive bacteria.

Pharmacokinetics: Fluoroquinolones in general are drugs with excellent oral bioavailability and have low-plasma protein binding of about 30% (Table 13.1). They readily and rapidly penetrate the body tissues, achieving tissue and fluid concentrations that are generally higher than those in plasma. Peak serum concentrations occur within one to two hours of oral doses. Longer half-lives (10 hours) of some quinolones (trovafloxacin, grepafloxacin, moxifloxacin) permit once-daily dosing. Although levofloxacin has a short half-life, it is used once daily. Fluoroquinolones are eliminated by both renal and nonrenal mechanisms (Table 13.1).

TABLE 13.1: Pharmacokinetic features of fluoroquinolones

Drug	*Half-life (hours)*	*Bioavailability (%)*	*With respect to food*	*Route of elimination*	*Dose adjustment*
Ciprofloxacin	3-5	60-80	Empty stomach	Renal > hepatic	Cr clearance < 30 ml/min
Ofloxacin	4 - 5	~ 100	No effect	Renal	Cr clearance < 50 ml/min
Gatifloxacin	7 - 14	95	No effect	Renal	Renal dysfunction
Gemifloxacin	7	70	No effect	Renal > hepatic	Cr clearance < 40 ml/min
Levofloxacin	7	90	No effect	Renal	Cr clearance < 50 ml/min
Moxifloxacin	13	99	No effect	Hepatic > Renal	Cirrhosis
Lomefloxacin	8	>90	Empty stomach	Renal	Renal dysfunction
Pefloxacin	8 -13	>70	Empty stomach	Hepatic	Hepatic dysfunction
Grepafloxacin	12	70	No effect	Hepatic	Hepatic dysfunction

TABLE 13.2: Classification and spectrum of quinolones[1]

Classification	*Drugs*	*Antimicrobial spectrum*
First generation	Nalidixic acid, Cinoxacin	Gram-negative organisms (but not Pseudomonas)
Second generation	Norfloxacin, Lomefloxacin, Enoxacin, Ofloxacin, Ciprofloxacin	Gram-negative organisms (including Pseudomonas), some gram-positive organisms (*Staphylococcus aureus*, but not *Streptococcus pneumoniae*) and some atypical pathogens
Third generation	Levofloxacin,Sparfloxacin, Gatifloxacin, Moxifloxacin	Same as of second-generation agents plus expanded gram-positive coverage (penicillin-sensitive and penicillin-resistant *S. pneumoniae*) and expanded activity against atypical pathogens
Fourth generation	Trovafloxacin	Same as of third-generation agents plus broad anaerobic coverage

Spectrum, pulmonary indications and dosage: Till date four generations of quinolones have been developed (Tables 13.2 and 13.3).[22] The first-generation compounds have activity against both gram-negative and gram-positive organisms. However, compared to quinolones of subsequent generations, the activity is not very potent. The second-generation agents have good activity against gram-negative organisms and moderately good activity against gram-positive organisms. While good activity against pseudomonas (ciprofloxacin in particular) is an advantage, methicillin-resistant staphylococci and streptococcal infections may not respond to this group, except to levofloxacin, which may have superior efficacy.

Most of the newer fluoroquinolones are effective in sinusitis, acute bacterial exacerbations of chronic bronchitis, and for presumptive therapy for pneumonia in adults with chronic bronchitis or alcoholism. Some of them are also indicated in community- and hospital-acquired pneumonia. Mild to moderate respiratory exacerbations owing to *P. aeruginosa* in patients with cystic fibrosis also respond to oral fluoroquinolone therapy. Unlabeled respiratory indications of fluoroquinolones include pulmonary tuberculosis, anthrax, Legionnaires' disease and community-acquired pneumonia in children.

Adverse drug reactions and drug interactions: Fluoroquinolones are relatively safe drugs, the adverse effects are generally mild and rarely need discontinuation of therapy. The overall incidence of adverse reactions with fluoroquinolones is low (approximately 6% to 7%), the most common are gastrointestinal (mild nausea, vomiting and/or abdominal discomfort) reported in 3 to 17% of patients. Mild headache and dizziness have been reported in up to 11% of patients.

A typical, but rare adverse effect seen with these drugs is the photosensitivity or phototoxicity reaction, which can be moderate to severe. It may include exaggerated sunburn reactions (burning, erythema, exudation, vesicles, blistering, edema) on areas exposed to sun or artificial Ultraviolet (UV) light. Relative potential of the various fluoroquinolones to cause photosensitivity/phototoxicity is unclear. Patients should be advised to avoid unnecessary or excessive exposure to sunlight and artificial UV light, cover the skin with clothing or use sunscreen. The drug should be discontinued if this adverse reaction occurs.

The effect of quinolones on cartilage has been a matter of debate, precluding their use in immature animals. Ciprofloxacin, norfloxacin and nalidixic acid have been given safely in children with cystic fibrosis with few reports of reversible joint symptoms. Achilles tendon rupture or tendinitis had occurred with their use prompting US Food and Drug Administration to add a black box warning with the use of all fluoroquinolones. Leukopenia, eosinophilia and mild elevations in serum transaminases occur rarely. As with most antimicrobials, *Clostridium difficile*-associated diarrhea and colitis (antibiotic-associated diarrhea or pseudomembranous colitis) have been reported in patients receiving fluoroquinolones.

Rarely, serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have occurred usually after multiple doses. Sometimes there is concomitant cardiovascular collapse, loss of consciousness, tingling, edema (pharyngeal or facial), dyspnea, urticaria or pruritus. Fever, rash or severe dermatologic reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome), vasculitis, arthralgia, myalgia, serum sickness, allergic pneumonitis, interstitial nephritis, acute renal insufficiency or failure, hepatitis, jaundice, acute hepatic necrosis or failure, anemia (including hemolytic and aplastic), thrombocytopenia (including thrombotic thrombocytopenic purpura), leukopenia, agranulocytosis, and pancytopenia have all been reported. They require

TABLE 13.3: Approved respiratory indications of fluoroquinolones

Drug	*Indication*	*Dosage*	*Route*
Ciprofloxacin	Ear, nose, and throat infections (including otitis externa, otitis media, and sinusitis)	250 to 750 mg BD. IV dose is 200-400 mg BD	PO, IV
	Lower respiratory tract infections (including pseudomonal infections in cystic fibrosis, but excluding infections due to *S. pneumoniae)*	In cystic fibrosis, 40 mg/kg/day PO	
	Respiratory infections in cystic fibrosis patients	div q12h	
	Anthrax	In anthrax, : 400 mg IV q12h or 500 mg PO q12h	
Lomefloxacin	Acute exacerbation of chronic bronchitis caused by *Haemophilus influenzae* or *Moraxella catarrhalis*	400 mg OD for 10 days	PO
Gemifloxacin	Acute exacerbation of chronic bronchitis caused by *S. pneumoniae, H. influenzae, Haemophilus parainfluenzae,* or *M. catarrhalis*	320 mg OD for *5 days* in the treatment of acute exacerbation of chronic bronchitis	PO
	Mild-to-moderate community acquired pneumonia caused by *S. pneumoniae* (including penicillin-resistant strains), *H. influenzae, M. catarrhalis, Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Klebsiella pneumoniae*	320 mg OD for 7 days in the treatment of community-acquired pneumonia	
Levofloxacin	Acute mild to moderate sinusitis due to *S. pneumoniae, H. influenzae,* or *M. catarrhalis*	For sinusitis, 500 or 750 mg OD for 5 days	PO, IV
	Mild to moderate acute exacerbation of chronic bronchitis due to *S. aureus, S. pneumoniae, H. influenzae, H. parainfluenzae* or *M. catarrhalis*	For acute exacerbation of chronic bronchitis, 500 mg OD for 7 days or 750 mg OD for 5 days	
	Mild, moderate or severe community-acquired pneumonia caused by *S. aureus, S. pneumoniae* (including penicillin-resistant strains), *H. influenzae, M. catarrhalis, M. pneumoniae, C. pneumoniae, Legionella pneumophila* or *K. pneumoniae.*	For community acquired pneumonia, 500 mg OD for 7–14 days or 750 mg OD for 5 days	
	Nosocomial pneumonia due to methicillin-suscpetible *S. aureus, P. aeruginosa, Serratia marcescens, E. coli, K. pneumoniae, H. influenzae* or *S. pneumoniae*	For nosocomial pneumonia, 750 mg OD for 7–14 days	
Moxifloxacin	Acute bacterial sinusitis caused by *S. pneumoniae*, *H. influenzae* or *M. catarrhalis*	For sinusitis 400 mg OD for 10 days.	PO, IV
	Acute exacerbations of chronic bronchitis due to *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *K. pneumoniae*, *S. aureus* (methicillin-susceptible strains), or *M. catarrhalis*	Acute exacerbations of chronic bronchitis 400 mg OD for 5 days	
	Community-acquired pneumonia due to S. *pneumoniae* (including multidrug-resistant strains), *S. aureus* (oxacillin-susceptible strains), *K. pneumoniae*, *H. influenzae*, *M. pneumoniae*, or *M. catarrhalis*.	For community-acquired pneumonia (CAP), 400 OD for 7–14 days.	

BD: twice daily; OD: once daily; PO: orally; IV: intravenous immediate termination of therapy. QT_c prolongation has been observed with sparfloxacin (withdrawn in some countries) and to a lesser extent with gatifloxacin and moxifloxacin warranting their use with care in patients on class III (*amiodarone*) and class IA (*quinidine, procainamide*) antiarrhythmics.

In conjunction with theophylline or Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), hallucinations, delirium and seizures may rarely occur. Ciprofloxacin and pefloxacin inhibit the metabolism of theophylline, and toxicity from elevated concentrations of methylxanthine may occur. Concomitant use of corticosteroids increases the risk of severe tendon disorders (tendinitis, tendon rupture), especially in geriatric patients of older than 60 years of age. Antacids, sucralfate, metal preparations and multivitamins should be taken at least two hours prior or two hours after the administration of some of the oral fluoroquinolones (like levofloxacin) and four to eight hours for moxifloxacin. Quinolones may enhance the effects of warfarin, therefore, it is advisable to closely monitor coagulation parameters.

8. Aminoglycosides

Aminoglycosides are bactericidal drugs and their importance lies in their ability to synergize with the action of penicillins especially against enterococci and streptococci. Agents in this class are derived from either *Streptomyces* (framycetin, kanamycin, neomycin, paromomycin, streptomycin and tobramycin) or the genus *Micromonospora* [gentamicin (which is why it is not spelled *gentamycin*) and sisomicin]. They act by several mechanisms, but mainly through the inhibition of 30 S and 50 S portions of bacterial ribosomes. They are also known to disrupt the integrity of bacterial cell membrane.

Spectrum: The antimicrobial spectrum of aminoglycosides includes aerobic gram-negative bacilli. As mentioned earlier, their action may be extended to gram-positive bacteria when given with penicillins. The most clinically important mechanism of resistance is their inactivation by aminoglycoside modifying enzymes acetyltransferases, adenyltransferases or phosphotransferases. The other mechanisms include (i) decreased permeability of the antimicrobial into the cells because of alteration in their transport system, inadequate membrane potential, or modification in the lipopolysaccharides, and (ii) mutations in chromosomal genes encoding ribosomes leading to alteration in their targets. Cross resistance to other aminoglycosides may occur, but is less with amikacin.

Pharmacokinetics: This group of antibiotics is not absorbed orally and needs to be administered either via intramuscular or as intravenous infusion. Aminoglycosides exhibit concentration dependent kinetics and have considerable post-antibiotic effect. These two properties make it prudent to administer aminoglycosides as a single large dose rather than multiple small doses. With once a day regimen, the propensity for toxicity is also reduced once daily dosing allows for longer periods for which the drug remains below the threshold concentration. Additionally, once a day administration has the advantage of enabling treatment in an outpatient setting.

The polar nature of these compounds does not allow intracellular penetration, thereby considerably reducing the volume of distribution. Since aminoglycosides are largely eliminated renally, the dose has to be adjusted in accordance with creatinine clearance.

Therapeutic drug monitoring may be required with their use. The doses are adjusted so as to achieve a target concentration of less than 1 mcg/ml between 18 to 24 hours after the dose administration. Obtaining blood sample eight hours after drug administration will enable dose adjustment to achieve target concentration at 18 hours. When they are administered in multiple dose regimens, both peak and trough concentrations need to be measured.

For respiratory tract infections there are a few indications like infections due to gram-positive organisms, such as staphylococci, streptococci or pneumococci, where these antibiotics must be used. But they should be used in combination with penicillins. They are primarily indicated for infections (including serious infections of the respiratory tract) caused by gram-negative bacteria, including Pseudomonas, *E. coli*, Proteus, Providencia, *Klebsiella,* Enterobacter, Serratia and Acinetobacter. In spite of a large number of adverse effects associated with their use, they remain drugs of choice in many serious infections like septicemia, bacterial endocarditis and other serious infections caused by gram-negative bacilli.

i. *Gentamicin:* It is used in many severe systemic infections caused by susceptible organisms, including pneumonia, septicemia, endocarditis, cystic fibrosis, plague, meningitis, infections in immunocompromised patients and patients admitted in intensive care units. It is seldom used alone and is commonly prescribed with penicillins for streptococcal and enterococcal infections, with antipseudomonal beta-lactams for Pseudomonas, and with metronidazole (clindamycin) for mixed aerobic-anaerobic infections.

ii. *Tobramycin:* It is similar to gentamicin, but has been specifically used in pseudomonal infections.

iii. *Kanamycin:* It is also similar to gentamicin. Development of resistance is a bigger problem with kanamycin as compared to other aminoglycosides, which has led to a decline in its use.

iv. *Amikacin:* Its indications are similar to those of gentamicin except that should be reserved for the treatment of gentamicin- and tobramycin-resistant severe infections. It is also useful in nontuberculous mycobacterial infections. It is also used in combination with other antibiotics like gentamicin.

v. *Netilmicin:* It is similar to amikacin and can be used as its alternative. It was suggested that it is less nephrotoxic and ototoxic than other aminoglycosides. This has not been substantiated in all studies.

vi. *Streptomycin:* It is mainly used as an antitubercular drug and is covered elsewhere.

Adverse Effects of Aminoglycosides

Ototoxicity and nephrotoxicity are the major limitations. Ototoxicity manifests as vestibular disturbance and/or auditory dysfunction. The irreversibility of ototoxicity makes it a cause of concern. Mild ototoxicity may be seen in up to 25% patients, but overt ototoxicity occurs in 2% to 10%. A high pitched tinnitus is the first sign of cochlear toxicity. If the drug is not discontinued, permanent auditory dysfunction may occur. Vestibular toxicity is more difficult to diagnose and headache may precede vestibular toxicity. This progresses onto loss of coordination, mental past pointing and positive Romberg’s test. Predisposing factors include extremes of age, higher dose/duration of use, raised peak and trough levels, and concurrent use of other ototoxic drugs. Aminoglycosides constitute the single most common cause of bilateral vestibulopathy, accounting for 15% to 50% of all cases.[23]

Nephrotoxicity caused due to the accumulation of drugs in proximal convoluted tubule is seen in 8% to 26% patients, its incidence is similar with different aminoglycosides. Unlike ototoxicity, nephrotoxicity is almost always reversible if treatment is promptly discontinued. Typical picture is that of nonoliguric renal failure; elevation of serum creatinine; albuminuria; presence of red cells, white cells and casts; and development of hypoosmolar urine after several days of therapy. Azotemia and oliguria have also been reported. Predisposing factors include high dose and long duration of drug administration, high peak and trough levels, extremes of age, compromised renal function, dehydration and concurrent use of other nephrotoxic drugs.

The third important adverse effect of aminoglycosides is neuromuscular-blocking action leading to respiratory depression and muscle paralysis. Other adverse reactions (seen rarely) include rash, fever, headache, anaphylaxis, nausea and vomiting, tremor, arthralgia, hypotension, blood dyscrasias, purpura, stomatitis, liver dysfunction, peripheral neuropathy, meningeal irritation encephalopathy, confusion, lethargy, hallucinations and convulsions. Liposomal formulations of some aminoglycosides like gentamicin and amikacin are being developed with the hope of reducing adverse effects.

9. Tetracyclines

Tetracyclines are protein synthesis inhibitors. They bind to the 30 S subunit of bacterial ribosome blocking the binding of aminoacyl-tRNA to the acceptor site on the m-RNA ribosome complex. They are bacteriostatic broad spectrum antibiotics with susceptibility extending to gram-positive, gram-negative, aerobes, anaerobes, rickettsia and mycoplasma. Resistance to the tetracyclines is common, is mediated by plasmids preventing drug accumulation within the cell by decreasing active transport of the drug or by increasing efflux.

Tetracyclines differ amongst each other mainly for pharmacokinetic parameters (Table 13.4). Antimicrobial spectrum of different tetracylines is largely the same. However, organisms showing resistance to certain tetracyclines may still be susceptible to doxycycline, minocycline and tigecycline, the new generation tetracyclines.

Indications and Dosage: Tetracyclines are broad-spectrum antimicrobials active in rickettsial infections, pharyngitis, sinusitis, or pneumonia due to *C. pneumoniae* and by *M. pneumoniae* (Table 13.5). They can also be used in community-acquired bacterial pneumonia caused by penicillin-susceptible *S. pneumoniae*, including in patients with associated bacteremia, beta-lactamase negative *H. influenzae* and *L. pneumophila.* They are also used (along with streptomycin) in brucellosis and plague. They are also effective in anthrax and chronic bronchitis.

Doxycycline, minocycline, tetracycline hydrochloride are commonly used for acute respiratory exacerbations of chronic bronchitis .[24] Doxycycline is also used for empirical therapy of pneumonia in previously healthy patients with no history of antibiotic intake. Though not approved for this indication, tigecycline has been shown to be as effective as levofloxacin in hospitalized adult patients with community-acquired pneumonia.

Adverse effects: The most common gastrointestinal (nausea, vomiting and diarrhea) adverse effects of

TABLE 13.4: Important pharmacokinetic aspects of tetracyclines

Tetracycline	*Oral bioavailability*	*Half-life*	*Duration of action*	*Metabolism and elimination*
Chlortetracycline	30%		Short acting	Mainly eliminated by kidney, though undergoes enterohepatic recirculation
Oxycline	60-80%	6-12 hrs	Short acting	Mainly eliminated by kidney, though undergoes enterohepatic recirculation
Demeclocycline	60-80%	16 hrs	Intermediate acting	Mainly eliminated by kidney, though undergoes enterohepatic recirculation. Photosensitivity reactions are common. Known to cause nephrogenic diabetes insipidus
Tetracycline	60-80%	6-12 hrs	Short acting	Mainly eliminated by kidneys, though undergoes enterohepatic recirculation
Doxycycline	95%	16-18 hrs	Long acting	Mainly eliminated by kidneys
Minocycline	100%	16-18 hrs	Long acting	Significantly metabolized by the liver. It is also retained in fatty tissues
Tigecycline	Not given orally due to poor oral bio-availability	36 hrs	Long acting	59% eliminated by biliary/fecal excretion, and 33% excreted in urine

TABLE 13.5: Doses and some features of tetracyclines

Drug	*Dose*	*Remarks*
Tetracycline	250 or 500 mg four times a day (maximum 4 g/day) orally or by slow IV infusion or intramuscularly	1 hour before or 2 hours after meals Avoid in patients with renal impairment
Demeclocycline	600 mg/day in 2 or 4 divided doses. Preferably for atypical pneumonia, 900 mg/day in 3 divided doses	1 hour before or 2 hours after meals. In patients with liver disease, maximum dose is 1 g/day
Doxycycline	200 mg on day 1, followed by 100 mg/day orally or IV. In severe infections 200 mg/d throughout	May be used in patients with renal impairment.
Minocycline	200 mg loading dose followed by 200 mg/day in 2 divided doses orally or by slow IV infusion	More active against *S. aureus*, Streptococci, *Acinetobacter*, *Bacteroides*, *Hemophilus*, and some mycobacteria
Tigecycline	100 mg loading dose followed by 50 mg twice daily by IV infusion over 30 to 60 minutes	Effective against tetracycline-resistant organisms

tetracycline occur because of mucosal irritation. Esophageal ulceration can occur, therefore, oral preparations should be taken with sufficient water, in sitting or supine position, and a few hours before bedtime.

Glossitis, stomatitis, dysphagia, oral candidiasis, vulvovaginitis may occur due to overgrowth with *Candida albicans*. Antibiotic-associated diarrhea can occur as with most antimicrobials. Doxycycline may be less prone to cause GI adverse effects because of better absorption. Other serious complications of tetracycline therapy may include side effects such as, renal dysfunction, especially in patients with preexisting renal disease; increases in liver enzymes; rarely severe hepatotoxicity; and pancreatitis. They are deposited in both milk teeth and permanent teeth leading to permanent discoloration and enamel hypoplasia. Tetracyclines are also deposited in calcifying areas in bone and nails and may interfere with bone growth.

Abnormal pigmentation of skin, conjunctiva, oral mucosa, tongue, and internal organs such as the thyroid has occurred rarely. Permanent discoloration of cornea has been reported in infants born to mothers given tetracycline in high doses during pregnancy. Intracranial hypertension with headache, dizziness, tinnitus, visual disturbances and papilledema have been reported. Transient myopia, muscle weakness in patients with myasthenia gravis, lupus exacerbation, hypersensitivity reactions, phototoxicity, and rarely agranulocytosis, aplastic anemia, hemolytic anemia, eosinophilia, neutropenia, and thrombocytopenia have been reported. They can also cause hypoprothrombinemia and reduction in serum-vitamin B concentrations. Outdated tetracyclines can cause Fanconi-type syndrome.

Drug interactions: The absorption of tetracyclines is reduced by antacids, iron, and milk and dairy products. Therefore it is advisable to have a gap of one to three hours in between. Nephrotoxicity and hepatotoxicity of tetracyclines may be increased by other nephrotoxic and hepatotoxic drugs, respectively. Concomitant use with retinoids may lead to an increased incidence of benign intracranial hypertension. Tetracyclines may decrease the efficacy of oral contraceptives. Bactericidal drugs like penicillins should not be used with tetracyclines (bacteriostatic).

10. Glycopeptides

They include vancomycin, teicoplanin, and others like telavancin, ramoplanin, decaplanin. Their mechanism of action is the inhibition of cell wall synthesis by binding to d-Ala d-Ala terminus of nascent peptidoglycan inhibiting synthesis of peptidoglycan. This group of drugs should be reserved for serious, multidrug-resistant infections since resistance to these drugs is uncommon, and also because of their toxicity profile.

i. *Vancomycin:* It is active against *S. aureus, S. epidermidis* (including meticillin-resistant), *S. pneumoniae, S. pyogenes, Viridans streptococci, Enterococci, Clostridium, Actinomyces, Bacillus anthracis, Corynebacterium*, lactobacilli and *Listeria.* Like other beta-lactams, it is synergistic with the aminoglycosides. Resistance is plasmid-mediated and may be transferable to other gram-positive organisms; it has been seen in *Lactobacillus* and enterococci.

   Its major indication is serious gram-positive infections like methicillin-resistant staphylococcal infections (brain abscess, meningitis, sepsis), nosocomial pneumonia, neutropenic and immunocompromised patients when other beta-lactams cannot be used because of microbial resistance, adverse effects or hypersensitivity.

   It may cause histamine release leading to erythema, flushing, or rash over the face and upper torso (“red man syndrome”); rarely hypotension and shock may occur.

   Nephrotoxicity and ototoxicity are two other serious adverse effects, which are more likely to occur in patients with renal impairment or with high dose. Ototoxicity (may be irreversible) is more common in patients with preexisting hearing problems and with concomitant use of other ototoxic drugs. Tinnitus is usually the first sign of impending ototoxicity and warrants stoppage of treatment. Because of its irritant nature, thrombophlebitis can occur, but is rare if it is used diluted and infused slowly. Inhalational use has caused bronchoconstriction, which is treated with inhaled beta agonists.

ii. *Teicoplanin:* Its spectrum and resistance patterns are similar to vancomycin. Cross-resistance with vancomycin occurs, but may not be complete. It is not orally absorbed and is given parenterally. It is excreted by the kidneys with a half-life of about 60 hours. Incidence of “red man” syndrome is less. It is also less irritant and, therefore, incidence of thrombophlebitis is less.

iii. Dalbavancin and telavancin are two other glycopeptides under development. The former is characterized by a long half-life permitting once a week administration. Telavancin has activity against gram-positive bacteria and against strains with intermediate sensitivity to vancomycin. It has dual mechanism of action as it inhibits both cell wall and cell membrane.

11. Miscellaneous Antimicrobials

i. *Trimethoprim-Sulfamethoxazole:* The combination of trimethoprim and sulfamethoxazole is synergistic in action by the virtue of its action on two sequential steps in the synthesis of folic acid. Sulfamethoxazole inhibits the incorporation of Para Aminobenzoic Acid (PABA) into folic acid while trimethoprim prevents the reduction of dihydrofolate to tetrahydrofolate. Both of these steps are required in the synthesis of folic acid. The antimicrobial spectrum of the combination includes *Chlamydiae diphtheria, S. aureus, S. epidermidis, Streptococcus pyogenes, Klebsiella sp.*, pneumocystis and *Yersinia pseudotuberculosis*. Methicillin-resistant strains of *S. aureus* may be susceptible to trimethoprim-sulfamethoxazole. Widespread resistance is common in streptococci. Resistance has been commonly observed in both gram-positive and gram-negative organisms.

Indications and dosage: The combination is available as 80 mg trimethoprim and 400 mg sulfamethoxazole and as Double Strength (DS) tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole. For the treatment of acute exacerbations of chronic bronchitis (it is not first or even second choice) due to susceptible strains of *S. pneumoniae* or *H. influenzae,* it is used as one DS tablet twice daily for 10 to 14 days. The daily dose for treatment of *P. carinii* pneumonia is 15 to 20 mg/kg trimethoprim and 75 to 100 mg/kg sulfamethoxazole in equally divided doses every six hours for 14 to 21 days. For prophylaxis of *P. carinii*, the dose is one DS tablet once daily. Doses will need to be adjusted for creatinine clearance.

Adverse effects: Adverse effects are common, include gastrointestinal disturbances (nausea, vomiting, anorexia) and skin reactions (rash and urticaria). Blood dyscrasias may occur. Caution needs to be exercised in patients with hepatic or renal impairment. It is contraindicated in patients with megaloblastic anemia due to folate deficiency. Folate supplementation is required if the drug is given for a proloned period or when used in elderly patients with a tendency for folate deficiency. Rarely, fatal reactions like Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, other blood dyscrasias, and hypersensitivity of the respiratory tract have occurred. Renal failure, interstitial nephritis, hyperkalemia, hyponatremia, aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache, hallucinations, depression, apathy, nervousness, arthralgias, myalgias, cough, shortness of breath, and pulmonary infiltrates have all been reported.

ii. *Chloramphenicol:* It is a broad-spectrum bacteriostatic antimicrobial effective against gram-positive and gram-negative bacteria, as well as several others that acts by binding to the 50 S subunit of the bacterial ribosome leading to the inhibition of protein synthesis. Its spectrum includes *H. influenzae*, *N. meningitidis*, *S. pneumoniae*, *S. pyogenes, Viridans streptococci, S. epidermidis, S. aureus* (not all strains), and streptococci such as *Str. pneumoniae*, *S. pyogenes*, *B. anthracis*, *C. diphtheriae*, *Peptococcus, Peptostreptococcus, Bordetella pertussis, Brucella abortus*, *Campylobacter*, *Legionella pneumophila* and *B. fragilis*.

Bone marrow depression is the most important and potentially fatal adverse effect. The depression is generally reversible, related to the dose. Rarely, (1 in 50,000) it is dose-independent and irreversible. "Grey baby syndrome" is typically seen in premature infants characterized by ashen color of skin, abdominal distension, vomiting and hypothermia, progressing as to development of cyanosis, disturbed breathing, circulatory collapse and death. Bleeding, hemolytic anemia (especially in G-6-PD deficiency), neuritis (including optic), encephalopathy, headache, and ototoxicity have all been seen with its use.

iii. *Linezolid:* The oxazolidinone *linezolid* has activity against gram-positive organisms, including the vancomycin-resistant enterococci and methicillin-resistant *S. aureus*. It is a bacteriostatic drug and acts by the inhibition of ribosomal proteins.

It is well-absorbed after oral administration. It is an alternative to vancomycin for community-acquired pneumonia due to methicillin-resistant *S. aureus* (MRSA) and for hospital-acquired pneumonia, where the possibility of MRSA infection exists. It is also used for infections of the respiratory tract, including those due to vancomycin-resistant enterococci and methicillin-resistant *S. aureus.* It has been also used in the treatment of nocardiosis.[25]

Lactic acidosis, convulsions, bullous skin eruptions, including Stevens-Johnson syndrome, peripheral neuropathy, optic neuropathy (leading to blindness), and reversible myelosuppression have been rarely reported. It should not be used in gram-negative infections; increased mortality in patients with gram-negative or mixed infections was seen in a trial comparing linezolid to vancomycin, oxacillin or dicloxacillin (21.5% vs 16%) leading to an FDA alert in 2007.[26] It is a reversible and nonselective inhibitor of enzyme Monoamine Oxidase (MAO) and, therefore, can interact with adrenergic and serotonergic drugs similar to antidepressant MAO inhibitors. Serotonin syndrome may be precipitated when linezolid is used with Selective Serotonin Reuptake Inhibitors (SSRIs). Marked increase in blood may be seen with dopamine or adrenaline, reduction in the doses of these pressor agents may be needed.

iv. *Streptogramins:* Quinupristin and dalfopristin are semisynthetic derivatives of pristinamycin I and II respectively, used in a ratio of 3:7. They act by inhibiting protein synthesis by binding to the 50 S ribosomal subunit. The action of quinupristin and dalfopristin is synergistic. The spectrum includes MRSA, multidrug-resistant *Staphylococcus aureus,* vancomycin-resistant *Enterococcus faecium* (but not *E. faecalis*), penicillin- and macrolide-resistant *Streptococcus pneumoniae,* and gram-negative bacteria (*Legionella pneumophila*, *Moraxella catarrhalis* and *Mycoplasma pneumoniae).*

They are not absorbed orally. They are rapidly metabolized, the main route of elimination is fecal (3/4th) and the rest is eliminated in urine with half-lives of about one hour. They are approved for use in Europe for the treatment of nosocomial pneumonia and infections caused by MRSA. They are also indicated for the treatment of serious infections caused by gram-positive organisms, as well as vancomycin-resistant *E. faecium.*

Liver enzyme elevation, myalgias and arthalgias, anemia, neutropenia, eosinophila and thrombocytopenia may occur. They inhibit CYP3A4 and can increase blood levels of drugs metabolized by these enzymes. They may cause QT interval prolongation when given with other drugs having actions (like astemizole, terfinadine and cisapride).

v. *Lincosamides:* Lincomycin and clindamycin are not related structurally to erythromycin and the other macrolide antibacterials, but have similar antimicrobial activity. They act at the same site on bacterial ribosome. The lincosamides have a potential for use as alternatives to penicillin, however, pseudomembranous colitis limits their use for this indication. Currently, they may be considered for the treatment of severe anaerobic infections.

vi. *Polymyxins*: This group includes polymyxin B and colistin (also known as polymyxin M). In 1962, Edgar and Dickinson wrote,*"Attempts to cure infections caused by Pseudomonas…are often unsuccessful. Many strains of the organism are resistant to almost all chemotherapeutic agents, and strains initially sensitive may become resistant during treatment."*This statement holds true even today and this group of agents have emerged as a "last resort" antimicrobials for gram-negative infections resistant to all existing drugs.

They replace the Ca^{++} and Mg^{++} ions on the LPS layer of gram-negative cell wall leading to permeability changes and cell death. They also have a unique antiendotoxin activity for which they have been utilized in gram-negative bacterial sepsis and endotoxin-mediated shock.

They are bactericidal against most gram-negative bacilli except *Proteus* spp and are particularly effective against *Ps aeruginosa. Acinetobacter, E coli, Enterobacter* and *Klebsiella, H influenzae, B pertussis, Salmonella, Shigella Serratia, Burkholderia, and Providencia* , and *B fragilis* are usually resistant. They are also not active against *Neisseria* spp., obligate anaerobes, and gram-positive bacteria.

Polymyxins are not absorbed from GIT, through mucous membranes, or intact or denuded skin. They do not cross blood-brain barrier, pleura, synovial fluid, or placenta. The half-life is 6 hours and is prolonged in renal impairment. They can be administered topically for skin, ear, and eye infections; orally for selective digestive tract decontamination (SDD); parenterally for systemic infections; intrathecally for meningitis and subconjunctivally for ocular infections.

The dose for polymyxin B is 15,000 - 25,000 u/kg/day (max 2 million u/day). 5 lac units should be dissolved in 500 mL of D5 and infused over 24 h or it can be given in two divided doses every day - infused over one hour. It is also given by aerosolization for gram-negative nosocomial pneumonia and respiratory failure requiring mechanical ventilation. For this purpose, 25000 u/kg/d divided into 4 doses as 0.5% solution in NS is administered.

It is important to note that polymyxin B should be stored at controlled room temperature 15° to 30°C before reconstitution but it should be protected from light for which it may be retained in carton until time of use. After reconstitution it must be stored under refrigeration, between 2° to 8°C and any unused portion should be discarded after 72 hours.

Colistin is administered parenterally as colistimethate, in doses of 6 mln u/day in 3 divided doses up to a maximum of 6 mln u/d. It can be given as direct intermittent injection over 3-5 min every 12 h or by continuous infusion. For the latter, ½ of total daily dose is given over 3-5 min and the remaining ½ of total daily dose is dissolved NS or DNS or 5% D or Ringer Lactate and administered by slow IV infusion, starting 1-2 h after the initial dose, over the next 22-23 h. Colistimethate infusion should be freshly prepared and used within 24 h.

The oral dose for colistin is 1.5-3 mln units tid; as inhalation it is used in doses of 1-2 mln units bid-tid.

The major dose-related toxicity of polymyxins is neurotoxicity and nephrotoxicity for which they were infrequently used until a few years back. They can also cause hypersensitivity reactions including those due to histamine release leading to bronchoconstriction and anaphylactoid symptoms. The neurotoxicity is seen in about 7% of patients with normal renal function and manifests as paresthesias, visual disturbances, dizziness, ataxia, confusion, or drowsiness. Neuromuscular blockade is a serious complication and can lead to respiratory paralysis and apnea for which the only treatment is artificial respiration. Nephrotoxicity is the major adverse effect and older literature quotes the incidence as about 20%. However, it is believed that for the newer more purified polymyxins the incidence may be less.

In conclusion, polymyxins should be reserved only for serious gram-negative infections by bacteria resistant to all currently available β-lactams, aminoglycosides, and fluoroquinolines. Although both polymyxin B and colistin are similar in most aspects, polymyxin B may be superior to colistin for MDR *P. aeruginosa*. Patients with abnormal RFT should receive lower doses.

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14

Antiviral Drugs

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INTRODUCTION

The development of antiviral drugs has lagged behind that of antibacterial drugs. Although the first antibacterial drugs became available in the 1930s, the discovery of the first antiviral compounds occurred some two decades later. The first antivirals in clinical use were idoxuridine for herpetic keratitis and methisazone for the prophylaxis of smallpox in contacts and the treatment of the infective complications of smallpox in the 1960s.[1]

Advancements in combinatorial chemistry, computer-assisted drug design and elucidation of microorganisms' genomes coupled with the increasing understanding of viral replication mechanisms have provided information on several novel targets for new drug development with the result that we have been able to discover, over the past few years, several new drugs that are effective, selective for viruses and spare the host cells. Many viral infections for which no treatment was available until a few years ago are now amenable to treatment, e.g. HIV, hepatitis C (HCV) and B (HBV) viruses, herpes viruses, papillomavirus and influenza. However, there still exist several viral infections that have no treatment, for instance, poliomyelitis, common cold, rabies, mumps, rubella and others.

There are several reasons for the inability to discover novel, safe and effective antiviral drugs. Viruses are obligate intracellular parasites that, on entry into their host, need metabolic processes of the host cell to replicate. Consequently, the antiviral drug should either be able to block entry of the virus into the host cells or exit or be able to kill the virus within the host cells, but do it without interfering with the functions of the host cells. Therefore, selective inhibitors of these viral processes that do not cause toxicity to the host cells are difficult to develop. Moreover, viruses constantly change their antigens leading to alterations in drug target enzymes that not only makes drug development difficult, but also leads to the emergence of drug resistant strains. Some general features of antiviral chemotherapy are outlined below (Table 14.1).

TABLE 14.1: General features of antiviral chemotherapy

- None of the antiviral drugs is virucidal; these drugs are only able to inhibit viral replication (virustatic). Therefore, if the immune system of the host is compromised, viruses start replicating once treatment is stopped leading to disease recurrence and drug-resistance.
- The antiviral drugs are not effective against latent viruses and need active replication of the viruses to be effective.
- Early initiation of antiviral drug treatment is crucial for effectively controlling the infection.
- For most viral infections multi-drug therapy is needed.
- The correlation of culture sensitivity testing with clinical use is weaker as compared to antibacterial drugs mainly for the reason that these tests are not standardized for antiviral agents. Moreover, the antiviral drugs lead to adverse effects because of insufficient selectivity, which may make it difficult to choose a drug even if virus is sensitive to it in the lab.
- Antiviral drugs are not substitutes to immunization for prophylaxis of viral infections.
- An important property of any antiviral drug is its ability to penetrate the infected cells to be effective.
- Because of the relative ineffectiveness of most antiviral drugs, the role of symptomatic, supportive treatment must not be ignored.

MECHANISM OF ACTION OF ANTIVIRAL DRUGS

The basic processes for viral replication include viral attachment to certain host cell surface receptors followed by viral entry into the cell.[2] The virus then uncoats its nucleic acid and starts to synthesize the regulatory proteins necessary for synthesis of new viral RNA or DNA. With the help of host metabolic machinery, the virus is now capable of synthesizing structural proteins needed for the maturation of new viral particles. These newly formed viruses then leave the host cell to infect more cells. Currently available antiviral drugs utilize these steps in the viral replication process.

Anti-Influenza Drugs

Influenza is an acute respiratory-tract infection caused by Orthomyxoviridae family of RNA viruses. Of the three types of known influenza viruses (A, B and C), type A is the most important as it causes most infections (including the outbreaks) whereas types B and C are less commonly implicated and lead to mild infections. “Bird flu” (first reported in 1997 in Hong Kong) is also a form of influenza (avian or H5N1 influenza), may cause severe illness and has high mortality rates. “Swine flu” (H1N1 and other strains like H1N2, H3N1, etc.), first reported in 1918, had its most recent outbreak in humans in 2009.

There are two main classes of antiviral drugs for influenza: M2 ion channel inhibitors (amantadine, rimantadine) and neuraminidase inhibitors (oseltamivir, zanamivir). None of them is effective against all the types of influenza; and none of them has been proven to be conclusively effective against serious influenza infections when the risk of development of complications is high.

M2 Ion Channel Inhibitors

Amantadine and rimantadine inhibit viral uncoating and may reduce viral assembly probably via hemagglutinin pathway by acting on influenza A virus M2 protein, which is a membrane protein and is basically an ion channel. Although primary drug resistance is seen in less than 2% of viruses, acquired resistance is much more common (1/3rd of cases).[3]

Both these drugs are used for prophylaxis, as well as for the treatment of influenza A virus infections. For prophylaxis, 200 mg/day in one or two divided doses in young adults is about 70% to 90% protective.[4] For treatment, 200 mg/day for five days of either drug is considered useful although it reduces the duration of fever and systemic complaints by just about one to two days. These drugs are also used in hepatitis C, Parkinsonism is an unrelated indication. They are ineffective against influenza B, or avian influenza H5N1 strain or the H1N1 swine flu.

The most common adverse effects are minor Gastrointestinal (GI) disturbances (loss of appetite, nausea) and Central Nervous System (CNS) symptoms (anxiety, lightheadedness, difficulty concentrating, insomnia, etc.). The latter are seen in up to 30% of patients on amantadine, but are less common with rimantadine.[5] Rarely, serious adverse effects like cardiac arrhythmias, delirium, hallucinations, seizures and coma may occur.

Neuraminidase Inhibitors

Neuraminidase enzyme is important for the release of virus from infected cells and neuraminidase inhibitors cause a conformational change in the active site of the enzyme leading to its inhibition. Resistance occurs in 5% to 15% of cases. Oseltamivir is given orally and is rapidly absorbed. Zanamivir is not absorbed after oral administration and is used by inhalation when about 15% is deposited in the lower respiratory tract and about 80% in the oropharynx.[6] The plasma half-life of oseltamivir carboxylate is 6–10 hours and that of zanamivir is 2.5–5 hours after inhalation (1.7 hours after IV). Both the drugs are predominantly eliminated unchanged in the urine.

Both the drugs are effective in prophylaxis and treatment of influenza A and B virus infections. For prophylaxis, oseltamivir is given orally 75 mg or zanamivir intranasally once daily. For treatment, oseltamivir 75 mg twice daily or zanamivir 10 mg twice daily for five days are effective in reducing the duration of disease (by one day) and may reduce the risk of complications. These drugs also have some efficacy against some strains of avian influenza and swine flu.

Oseltamivir causes GI irritation leading to nausea, abdominal discomfort and vomiting, but these symptoms are self-limiting even if treatment is continued. They are also decreased if drug is taken with food. Headache may also occur, but is uncommon. Zanamivir inhalation can cause wheezing and bronchospasm that leads to deterioration in lung function. Occasionally, deaths have been reported especially in patients with underlying lung disease.

Second generation long-acting neuraminidase inhibitors: Single-dose or once weekly treatment may offer several advantages like superior patient compliance and greater protection in a population. The first Long-Acting Neuraminidase Inhibitor (LANI), hence the name **laninamivir,** has recently completed phase 3 of clinical new drug development and may be marketed within a few years of publication in some countries. It has been shown to have efficacy similar to that of oseltamivir in patients with influenza A or B. In another study, it reduced the median time to illness alleviation in pediatric patients with oseltamivir-resistant influenza A virus.[7] Besides influenza A and B, it may also have activity against other influenza viruses.

In conclusion, there is some evidence to show that neuraminidase inhibitors may be superior to M2 ion channel inhibitors in the view of their lesser incidence of resistance, fewer adverse effects and greater efficacy against influenza B. Neuraminidase inhibitors may also be effective against strains resistant to M2 ion channel inhibitors. Combination regimens of amantadine, ribavirin and oseltamivir have been shown to be effective for viruses resistant to neuraminidase inhibitors. However, these findings are only experimental and adverse effect profile of such combinations would need consideration.[8]

Antiviral Drugs for Respiratory Syncytial Virus (RSV) Infection

RSV is an RNA virus of the Paramyxoviridae family that causes respiratory infections in all age groups, although infants and young children are more susceptible. RSV is an important cause of serious respiratory illness in Blood and Marrow Transplant (BMT) recipients. In some subsets of these immunocompromised patients, RSV upper respiratory illnesses frequently progress to fatal viral pneumonia. The management is primarily supportive. Ribavirin is the only approved specific antiviral drug for RSV and palivizumab is a recently approved humanized monoclonal antibody.

Ribavirin

It is a synthetic nucleoside analogue structurally related to guanine and acts by inhibiting viral nucleic acid synthesis. It is rapidly and extensively absorbed after oral administration. Aerosolized ribavirin achieves high concentrations in the respiratory tract, but is also absorbed systemically. It is not metabolized, gets stored in the tissues and is slowly eliminated by the kidneys with a half-life of about 300 hours. It is indicated for severe RSV bronchiolitis and is preferably given by aerosol. It is also active against influenza, parainfluenza, Severe Acute Respiratory Syndrome (SARS), measles, mumps, HIV, herpesviruses, adenoviruses and poxviruses. The most common adverse effects of oral ribavirin are flu-like symptoms and neuropsychiatric disturbances (anxiety, depression, insomnia and irritability). Bacterial infections, hemolytic anemia, leukopenia, thrombocytopenia, aplastic anemia and several other complications may also occur. When given by inhalation, it can cause lung function worsening, bacterial pneumonia, pneumothorax and hypotension.

Palivizumab

Produced by recombinant DNA technology, it is an antibody against an epitope in the A antigenic site of F protein of RSV. It was approved for use in infants with high risk for RSV infection. It effectively neutralizes a broad range of clinical isolates of RSV and may be several times more active than RSV-IGIV. Palivizumab is administered in a dose of 15 mg/kg IM once a month during the RSV season, which may occur predominantly between December to February in India. Given with ribavirin, palivizumab has shown improvement in response rate.[9] Side effects include erythema, pain, induration and bruising at the injection site. Vomiting, diarrhea and fever, and mild to moderate elevation of aspartate aminotransferase may also occur.

Antiherpesvirus Drugs

Two types of herpesviruses are common pathogens—Herpes Simplex Virus Type 1 (HSV-1) and HSV-2. HSV-1 leads to oral, esophageal, facial, dermatological or brain infections whereas HSV-2 leads to genital, rectal, dermatological or meningeal infections. The major drugs used in these infections are synthetic nucleoside analogues—**acyclovir, valacyclovir, ganciclovir, valganciclovir, famciclovir** and **penciclovir,** and non-nucleoside pyrophosphate **foscarnet**. They inhibit viral DNA synthesis. Resistance is common and occurs by alterations in viral enzymes (thymidine kinase, DNA polymerase) involved in their mechanisms of action.

Nucleoside Analogues

Besides HSV infections, these drugs are also effective against Varicella-Zoster Virus (VZV) and prophylaxis of Cytomegalovirus (CMV) in immunocompromised patients, but they are ineffective against established CMV infections. Ganciclovir is also effective against HIV and hepatitis B virus. The dose of oral acyclovir is 200 mg five times daily or 400 mg three times daily for 7 to 10 days and that of valacyclovir is 1000 mg twice daily for 7 to 10 days. Intravenous acyclovir is used in doses of 5–20 mg/kg every eight hours. Ganciclovir is more effective against CMV and is used in doses of 5 mg/kg by IV infusion every 12 hours. Penciclovir is used topically as a 1% cream every two hours during waking hours for four days in the treatment of herpes labialis.[10] Famciclovir is given orally in doses of 250 mg three times daily, or 500 mg twice daily or 750 mg once daily.

These drugs can lead to nausea, diarrhea, rash, headache, renal insufficiency and neurotoxicity. Confusion and hallucinations can occur with high doses. Thrombocytopenia may also occur especially in immunocompromised patients.[11] Increased liver enzymes, hair loss, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis and anaphylaxis have also been reported. Injection site reactions and even lead to tissue necrosis can occur with IV use. Hematological adverse effects are more common with ganciclovir.

Foscarnet

Besides herpesviruses it is also effective against CMV infections (pneumonia in bone marrow transplant patients and retinitis), including ganciclovir-resistant infections; HSV and VZV (including acyclovir-resistant); Epstein-Barr virus; VZV, HBV and HIV. The usual dose is 40–60 mg/kg infused over one hour every eight hours.

The most common serious dose-limiting toxicity is nephrotoxicity. It can also cause anemia, granulocytopenia and thrombocytopenia. It is a chelator of bivalent metal ions and lead to hypocalcemia with normal plasma levels of calcium. It can also cause injection site reactions, GI symptoms (nausea, vomiting, diarrhea), malaise, fatigue, fever, CNS disturbances (headache, tremors, dizziness, irritability, seizures, hallucinations and mood disorders), paresthesias, rash, increases in liver function tests, blood pressure, ECG abnormalities and pancreatitis.

Idoxuridine

It is a thymidine analog that inhibits replication of various DNA viruses, including (herpesviruses and poxviruses) mainly used for topical treatment of HSV keratitis. **Trifluridine** is a pyrimidine nucleoside that has activity against HSV 1 and 2, CMV, vaccinia, and some adenoviruses. It is used for primary keratoconjunctivitis and recurrent epithelial keratitis owing to HSV types 1 and 2.

Antiviral Drugs for Severe Acute Respiratory Syndrome (SARS)

Severe acute respiratory syndrome is a respiratory illness caused by a newly identified coronavirus.[12] It is a serious disease and the mortality during the 2002–2003 outbreak was about 9.5%. Besides supportive treatment, corticosteroids, ribavirin, interferons, immunoglobulins and ritonavir-lopinavir have been tried, but convincing evidence for their efficacy is lacking.

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Antifungal Drugs

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INTRODUCTION

Systemic infections caused by fungi pose a major health problem in both the developed and the developing countries.[1] Fungi are recognized as fourth leading pathogen of nosocomial sepsis in USA.[2] The use of large number of antibiotics and the increasing number of immunocompromised patients in hospital care are the major factors responsible for the rising incidence of fungal infections.[3] Mortality among infected patients may be as high as 75 to 100%, presenting an enormous challenge for health care providers.[4]

There are estimated to be several hundred thousand species of fungi. However, only 150–200 were considered to be pathogenic for humans, which now are increasing at an alarming rate. The endemic fungal infections are acquired from the environmental sources, e.g. coccidioidomycosis, while the opportunistic mycoses are caused by the fungi, which are present in the normal human flora in an immunocompromised host, e.g. *Candida* (yeast) and *Aspergillus* (mould).[5]

All the fungal infections tend to be more aggressive in immunocompromised patients.[6] There is also an increasing incidence of infections with other moulds, including *Fusarium spp.*, *Scedosporium spp*, (Hyalohyphomycosis), and *Rhizopus spp.* (mucormycosis or zygomycosis).[7] It has intensified the search for newer, safer and more efficacious agents to combat serious fungal infections.[8] The number of agents available to treat fungal infections have increased by 30% since the year 2000.[9]

It is important to know the differences in the antifungal spectrum of activity, bioavailability, drug interactions and adverse effects of the various antifungal agents.[9] They are broadly classified into the following classes. These agents are mainly used for the systemic fungal infections.[10]

I. **Polyenes:** Amphotericin B (AMB), Nystatin
II. **Azoles**
   Imidazoles: Miconazole, Ketoconazole, Econazole
   Triazoles: Fluconazole, Itraconazole, Voriconazole, Posaconazole
III. **Antimetabolites/Nucleoside analogues:** Flucytosine
IV. **Echinocandins:** Caspofungin, Micafungin, Anidulafungin
V. **Miscellaneous:** Griseofulvin, Terbinafine and others.

Polyenes

Amphotericin B (AMB) and Nystatin are the currently available polyenes. They have an important role in antifungal management plans due to their broad spectrum of action against fungi and rarity of resistance.[11]

Amphotericin B (AMB)

It is an amphoteric polyene macrolide. It is almost insoluble in water, therefore, prepared as a colloidal suspension of AMB and sodium desoxycholate for Intravenous (IV) injection.[12] It binds to ergosterol present within the fungal cell wall membrane and leads to the formation of pores resulting in subsequent efflux of potassium and intracellular molecules causing fungal cell death (Fig. 15.1).[13]

Antifungal spectrum: AMB has useful activity against *Candida spp.*, Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Sporothrix schenckii, Coccidioides immitis, Paracoccidioides brasiliensis, *Aspergillus spp.*, Penicillium marneffei and the agents of mucormycosis/zygomycosis.[14] Although conventional AMB (Fungizone in the form of micelles) remains the standard therapy for many invasive or life-threatening mycoses, the use of this drug is often limited by its toxicity, especially drug-induced renal impairment.[15] Consequently, it led to the development of Lipid Formulations of AMB (LFAmBs) - Amphotericin-B Lipid Complex (ABLC; in the form of ribbons), Liposomal Amphotericin-B (L-AMB) and Amphotericin-B colloidal dispersion (ABCD; in the form of disks). AMB is complexed to cholesteryl sulfate in all these preparations.[16]

Pharmacokinetics: AMB is poorly absorbed from the Gastrointestinal (GI) tract. Hence, oral AMB cannot be used for systemic fungal infections.[12] The drug is 90% bound to plasma proteins, largely β-lipoproteins. The penetration of AMB is very little into Cerebrospinal Fluid (CSF), vitreous humor and normal amniotic fluid.[14] Most of the drug is excreted unchanged by the kidney or the liver.[17] The half-life is approximately 15 days.[12]

There are striking differences in their plasma pharmacokinetics of lipid formulations. The L-AMB contains rigid, charged phospholipids and cholesterol to retain AMB within the bilayer membranes of the circulating liposomes. This lipid vehicle serves as an amphotericin reservoir, reducing nonspecific binding to human cell membranes. This helps in limiting the adverse effects without sacrificing the efficacy and also allows for the use of a larger dose of the drug.[12] Amongst the various LFAmBs, L-AMB has the greatest renal protection.[18] Different formulations of AMB have been given by the inhalational route also to avoid nephrotoxicity associated with systemic administration.[9]

Adverse effects: The main adverse effects of conventional AMB include infusion-related events like chills, fever, headache, nausea, vomiting and dose-limiting nephrotoxicity.[19] An increase in intrarenal vascular resistance is the major cause of nephrotoxicity.[14] AMB-associated nephrotoxicity can be reduced by the maintenance of intravascular volume, by avoiding diuretic drugs and saline-loading with 500–1000 ml of normal saline before the infusion of AMB.[20] AMB can also lead to bone marrow depression manifested by anemia.[21] The lipid formulations have several advantages over conventional AMB, such as the increased daily dose of the parent compound (up to 10 fold); high tissue concentration in the lungs, liver and spleen; less infusion related adverse effects (mainly with L-AMB); and marked decrease in nephrotoxicity with L-AMB.[22,23] The three lipid formulations, collectively reduced the risk of the patient's serum creatinine doubling during therapy by 58%.[24] They are now preferred as initial therapy in patients, who are at high risk for nephrotoxicity.[25] They have also proven to be cost-effective as the duration of hospital stay is reduced due to less toxicity.[9]

Indications: The broad antifungal spectrum and experience with the use of AMB accounts for its continued use despite its toxicity problems.[9] It is often used as the initial induction regimen for serious fungal infections and is then replaced by one of the newer azole drugs for chronic therapy or prevention of relapse.[12] AMB is the drug of choice for most forms of invasive candidiasis.[14] LFAmBs are used as second-line or salvage therapy for the treatment of invasive aspergillosis.[26] L-AmB is currently the first-line therapy for disseminated histoplasmosis in HIV-positive or HIV-negative patients, coccidioidomycosis, blastomycosis and sporotrichosis.[9,11] AMB in combination with flucytosine, remains the drug of choice for the treatment of cryptococcal meningitis in patients, whether infected with HIV or not.[11] It is also approved as empiric therapy for the neutropenic patients who have persistent fever despite the use of broad spectrum antibiotics. High doses of L-AMB represents an effective first-line treatment for zygomycosis or mucormycosis.[11] A delay in therapy in patients infected with one of the zygomycetes has resulted in a two fold greater risk for death.[27]

Dose: The recommended dose of IV conventional AMB ranges between 0.7 and 1 mg/kg. Escalating doses of lipid formulations of AMB may be indicated when alternative agents are not available or have been found to be ineffective.[9] The dose range for L-AMB (AmBisome) is 3–5 mg/kg/day; for ABLC (Abelcet) is 5 mg/kg/day and for ABCD (Amphotec) is also 5 mg/kg/day. Intrathecal AMB doses in adults normally range from 0.25 to 0.5 mg diluted in 5 ml of 5% glucose.[28,29]

Azoles

The azole antifungals include two broad classes, imidazoles and triazoles. Both have same antifungal spectrum and mechanism of action.

a. Imidazoles

Imidazoles (clotrimazole, miconazole, ketoconazole, econazole, butoconazole, oxiconazole, sertaconazole and sulconazole) are predominantly used.[14] They have been replaced for systemic administration by triazoles,[30] which include terconazole, itraconazole, fluconazole, voriconazole and posaconazole. Triazoles have more favorable pharmacokinetic profile and improved safety profile than imidazoles. They also have enhanced clinical efficacy in the treatment of systemic mycoses.[31-33]

b. Triazoles

Mechanism of action: They inhibit the Cytochrome P450 enzyme 14 α-sterol demethylase, which prevents the conversion of lanosterol to ergosterol (Fig. 15.1). Inhibition of this enzyme leads to accumulation of toxic methylsterols and results in inhibition of fungal cell growth and replication.[9] The spectrum of action of azoles ranges from many Candida species, cryptococcus neoformans, and the endemic mycoses (blastomycosis, coccidioidomycosis, histoplasmosis), to the dermatophytes, and even the aspergillus infections.[12]

i. *Fluconazole:* It remains one of the most frequently prescribed triazoles because of its excellent bioavailability, tolerability and side effect profile.[9] It is water soluble and well absorbed from the gastrointestinal tract. Its absorption is not affected by food or gastric pH.[34] It has least protein binding and a long half-life of 27–34 hours (in the presence of normal renal function), which can allow once-a-day administration.[16] It has high penetration into CSF ($\geq$ 70% of serum levels) and therefore, used for treating cryptococcal and coccidioidal meningitis.[20] It undergoes 90% of elimination by the renal route.[14]

Adverse effects and drug interactions: Nausea and vomiting may occur at high doses above 200 mg daily. More severe toxicity is unusual. Reversible alopecia, hepatic failure or Stevens-Johnson syndrome have been reported.[14] It has fewer drug-drug interactions than other triazoles. It is an inhibitor of CYP3A4 and CYP2C9. It increases the serum levels of phenytoin, glipizide, glyburide, warfarin, amprenavir and cyclosporine.[14]

Indications: Fluconazole is used in the treatment of candidemia in non-neutropenic patients and is shown to be as effective as AMB in two large randomized trials.[35,36] Fluconazole may be inappropriate for the empirical treatment of suspected fungal infection in neutropenic patients, because prior exposure, as treatment or prophylaxis is associated with resistant candidal strains and also because of its lack of activity against moulds.[37] It is active against most of the *Candida spp.* except C. *Krusei* and *C. glabrata* isolates. If a *C. glabrata* isolate is found susceptible to fluconazole, higher doses (12 mg/kg/d) should be used.[37,38] There is no appreciable activity against; Aspergillus, Fusarium, Pseudallescheria or the Zygomycetes.[9]

It has become the agent of choice for the treatment of coccidioidal meningitis, although relapses have followed therapy with this agent. It is useful for both consolidation and maintenance

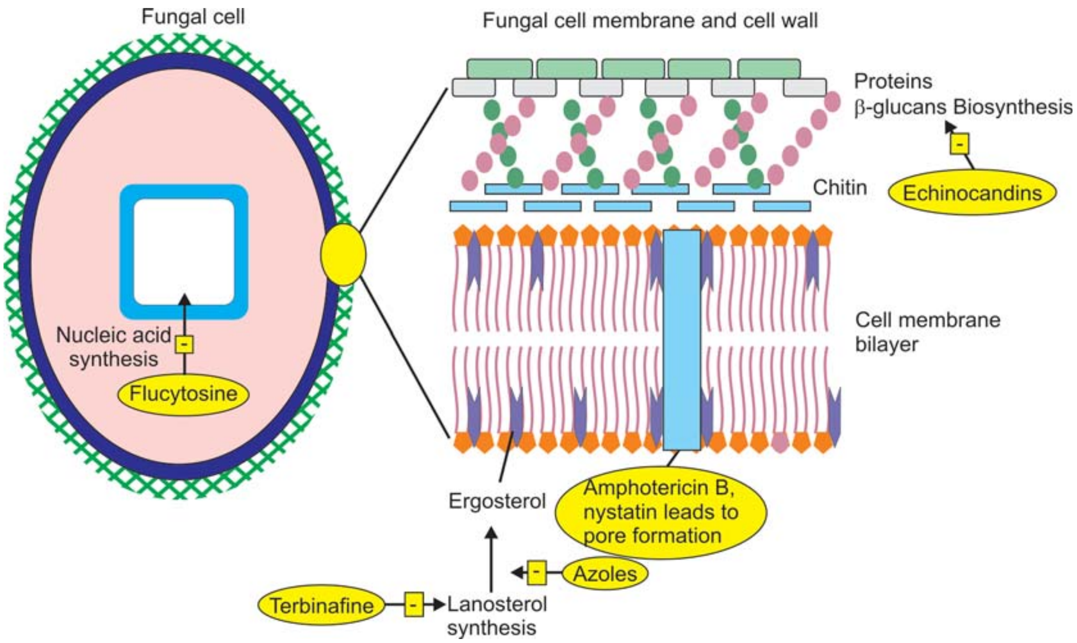

Fig. 15.1: Antifungal agents: Mechanism of action

therapy for cryptococcal meningitis. As, it has greatest penetration into the CSF and vitreous fluid, it is used in the treatment of CNS and intraocular infections.[39,40] Recommended dosage is 50–800 mg once daily, identical for oral and intravenous administration. Children are treated with 3 to 6 mg/kg once daily.[14]

ii. *Itraconazole:* It has a wider spectrum than fluconazole.[7] It is active against yeasts and moulds, with the exception of *Fusarium spp.*, *Scedosporium spp.*, and the Zygomycetes.[41,42] There are few data that examine the use of itraconazole in the treatment of invasive candidiasis.[40] It is generally reserved for patients with mucosal candidiasis, especially those who have experienced treatment failure with fluconazole.[43]

Pharmacokinetics: Maximal absorption of itraconazole capsules depend on the acidic pH. The absorption of the drug is erratic and unpredictable on the concomitant administration of H2-receptor antagonists, proton-pump inhibitors or antacids. It is recommended that itraconazole capsules be taken with food or a cola beverage to increase the absorption.[44] The bioavailability is unpredictable, hence, therapeutic drug monitoring is recommended. Itraconazole is found in equal amounts in plasma as the native drug and as a metabolite, hydroxyitraconazole, which has equivalent antifungal activity to the parent compound. Both molecules are bound more than 99% to plasma proteins. It does not penetrate the CSF.[30]

Indications: This drug has become the standard treatment for lymphocutaneous sporotrichosis, as well as for mild or moderately severe histoplasmosis, blastomycosis and paracoccidioidomycosis and also in certain types of chromoblastomycosis.[20] The development of newer and more effective antifungal agents like voriconazole has relegated itraconazole to second-line therapy during the treatment of Invasive Aspergillosis (IA). Itraconazole is licensed in the United States only for salvage therapy of IA.[26] It is also approved for allergic bronchopulmonary aspergillosis.[26] Oral formulations are dosed in adults at 200 mg 3 times daily for 3 days, then 200 mg once or twice daily thereafter.[40]

Adverse effects and drug interactions: The adverse effects include gastrointestinal symptoms (<10%), headache, dizziness, raised hepatic transaminases (5%), menstrual disorders, peripheral neuropathy and allergic reactions (2%).[45,46] The patients on high doses of itraconazole for prolonged periods are reported to have cardiac failure.[7]

It is metabolized in liver and is a substrate and strong inhibitor of CYP3A4.[30] An important drug interaction is reduced bioavailability of itraconazole when taken with rifamycins.[12]

iii. *Voriconazole:* The spectrum of this drug is similar to that of itraconazole, which also extends to several emerging moulds, including *Fusarium spp.* and *Scedosporium spp.* with the exception of Zygomycetes.[47,48] It also has in vitro activity against many fluconazole resistant *Candida spp.*[49]

Pharmacokinetics: It is formulated as tablets or as a Sulfobutyl-Ether Cyclodextrin (SBECD) solution for IV administration. SBECD and voriconazole dissociate in plasma and follow their own disposition. The cyclodextrin molecule undergoes renal clearance. There are the chances of accumulation of the vehicle in individuals with renal insufficiency.[26] Significant accumulation of SBECD occurs with a creatinine clearance below 50 ml/min. As the toxicity of SBECD at high plasma concentration is unclear, oral voriconazole is preferred in azotemic patients.[14] Bioavailability is 96% after oral administration as either tablet or solution. Oral absorption is reduced by 22% when taken with food, while fatty food reduces bioavailability by 80%.[30,50] The volume of distribution is good (4.6 l/kg), protein binding of the drug is 56%. It is widely distributed in mammalian tissues, with the CSF levels of equivalent to 50% in plasma levels. The elimination half-life is around six hours, which warrants twice-daily dosing.[26]

Indications: It is licensed for the primary treatment of invasive aspergillosis and has been compared with AMB in a non-blinded trial.[51] Significantly, more patients experienced adverse effects with AMB than with voriconazole.[7] Voriconazole is as effective as fluconazole, but less well tolerated in the treatment of esophageal candidiasis.[52] It is also approved for use as salvage therapy in patients with Scedosporium and Fusarium infections.[14] Penicilliosis marneffei also responds well to voriconazole.[53]

Treatment is usually started with IV infusion of 6 mg/kg every 12 hours for 2 doses, followed by 4 mg/kg every 12 hours. It should be administered at 3 mg/kg/hour, not as a bolus. After improvement, the drug is continued as 200 mg every 12 hours. If there is no response, it may be given as 300 mg every 12 hours. It is available as 50 or 200 mg tablets or a suspension of 40 mg/ml when hydrated. Oral drug should be given either one hour before or one hour after meals, as the bioavailability of the drug is reduced by high fat meals.[14] Pediatric patients are known to hyper metabolize voriconazole and for this reason, an IV dose of 7 mg/kg twice daily and oral dosing of 200 mg twice daily without loading is recommended.

Adverse effects and drug interactions: Voriconazole is usually well tolerated. The most common adverse effects include transient visual disturbances with an incidence of 20 to 23%, which are mainly characterized by photopsia, blurred vision and color changes 30 minutes to 1 hour after dosing. Other adverse effects include hepatotoxicity, which may be dose limiting and is manifested by elevated serum bilirubin, alkaline phosphatase and hepatic aminotransferase enzyme levels; skin rash (usually in sunlight exposed areas).[54] QTc prolongation and torsades de pointes should be a consideration in patients with predisposing factors.

Coadministration with rifampin, rifabutin or ritonavir is contraindicated because of accelerated voriconazole metabolism. The dose of voriconazole should be doubled when coadministered with phenytoin, cyclosporine, tacrolimus, rifabutin and warfarin. Coadministration with Sirolimus is contraindicated, as voriconazole increases its area under curve by eleven fold.[14]

iv. Posaconazole: It is an orally-active, extended spectrum triazole.[55] It is insoluble in water and no IV formulation has yet been developed. It is administered as a cherry-flavored suspension using polysorbate 80 as the emulsifying agent. It has a broad spectrum of antifungal activity against moulds like *Aspergillus spp.,* zygomycetes like rhizopus, absidia; dimorphic fungi like blastomyces, coccidioides and *Histoplasma spp.; Fusarium spp.* and dermatophytes like *trichophyton spp.;* and yeasts, e.g. *Candida spp., Cryptococcus spp.* This drug is active against *Candida spp.* isolates that exhibited resistance to other triazoles like fluconazole, itraconazole and voriconazole.

It is available only as a suspension for oral use. Absorption is increased when taken with food, especially with fatty meals. Each dose of posaconazole should be administered with a full meal or with a liquid nutritional supplement in patients who cannot eat a full meal. Moreover, oral absorption is better in divided daily doses and optimal when administered four times daily. It exhibits not only linear kinetics, but also saturable absorption; thus, oral loading doses are not possible. It has large volume of distribution indicating extensive tissue penetration and is highly plasma protein bound (>98%), predominantly to albumin. It undergoes hepatic metabolism and minimal glucuronidation. Renal clearance plays a minor role in its clearance. It is predominantly eliminated unchanged by the fecal-oral route.[9]

Indications: It is approved for the prevention of invasive aspergillosis and candida infections in patients aged $\geq$ 13 years who are at high risk of developing these infections due to the severely immunocompromised state, such as Graft Versus Host Disease (GVHD) in Hematopoietic Stem Cell Transplant (HSCT) patients and also in patients with hematological malignancies with prolonged neutropenia from chemotherapy; it can also be used as salvage therapy for refractory invasive aspergillosis.[56-58]

It is administered as an oral suspension for prophylaxis in the dose of 200 mg three times daily. The duration of therapy is based on recovery from neutropenia or immunosuppression. The dosage for salvage treatment is 800 mg administered in two or four divided doses. Improved efficacy is seen with higher posaconazole levels.[56] It is administered in the dose of 100 mg daily or up to 400 mg twice daily for oropharyngeal candidiasis, which is refractory to fluconazole and itraconazole.[59]

Adverse effects and drug interactions: It is usually a well tolerated drug and the safety profile seems to be more favorable than that of voriconazole. The most frequent adverse effects are headache, gastrointestinal complaints like nausea, diarrhea and vomiting (3 to 12% each in several studies).[56-60] Others include transaminase elevation and hyperbilirubinemia occurring in 3%.[57] QTc prolongation was reported to be as high as 4% in one study.[58] The safety of posaconazole has not been evaluated in children under 13 years old.[30]

v. Newer Triazoles: Despite the incoming of new effective drugs, there are several therapeutic problems, such as new pathogenic fungal species; slow microbiological diagnosis; variable drug bioavailability; toxicity, lack of oral or IV preparations; significant drug interactions for some agents; the development of resistance; and breakthrough infections. Several newer triazoles are in the advanced stages of development to address some of these problems (Table 15.1).

Antimetabolites/Nucleoside Analogues

Flucytosine (5FC; ANCOBON)

Flucytosine has been used to treat candidiasis and other invasive mycoses since 1968.[61] Although not used as

TABLE 15.1: New triazoles on the frontline

Drug	*Route*	*Spectrum*	*Advantages*	*Disadvantages*
Isavuconazole	Oral and intravenous	*Candida spp., Aspergillus spp.,* Dermatophytes	Broad spectrum, water soluble (no need for cyclodextrin), long acting (allows OD up to once-weekly dosing), drug tolerability favorable, limited drug interaction	Most data available as meeting abstracts
Ravuconazole	Oral and intravenous	Similar to isavuconazole and also: *Cryptococcus spp., Chaetomium spp., Trypanosoma cruzi*	Long-acting drug similar to very isavuconazole	Potential for cross-resistance with other azoles
Albaconazole	Oral	*Candida spp., Aspergillus spp., Paecilomyces spp., Cryptococcus spp., Malassezia spp., Trypanosoma cruzi*	Broad spectrum, good pharmacokinetics, excellent oral bioavaialbility	Low concentration achieved in the CSF, Potential for cross-resistance with other azoles

monotherapy, 5FC can be used as an adjunct to AMB or azoles in the treatment of hematogenous candidiasis because of the rapid emergence of resistance when used alone.[62,63] It has clinically useful activity against Cryptococcus neoformans, *Candida spp.,* and the agents of chromoblastomycosis.[14]

It is currently available in only in an oral formulation. More than 90% of the drug is absorbed after an oral dose. The peak plasma concentration is achieved within one to two hours. It is poorly protein bound and has a good penetration into all the body fluid compartments, including CSF.[12] The half-life of the drug is three to six hours in normal individuals. The half-life may be as long as 200 hours in patients having renal failure.[14] The adverse effects are rare if peak levels are kept below 100 µg/ml.[64] Adverse effects like nausea, diarrhea, hepatotoxicity and bone marrow suppression are reversible on discontinuation of the drug.[64] Cytarabine reduces 5FC levels, hence, caution must be employed when used with other myelosuppressive drugs.[7]

The combination of AMB with 5FC has been shown to be effective in randomized controlled trials of patients with cryptococcal meningitis. It is given orally at 100 mg/kg/day, in four divided doses at six hour interval. Dosage should be adjusted for decreased renal function.[14] It is also recommended, in combination, in patients having endophthalmitis, meningitis and endocarditis due to *Candida spp.*[37]

Echinocandins

The newest class of antifungal drugs is the echinocandins. They inhibit β-1, 3-D glucan synthase responsible for the biosynthesis of β-1, 3-D glucan, which is the fungal cell wall biopolymer (Fig. 15.1) These drugs are effective against clinically relevant yeasts and moulds.[65]

Pharmacokinetics: They are synthetically modified lipopeptides. The molecular weight of all three echinocandins is large, which explains their poor oral absorption. All echinocandins have linear kinetics following single-dose IV administration, and have a terminal half-life of 8–13 hours, so once a day usage is appropriate.[66] They are slowly metabolized in the liver by nonenzymatic peptide hydrolysis and/or N-acetylation to inactive low molecular weight products. A lower dose (35 mg/day) is recommended in patients with hepatic insufficiency. Micafungin is metabolized by nonoxidative metabolism within the liver and anidulafungin undergoes nonenzymatic degradation within the kidney. Both these agents undergo fecal excretion. These agents do not require dose adjustment with hepatic impairement.[67] The concentration of these drugs is almost negligible in CSF, vitreous and urine.[68] The efficacy of echinocandins is predicted by peak to Minimum Inhibitory Concentration (MIC) ratios. Optimal fungicidal activity is obtained when peak concentrations exceed MICs by 5 to 10 fold.[67] Echinocandin resistance is uncommon, but may develop during therapy.[68]

A number of in vitro studies have shown a "paradoxical effect" of echinocandins. This refers to the growth of echinocandin-susceptible organisms at highly elevated drug concentrations, far in excess of the MIC (>16 µg/ml) showing break through growth. However, a normal susceptibility pattern is seen with a typical low MIC.[69] The exact mechanism has not been fully elucidated and the clinical significance remains uncertain.[70]

Adverse effects and drug interactions: Caspofungin is generally well-tolerated. The most frequent adverse effects include phlebitis/thrombophlebitis, fever, chills, headache, nausea, vomiting, abdominal pain, diarrhea and rash.[71] Caspofungin is a poor substrate for the Cytochrome P450 enzyme, so a fewer dug interactions occur with it.[65] Daily caspofungin dose should be increased, when administered along with inducers of hepatic metabolism like phenytoin, rifampicin, carbamazepine and dexamethasone. Tacrolimus blood concentration is reduced by 26% when coadministered with caspofungin. Monitoring of tacrolimus blood concentration is essential and the dosage should be adjusted accordingly.

Indications: These drugs have broad spectrum antifungal activity against candida and *Aspergillus spp.* without cross-resistance to existing antifungal agents and are effective against azole-resistant yeasts and moulds.[65,72] They are highly effective on biofilms.[73] They are less active against zygomycetes, cryptococcus neoformans or *Fusarium spp.*[65]

These drugs have excellent safety and tolerability profiles with few drug-related adverse events, which make them attractive options for various fungal infections over other available antifungals.[9] Caspofungin is licensed for the treatment of invasive candidiasis in non-neutropenic adults. It is as effective as AMB in the treatment of candidemia and is also better tolerated.[74] It has its use in the treatment of patients with esophageal candidiasis and is as effective as AMB and fluconazole.[75,76] Caspofungin can be prescribed in patients of invasive aspergillosis, who are refractory to or intolerant to AMB, lipid formulations of AMB and/or itraconazole.[77] For the empirical treatment of presumed fungal infections in patients with febrile neutropenia, caspofungin (50 mg once daily, followed by a loading dose of 70 mg on the first day), is no less effective than liposomal AMB (3 mg/kg once daily).[78]

Micafungin (100 mg IV daily) has been compared to L-AMB 3 mg/kg IV daily in an international, double-blind trial for candidemia and invasive candidiasis. The patients were assigned to IV treatment of 14 days and successful treatment was equivalent in each group. There were less adverse events with micafungin than there were with L-AMB.[79]

Anidulafungin MIC required to inhibit the growth of 90% of organisms (MIC90) value for *C. albicans* clinical isolates is generally lower than 0.5 µg/ml.[80] Also, the isolates of *C. parapsilosis* are susceptible to anidulafungin, but not to caspofungin or micafungin (MIC90 values 2 mg/l, 8 mg/l and 16 mg/l, respectively).[812] Anidulafungin, also, has in vitro activity against *Candida spp.*, growing as biofilms making it a useful addition to the Italian therapeutic armamentarium.[82]

Intravenous dosing regimens for invasive candidiasis with the three compounds are as follows: Caspofungin loading dose of 70 mg and 50 mg daily thereafter, anidulafungin loading dose of 200 mg and 100 mg daily thereafter, and micafungin, 100 mg daily.[40]

Candida and *Aspergillus spp.* (Predominantly *C. albicans* and *A. fumigates*) are two of the most common pathogenic fungi and are associated with significant morbidity and mortality in certain patient groups (e.g. neutropenic patients receiving cancer chemotherapy or patients undergoing stem cell transplantation). Mortality rates of up to 95% are being reported in rapidly progressive IA.[83] However, there has been an increased incidence of less common non-Aspergillus moulds that include zygomycetes, *Fusarium spp.*, and *Scedosporium spp.*[84] Reflecting a key need, important advances have been made in the antifungal armamentarium with the availability of lipid formulations of AMB, triazoles and echinocandins. As the number of patients exposed to echinocandin therapy broadens, the chances for the resistance will also increase.

Miscellaneous Antifungals[86,87]

Nystatin, a polyene antifungal is too toxic for parenteral administration and is mainly used topically for the suppression of local candidal infection. Imidazoles like clotrimazole, miconazole, econazole and others are used for superficial mycoses. Systemic use of ketoconazole has fallen out of clinical use because of its nonselective inhibition of cytochrome P450. Griseofulvin is used only in the systemic treatment of dermatophytoses and has been largely replaced by other antifungals like itraconazole and terbinafine. Terbinafine is a synthetic allylamine, used for the treatment of dermatophytoses especially onychomycosis. Agents like undecyclenic acid, benzoic acid and salicylic acid (Whitfield's Ointment) are very effective in the treatment of tinea pedis.[12,14]

TABLE 15.2: Recommendations for therapeutic drug monitoring of antifungals

Drug	*Indications*	*Timing (days)*	*Goal*
5 FC	Routine during first week of therapy, renal insufficiency, lack of response to therapy	3-5	10-50 µg/ml
Itraconazole	Routine during first week of therapy, lack of response to therapy, gastrointestinal dysfunction, comedication	4-7	Therapy: > 1 µg/ml Prophylaxis: > 0.5 µg/ml
Voriconazole	Lack of response to therapy, gastrointestinal dysfunction, comedication, children; IV to oral switch	4-7	> 0.5-2 µg/ml
Posaconazole	Lack of response to therapy, gastrointestinal dysfunction, comedication	4-7	> 1.5 µg/ml

SPECIFIC ISSUES

Antifungals in Pregnancy

The data on the safety of antifungals for treating patients who are pregnant or lactating are limited. The agents like azoles, griseofulvin and flucytosine should not be used in pregnancy as the risks clearly outweigh the therapeutic benefit. Breast-feeding should be discouraged in women receiving these agents. Successful treatment of systemic mycoses has been documented with AMB in pregnancy with no excess toxicity to either the mother or fetus. Thus, amphotericin B formulations have been the mainstay treatment of antifungal therapy in pregnancy.[85]

Therapeutic Drug Monitoring (TDM)

There is significant interpatient variability for several available antifungal drugs and exposure-effect relationships have been demonstrated for antifungal compounds. TDM is useful to both reduce drug toxicity and optimize efficacy for the following agents. TDM, very well can be incorporated into the patient management (Table 15.2).[86,87]

New Frontiers for Antifungal Therapy

Inhaled L-AMB has been found protective against the development of invasive aspergillosis when given twice weekly to neutropenic patients who have malignancy.[88] Lead compounds that appear promising for antimycotic therapy include nikkomycins, sordarins, lytic peptides, hydroxypyridones and cathelicidins. Other less conventional drug discovery approaches include targeting known traditional virulence factors (e.g. adhesions and secreted enzymes). This approach is based on the principle that killing of the microbe need not occur for an anti-infective agent to be efficacious in the reduction of disease.[85]

Clinical decisions about combination therapy should be based on patient-specific in vivo evaluations. Because of the limited clinical data, combination antifungal therapy should be initiated cautiously. Except for the treatment of cryptococcal meningitis and disseminated aspergillosis, combination therapy should be reserved for the cases of treatment failure (disseminated candidiasis) with no other established pharmacologic options for therapy or for mould infections with high mortality rates.[85]

CLINICAL IMPLICATIONS OF THE ANTIFUNGAL DRUGS

Pharmacotherapy of fungal disease has been revolutionized by the introduction of the newer agents. The following table highlights the Infectious Diseases Society of America (IDSA) guidelines for the management of fungal infections (Table 15.3).

TABLE 15.3: IDSA recommendations for the management of fungal infections

Condition	*Therapy*	
Aspergillosis	*Primary*	*Alternative*
Invasive pulmonary aspergillosis (IPA)	Voriconazole (6 mg/kg IV every 12 hours for 1day, followed by 4 mg/kg IV every 12 hours; oral dosage is 200 mg every 12 hours)	L-AMB (3–5 mg/kg/day IV), ABLC (5 mg/kg/day IV), Caspofungin (70 mg/day 1 IV and 50 mg/day IV thereafter), Posaconazole (200 mg QID initially, then 400 mg BID PO after stabilization of disease)
Invasive sinus aspergillosis	Similar to IPA	Similar to IPA
Tracheobronchial aspergillosis	Similar to IPA	Similar to IPA
Chronic necrotizing pulmonary aspergillosis (subacute IPA)	Similar to IPA	Similar to IPA
Aspergillosis of the CNS	Similar to IPA	Similar to IPA
Chronic cavitary pulmonary aspergillosis	Itraconazole or voriconazole	Similar to IPA
Allergic bronchopulmonary Aspergillosis (ABPA)	Itraconazole	Oral voriconazole (200 mg PO every 12 hours) or posaconazole (400 mg PO BID)
Candidiasis	*Primary*	*Alternative*
Candidemia: Nonneutropenic adults	Fluconazole 800 mg (12 mg/kg) LD[*], then 400 mg (6 mg/kg) daily or an echinocandin[#].	LFAmB 3–5 mg/kg daily; or AmB-d 0.5–1 mg/kg daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses, then 200 mg (3 mg/kg) bid.
Candidemia:Neutropenic patients	An echinocandin[#] or LFAmB 3–5 mg/kg daily.	Fluconazole 800 mg (12 mg/kg) LD[*], then 400 mg (6 mg/kg) daily; or voriconazole 400 mg (6 mg/kg) bid for 2 doses then 200 mg (3 mg/kg) bid.
Chronic disseminated candidiasis	Fluconazole 400 mg (6 mg/kg) daily for stable patients; LFAmB 3-5 mg/kg daily or AmB-d 0.5-0.7 mg/kg daily for severely ill patients; after patient is stable,change to fluconazole.	An echinocandin[#] for several weeks followed by fluconazole.
CNS candidiasis	LFAmB 3–5 mg/kg with or without 5 FC 25 mg/kg qid for several weeks, followed by fluconazole 400-800 mg (6-12 mg/kg) daily.	Fluconazole 400-800 mg (6-12 mg/kg) daily for patients unable to tolerate LFAmB.
Blastomycosis	*Preferred therapy*	
Moderately severe to severe pulmonary	LFAmB 3-5 mg/kg per day, or AmB-d 0.7–1 mg/kg /day for 1-2 weeks, followed by itraconazole, 200 mg bid for 6-12 months	
Mild to moderate pulmonary	Itraconazole 200 mg once or twice per day for 6-12 months	
Moderately severe to severe disseminated	LFAmB 3-5 mg/kg/day, or AmB-d, 0.7-1 mg/kg/day for 1-2 weeks, followed by itraconazole 200 mg bid for 12 months	
Mild to moderate disseminated	Itraconazole 200 mg once or twice per day for 6-12 months	
CNS disease	LFAmB 5 mg/kg/day for 4-6 weeks is preferred, followed by an oral azole for at least 1 year	

Contd...

Contd...

Histoplasmosis	*Preferred treatment*	
Acute pulmonary histoplasmosis: Moderately severe or severe	LFAmB (3-5 mg/kg daily) or AmB-d (0.7-1.0 mg/kg daily) for 1-2 weeks, followed by Itra (LD* of 200 mg 3 times daily for the first 3 days, then 200 mg twice daily for a total of 12 weeks) Methylprednisolone (0.5-1.0 mg/kg daily IV for 1-2 weeks)	
Mild to moderate	For symptoms of <4 weeks, none For symptoms of >4 weeks, Itra (200 mg once or twice daily for 6-12 weeks)	
Chronic cavitary pulmonary histoplasmosis	Itra (LD* of 200 mg 3 times daily for the first 3 days, then 200 mg once or twice daily for at least 12 months)	
Progressive disseminated histoplasmosis: Moderately severe to severe	LAmB (3 mg/kg daily), LFAmB (5 mg/kg daily), or AmB-d (0.7-1.0 mg/kg daily) for 1-2 weeks, followed by Itra (200 mg twice daily for at least 12 months)	
Mild to moderate	Itra (200 mg twice daily for at least 12 months)	
CNS histoplasmosis	LAmB (5 mg/kg daily for 4–6 weeks), followed by Itra (LD* of 200 mg 3 times daily for the first 3 days, then 200 mg 2–3 times daily for at least 12 months)	
Sporotrichosis	*Preferred treatment*	*Alternative treatment*
Pulmonary	LFAmB 3-5 mg/kg/day, then Itr 200 mg bid; or Itr 200 mg bid	AmB-d 0.7–1 mg/kg/d, then Itr 200 mg bid; surgical removal
Meningitis	LFAmB 5 mg/kg/d, then Itr 200 mg bid	AmB-d 0.7-1 mg/kg/d, then Itr 200 mg bid
Disseminated	Lipid AmB 3-5 mg/kg/d, then Itr 200 mg bid	AmB-d 0.7-1 mg/kg/d, then Itr 200 mg bid

*LD: Loading Dose; #Echinocandins: Doses given in the text

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16

Anti-inflammatory Agents for Asthma

Nusrat Shafiq, Samir Malhotra

INTRODUCTION

The major role of this class of drugs is for long-term control of asthma, these agents are not indicated when rapid bronchodilation is needed. Patients on these drugs must be instructed to keep Short-Acting Beta Agonists (SABAs) with them for quick relief.

CORTICOSTEROIDS

Corticosteroids are amongst the most universal anti-inflammatory agents thereby reducing airway inflammation and hyperresponsiveness. Therefore, they form the cornerstone of asthma management. Both inhalational and systemic routes of administration are used in the management of asthma. Inhalational therapy is highly suitable for maintenance therapy, it needs lower doses and delivers the drug directly to the site of action minimizing the systemic adverse effects associated with corticosteroids. A large number of steroids are available for inhalational therapy, their main differences are in pharmacokinetics, potency (budesonide > beclomethasone > flunisolide), dosing frequency and adverse effects, although most evidence suggests that they do not differ in the terms of efficacy (Table 16.1). Systemic steroids are indicated when inhaled therapy does not work due to severe spasm during acute exacerbations, and also in chronic severe asthma. Dose should not be a deterrent, high dose must be used, usually needed only for five to seven days. Prolonged use of systemic steroids requires to be tapered.

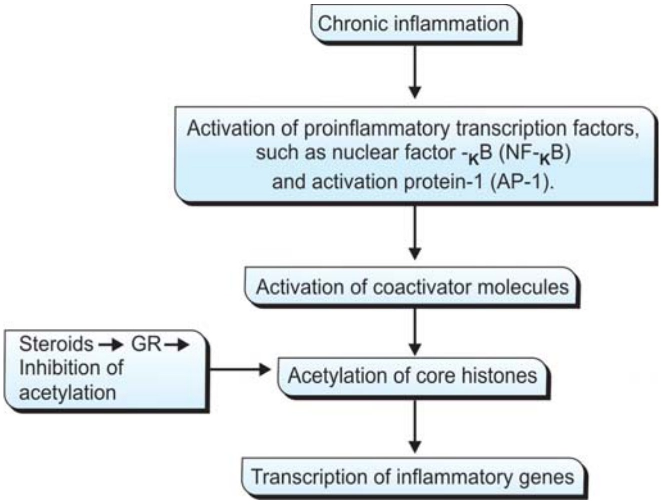
Chronic inflammation
Activation of proinflammatory transcription factors, such as nuclear factor -κB (NF-κB) and activation protein-1 (AP-1).
Activation of coactivator molecules
Steroids → GR → Inhibition of acetylation
Acetylation of core histones
Transcription of inflammatory genes

Fig. 16.1: Transcription of genes during chronic inflammation GR: Glucocorticoid receptor

Mechanism of Action

Their major actions (Fig. 16.1) include, but are not limited to:

- Suppression of inflammatory proteins (Panel 1) caused by the inhibition of genes that encode these proteins. Key among these are inflammatory cytokines (interleukins, TNF-α), chemokines (IL-8, RANTES, MIP-1 α, MCP-1, MCP-3, MCP-4, exotoxins), adhesion molecules (ICAM-1, VCAM-1, E-selectin), enzymes (nitric oxide synthetase and cyclooxygenase and cytoplasmic phospholipase A2), receptors (tachykinin NK-1 and NK-2, bradykinin B2) and peptides (endothelin-1).

- Inhibition of accumulation of mast cells, basophils, eosinophils, dendritic and other cells in the mucosa and submucosa of the lung tissue
- Reduced goblet cell hyperplasia
- Decreased epithelial cell injury
- Decreased vascularity and vascular permeability.

Besides suppressing inflammatory genes, steroids also switch on anti-inflammatory genes like annexin-1 (lipocortin-1), SLPI, interleukin-10 (IL-10) and the inhibitor of NF-κB (IκB-α). Although this effect occurs at high concentrations, it is questionable whether it is seen with therapeutic doses, especially of inhaled steroids. The above-mentioned mechanisms require a lag period of few days before steroid effects can be seen. It has been noted that steroids have other actions that appear earlier, which include: a. their ability to resensitize adrenergic receptors to catecholamines, thereby, potentiating the effects of beta-2 agonists, and b. Contraction of bronchial mucosal blood vessels. The exact mechanisms behind these actions remain unknown.

Pharmacokinetics

Corticosteroids are lipid soluble drugs, therefore, rapidly absorbed from the Gastrointestinal Tract (GIT), as well through inhalation and get widely distributed across the body tissues. They especially the natural steroids, are the highly protein (globulin, albumin and transcortin) bound drugs. Their metabolism occurs mainly in the liver and they are excreted by the kidneys. Natural steroids are metabolized faster than the synthetic steroids, thus, have shorter half-lives, which coupled with their higher affinity for plasma proteins makes them less potent than the synthetic preparations. Many steroids have high first-pass metabolism leading to very low systemic bioavailability, for instance 10% for budesonide, 20% for fluticasone and just 1% for flunisolide.

Systemic steroids are needed for emergency management of asthma, but frequently misused for maintenance therapy. Prednisone is commonly used in asthma (30–60 mg/day) orally in the morning or methylprednisolone 4 mg/kg/day intravenously in four divided doses for severe cases. Hydrocortisone is cheaper than methylprednisolone, but also has mineralocorticoid activity. Once symptoms improve, the doses can be reduced. Some authorities recommend late afternoon administration, if nocturnal asthma is a major problem. A Cochrane review[1] of pooled data from six trials had shown that oral prednisolone (7.5–12 mg/day) was as effective as inhaled steroid (300–2000 mcg/day), but was associated with more adverse effects.

TABLE 16.1: Some commonly used inhaled steroids

Steroids	*Doses*	*Remarks*
Beclomethasone	400 mcg/day in two to four divided doses. Maximum initial dose may go up to 1 mg/day. Pediatric dose is 50–100 mcg/day	Higher doses may be needed if asthma is severe or if usual dose is inadequate
Budesonide	400 mcg/day in two divided doses. Maximum initial dose may go up to 2 mg/day. Pediatric dose is 50–400 mcg/day	Metabolized by CYP3A4
Ciclosenide	160 mcg/day once daily as starting dose, decreased to 80 mcg once daily as maintenance dose	Not used in children
Flunisolide	1 mg/day in to divided doses. Maximum dose 2 mg/day. Maximum pediatric dose 500 mcg twice daily	Dose is lesser (160 mcg twice daily) for CFC free inhaler, maximum dose 320 mcg twice daily. Pediatric dose 80 mcg twice (maximum 160 mcg twice daily).
Fluticasone	200–500 mcg/day in two divided doses. Maximum dose 2 mg/day for severe cases. Pediatric dose 100–200 mcg/day, maximum dose 400 mcg	Most commonly used doses are 0.5–1 mg twice daily
Mometasone	400 mcg inhaled once daily initial dose followed by 200 mcg once or twice daily for maintenance. Maximum dose 800 mcg/day and pediatric dose 110 mcg once daily	The drug should be given in the evening
Triamcinolone	450–600 mcg in three to four divided doses up to a maximum of 1200 mcg/day. Pediatric doses 75 or 150 mcg three to four times up to a maximum of 900 mcg	Also available for oral and parenteral use

DISSOCIATED STEROIDS

There are several problems of steroid therapy in asthma (Table 16.2).

TABLE 16.2: Major drawbacks of steroid therapy for asthma

- Systemic adverse effects even with inhaled drugs
- Local adverse effects and dislike of inhaled steroids
- Poor patient adherence with inhaled steroids seen in 30% to 60% of patients[2]
- Lack of rapid symptom relief
- Complicated treatment regimens[3]
- Inability to properly use inhaler devices, especially in children and elderly

There have been attempts to discover oral novel steroids that lack the adverse effect potential of currently available steroids; such steroids are called dissociated steroids.[4] The concept of dissociated steroids was an attempt to dissociate side effects, which are presumably caused by DNA binding and gene activation (*trans-activation* or *cis repression*) from therapeutic anti-inflammatory effects, which are probably due to the inhibition of inflammatory gene expression by NF-κB and other proinflammatory transcription factors through a non-DNA binding mechanism (*transrepression*).[5,6] It is hoped that this novel class of "dissociated" steroids will have the property for *transrepression* with relatively little *transactivation* and therefore, lesser the incidence of adverse effects.

Adverse Effects of Steroids

Corticosteroids are life-saving drugs with an excellent risk benefit ratio in asthma. However, they have potential to cause a large number of adverse effects, some of which can be severe, and others serious. The adverse effect potential of inhaled steroids is lesser, but may be significant (Table 16.3). It is important to appreciate that while the dose-response curve of inhaled steroids plateaus at higher doses, the dose-systemic absorption curve is linear and continues to rise even at the high doses of inhaled steroids, with the result that even as the therapeutic effects plateau at a dose equivalent to 1600 mcg/day of beclomethasone, the probability of systemic adverse effects continues to rise with rising doses.

Systemic corticosteroid therapy is known to cause a vast number of adverse effects (Table 16.4), their incidence and severity are directly proportional to dose (<7.5 mg/day of prednisolone is usually considered physiological) and duration of treatment, but are not dependent on the type of steroid used. The long history of their use has shown that short-course treatment (<5–10 days) even at high doses does not cause much toxicity. On the other hand, long duration of treatment even at relatively low doses is likely to cause adverse effects. The most common adverse effects during a brief course as is used during asthma exacerbations are mood disturbances, increased appetite, impaired glucose control in diabetics and candidiasis.

TABLE 16.3: Potential adverse effects associated with inhaled steroids[7]

Adverse effect	*Risk*
Hypothalamic-pituitary-adrenal axis suppression	No significant risk until dosages of budesonide or beclomethasone increased to >1500 mcg/day in adults or >400 mcg/day in children
Bone resorption	Modest but significant effects at doses possibly as low as 500 mcg/day
Carbohydrate and lipid metabolism	Minor, clinically insignificant changes occur with dosages of beclomethasone >1000 ug/day
Cataracts	Anecdotal reports, risk unproven
Skin thinning	Dosage-related effect with beclomethasone dipropionate over a range of 400 to 2000 ug/day
Purpura	Dosage-related increase in occurrence with beclomethasone over a range of 400 to 2000 ug/day
Dysphonia	Usually of little consequence. Decreased by mouth rinsing after every inhalation
Candidiasis	Incidence <5%, reduced by use of spacer device and mouth rinsing after every inhalation
Growth retardation	Difficult to separate effect of disease from effect of treatment, but no discernible effects on growth when all studies are considered and normal predicted height is seldom affected

Steroid Withdrawal

There are two main risks of abrupt steroid withdrawal—adrenocortical insufficiency and relapse of disease for which a steroid was being given. It is generally recommended to gradually taper the dose. The UK Committee on Safety of Medicines (CSMs) recommends that moderate dosage with corticosteroids (up to 40 mg daily of prednisolone or equivalent), for up to three weeks, may be stopped without tapering, provided that the original disease is unlikely to relapse, although

TABLE 16.4: Adverse effects associated with systemic steroids

Adverse effects	*Risk and prevention*
Hypothalamic-pituitary-adrenal axis suppression	The most feared complication of steroid therapy, usually occurs with supraphysiological doses used for > 3 weeks and may last for a year or more. The incidence is less when a single morning dose is used, even lesser if used on alternate day.
Bone/joints	Avascular necrosis of bone, may occur with short courses of high-dose treatment (even with inhaled) although relatively uncommon. Osteoporosis is almost universal, if steroids are used for sufficiently long duration, and is greatest in spine, hip, distal radius, pelvis and ribs. Intermittent therapy (alternate day, twice a week) does not appear to reduce the risk. All patients on steroids should be prescribed calcium and vitamin D, advised to exercise regularly, and quit smoking and limit alcohol. There are case reports of rupture of tendons (Achilles and patellar) as well.
Carbohydrate, protein and lipid metabolism	Systemic steroids induce glucose intolerance although diabetic control may be worsened even with inhaled therapy (high doses). Steroids can also cause a catabolic state with protein loss. Besides hyperglycemia, steroids also lead to hypertension, hyperlipidemia, and obesity all of which are established coronary risk factors. Along with this steroids cause body fat redistribution leading to typical Cushingoid features with moon face and buffalo hump.
Immunity	Steroids are potent immunosuppressant drugs, their use can lead to increased susceptibility to infection, aggravation of existing infection, and activation of latent infection. This increased susceptibility to infection coupled with the masking of symptoms can lead to disseminated, often fatal infections (for instance, fungal) with unusual organisms at unusual sites.
Neuropsychiatric	Mood disorders (depression, mania, euphoria), delirium; in children, psychosis, insomnia, and hyperactivity. Memory loss has been reported with parenteral methylprednisolone, which is reversible.
Eye	Cataract, and rarely, retinal detachment.
GIT	It is widely believed that steroids cause peptic ulcers although not all studies have shown increased risk. There also are reports of steroid-induced gastrointestinal perforation with the additional hazard of masking of symptoms due to their anti-inflammatory actions, which can cause delay in the diagnosis.
Skin	Dermatological adverse effects include striae and skin thinning, acne ("steroid acne"), bruising and purpura.
Hypersensitivity	Paradoxically, steroids have been associated with Stevens-Johnson syndrome, hypersensitivity and anaphylaxis
Growth in children	Systemic steroids can impair growth in children and may be used intermittently to reduce this adverse effect.

prophylactic cover may be required for any stress within a week of finishing the course.[8] In practice, there is a large variation in how steroids are tapered from 1 mg monthly to more practical, 2.5 to 5 mg every two to seven days. It must be kept in mind that although gradual withdrawal leads to the normalization of adrenal function, it is not sufficient for conditions associated with stress, such as infection, surgery or trauma, when patients must be given supplementary steroids. It is recommended to withdraw steroids gradually even if patient had received a shorter course of therapy, if (a). higher doses were being given, (b). patient had risk factors for adrenocortical insufficiency, (c). patient had received repeated courses, and (d). patient was taking his or her doses in the evening.

Drug Interactions

Enzyme inducers like barbiturates, carbamazepine, phenytoin, primidone, or rifampicin increase their metabolism, leading to decrease in their effects. An increased risk of hypokalemia occurs with concomitant use of potassium-depleting diuretics, amphotericin B, xanthenes and beta-2 agonists. Concurrent administration with Nonsteroidal Anti-inflammatory Drugs (NSAIDs) leads to increased incidence of GI bleed and peptic ulcers. Reduced efficacy of antidiabetics and antihypertensives may need dose adjustment. There was a case report of severe peripheral edema caused by a synergistic effect of montelukast and prednisone on sodium and water retention in a patient, which did not recur when either drug was used alone.[9]

In asthma, inhaled steroids are the drugs of first choice for prophylaxis and maintenance treatment in patients whose symptoms need regular use of beta-2 agonists. Their regular use decreases bronchial reactivity, provides symptomatic relief, reduces the requirement for inhaled beta-2 agonist "rescue" and also has "systemic steroid sparing effect". Their effects are apparent within a few days to a week, but maximum effects need months of use. Despite these advantages, they cannot be considered as curative drugs; however, there is clinical trial evidence to show that discontinuation of steroids leads to disease exacerbation.

Fixed dose combinations: Fixed dose combinations of steroids with long-acting beta-2 adrenergic agonists are also available, for instance budesonide plus formoterol and fluticasone plus salmeterol. The combination has been shown to be synergistic and provides several advantages; the molecular mechanisms for the same have now been elucidated. It has been shown inhaled beta-2 agonists lead to the increased localization of steroid receptors in the nucleus and provide the additive suppression of release of inflammatory mediators.[10] Steroids in turn increase the expression of beta-2 receptors by increasing gene transcription and prevent their desensitization by restoring coupling of G-proteins with beta-2 receptors.[11,12]

Leukotriene Receptor Antagonists

Leukotrienes, the products of arachidonic acid metabolism have important role in bronchial asthma (Fig. 16.2). They are highly potent bronchoconstrictors, the action is primarily mediated via LT1 receptors.

While montelukast, zafirlukast and pranlukast are cysLT1 receptor antagonists, zileuton is lipoxygenase inhibitor; both the approaches are effective in asthma with decreased frequency of exacerbations (as effective as steroids) and improved asthma control seen in randomized trials. They have been shown to reduce symptoms, increase airway caliber, improve bronchial reactivity and decrease airway inflammation, but to a lesser degree than steroids. The response to therapy is less homogeneous as compared with other anti-asthma drugs and patients can be classified into responders and non-responders; only in responders can these drugs be considered as alternatives to steroids. There are no parameters that can help to predict, which patients will respond. They are taken orally, which leads to a better compliance amongst patients unable to handle inhalers well such as children. However, combination of anti-leukotriene drugs with inhaled corticosteroids may not be as efficacious as a combination of the steroids with Long-acting Beta Agonists (LABAs). Theoretically, zileuton provides several additional advantages over and above LT1 receptor antagonists. Firstly, it inhibits LTB4 synthesis, which is a potent chemotactic autacoid; secondly it inhibits the formation of other 5-lipoxygenase products, which also have a role in the pathogenesis of asthma; and lastly, it inhibit cys-LT effects that are not mediated via LT1 receptors.[13]

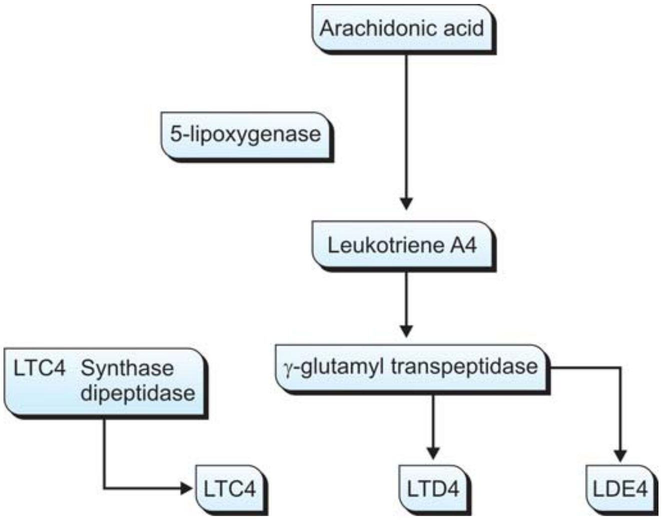

Fig. 16.2: Arachidonic acid metabolism and bronchial asthma

i. *Zafirlukast:* A selective, competitive antagonist of the LTC4, D4 and E4 receptors, this was the first marketed compound of this class. Its peak plasma concentrations occur in three hours; food reduces its bioavailability (by 40%) with reduction in both the rate and the extent of absorption. It is highly (99%) proteins bound, extensively metabolized in liver by CYP2C9, and excreted primarily (90%) by the GIT, the rest in urine, as metabolites. The most common adverse effects seen in 1 to 2% of patients include were headache, rash, abdominal pain, malaise and gastrointestinal disturbances (nausea, diarrhea, dyspepsia). An increased incidence of respiratory tract infection and depression may occur. Less common are fever, malaise, abdominal and joint/muscle pains, insomnia, dizziness, and elevations in liver function tests. Frank hepatitis is rare, but fatalities have been seen. Hypersensitivity reactions (rash, pruritus, urticaria, angioedema), agranulocytosis and bleeding are uncommon.

There are case reports of Churg-Strauss syndrome (systemic eosinophilia) with its use. It is recommended to discontinue treatment, although the causality has remained questionable.[14] In some patients it had occurred after steroid withdrawal, which had led to speculation that asthma might have been a part of some undiagnosed vasculitis, which got unmasked by steroid withdrawal. Others have contended that Churg-Strauss syndrome may have been a precursor of severe asthma. Lastly, similar systemic eosinophilias have been observed in patients taking fluticasone and cromoglycate, a finding that points towards a nondrug cause. On the contrary, Churg-Strauss syndrome has been seen with other leukotriene antagonists, montelukast and pranlukast as well, which points towards a class effect.[15] Therefore, it is now recommended to monitor ESR, CRP and TLC (particularly eosinophils) if the introduction of a leukotriene antagonist allows the physicians to reduce the dose of oral steroids.[16]

Zafirlukast is metabolized by CYP2C9 and inhibits CYP2C9 and CYP3A4. Therefore, use with drugs that are metabolized by these cytochromes may lead to the possibility of increases in plasma concentrations. Patients on warfarin may need dose adjustment as the prolongation of the prothrombin time can occur. Inducers of CYP29 may lead to reduction in plasma concentrations of zafirlukast. Zafirlukast has rarely been reported to increase plasma theophylline concentrations while the concentration of zafirlukast may be increased by aspirin (high dose).

ii. *Montelukast:* Montelukast is probably the most commonly used compound of this class. It reaches peak plasma concentration in three to four hours after oral dose, has an oral bioavailability of > 60%, is more than 99% bound to plasma proteins, metabolized by CYP3A4, CYP2A6 and CYP2C9, and excreted by the GIT. It is similar to zafirlukast in most aspects, but has a longer duration of action. It is also licensed for use in children in reduced doses.

These drugs have been tried with varied success in several other indications, such as in rhinitis, bronchiolitis, cystic fibrosis, eczema, eosinophilic esophagitis, graft-versus-host disease, mastocytosis, sleep-disordered breathing and urticaria. The adverse effect profile is similar to that of zafirlukast. Suspected post-marketing adverse effects reported to the regulatory agencies include edema, agitation and restlessness, allergy (anaphylaxis, angioedema, urticaria), chest pain, tremor, dry mouth, vertigo, arthralgia, depression, suicidality and anxiousness.[17,18]

iii. *Zileuton:* Zileuton is an orally active 5-lipoxygenase inhibitor for use as an alternative adjuvant to long-acting beta agonist and corticosteroids in chronic management of asthma. It is well absorbed from the GIT, the peak levels are seen in two hours. It is highly proteins (93%) bound, metabolized by CYP1A2, CYP2C9 and CYP3A4, and inactive metabolites are eliminated renally. The most common adverse effects are headache, pharyngolaryngeal pain, gastrointestinal disturbances, myalgia and sinusitis. Rarely, hypersensitivity, urticaria, rash, and leukopenia have occurred. Elevated liver enzymes and severe hepatic injury may rarely occur. It is therefore, advisable to monitor liver function once monthly particularly in the first three months of therapy. It may increase the plasma levels (leading to toxicity) of warfarin, propranolol and theophylline.

Leukotriene inhibitors inhibit early and late bronchoconstrictor responses to antigens, not suitable for the acute attacks of asthma. Recently, it has been shown in a randomized trial in adults with acute asthma that intravenous montelukast plus standard treatment produced significant relief of airway obstruction (FEV_1) with an early (10 min) onset of action.[19] These drugs are particularly useful for asthma induced by NSAIDs, cold air and exercise. They can be used along with inhaled steroids in patients with moderate persistent asthma and may have a steroid-sparing. Montelukast has been shown to improve both asthma control and asthma-related quality of life in patients insufficiently controlled with inhaled steroids or inhaled steroids plus LABAs.[20]

MAST CELL STABILIZERS

Two drugs in this category, cromolyn and nedocromil probably act by several mechanisms: Inhibition of the release of mediators from mast cells, inhibition of white blood cell trafficking in airways, reversal of increased leukocyte activation, antagonism of substance P, inhibition of the effects of Platelet-Activating Factor (PAF) and suppression of the effects of chemotactic peptides on blood cells. There is enough clinical evidence to show that pretreatment with these agents blocks allergen-induced bronchoconstriction making them suitable for use before exercise or allergen exposure. Moreover, their long-term use reduces the severity of symptoms and the need for bronchodilators. They are not as effective as inhaled steroids, but combination with steroids improves asthma control. Like anticholinergics, an n-of-1 trial for four weeks can help identify individual patients that respond best (or do not respond) to this class of drugs.

Cromolyn

The first agent in this class, cromolyn is available in inhalational forms, administered in a dose of 2 mg four times daily. The dose may be increased to six or eight times daily, if poor control is a problem. Besides prophylaxis of asthma, cromolyn is also used, with variable success, in prophylaxis and treatment of seasonal and perennial allergic rhinitis, acute and chronic allergic conjunctivitis, vernal keratoconjunctivitis, prevention of food allergies (orally), mastocytosis, Cogan's syndrome, cough associated with ACE inhibitor therapy, nonspecific cough in children, and moderately severe atopic dermatitis (in children).

Poor systemic bioavailability implies fewer incidences of systemic adverse effects. Local adverse effects, such as irritation in the throat, cough, dryness of mouth, bad taste, nasal congestion, tightness of chest, transient bronchospasm and wheezing (aggravation of existing asthma) may occur. Serious adverse effects are uncommon; dermatitis, myositis, joint pain and swelling or gastroenteritis (<2%), dysuria, urinary frequency, rarely pulmonary infiltration with eosinophilia and anaphylaxis, may occur.

Cromolyn is not indicated for the treatment of acute asthmatic attacks. Its withdrawal may lead to recurrence, should therefore be attempted under steroid cover if steroid doses were reduced because of its use. Also, the dose should be gradually tapered over a period of one week.

Nedocromil Sodium

It is similar to cromolyn in most aspects, generally considered to be its alternative except that its duration of action is somewhat longer. It is usually started in dose of 4 mg (inhaled) four times a day. The other uses are similar to cromolyn. It has poor systemic bioavailability from the GIT. The adverse effects are mild, infrequent, mostly transient and do not require the discontinuation of therapy. Paradoxical bronchospasm is rare.

The major indication for the use of mast cell stabilizers is to prevent asthmatic attacks in patients with mild-to-moderate asthma. Nedocromil is not approved for use in patients <12 years of age while cromolyn is approved for use in adults, as well as children.

Anti-IgE Monoclonal Antibodies

Monoclonal antibodies, which bind to the site on IgE antibody to prevent its binding to receptors (FCεR1 and FCεR2) present on mast cells and other inflammatory cells, are a new class of drugs approved for use in certain cases of asthma. Omalizumab is the prototype of this class of "biological drugs".

Omalizumab

It is a recombinant humanized monoclonal antibody targeted against IgE. Once it binds to IgE receptors on inflammatory cells, it prevents interaction of IgE with these inflammatory cells and prevents their release. It is produced in Chinese Hamster Ovary (CHO) cells in cell culture. It is approved for prophylactic use as add-on therapy to standard treatment in adult patients with moderate to severe, persistent, allergic, IgE-induced asthma.[20] It decreases exacerbations, improves quality of life and reduces steroid requirements.[21] It does not have a bronchodilator effect, has no role during acute exacerbations.

The dose is variable, ranging from 75–300 mg every four weeks to 225–375 mg every two weeks. The dose depends on the patient's body weight and pretreatment serum IgE concentrations. It is administered subcutaneously, it is not recommended to give more than 150 mg at one site. Injection site reactions, including erythema, stinging, bruising and induration are the most common adverse effects. Generalized pain, fatigue, arthralgia, dizziness, earache, GI disturbances, headache and alopecia are some other adverse effects. Flu-like syndrome and an increased incidence of infections (parasitic, viral) has been seen. Rarely, Churg-Strauss syndrome, hypersensitivity reactions, including urticaria, dermatitis, pruritus and anaphylaxis are reported. The temporal relation of anaphylactic reactions to omalizumab is unpredictable. The side effects may occur after the first dose or within a few days after a dose, or even more than one year after a patient is on regular therapy. Severe thrombocytopenia and an increased incidence of cancer are two other potentially serious adverse effects with its use.

MISCELLANEOUS DRUGS

Mepolizumab

Mepolizumab, a monoclonal antibody against IL-5 has received an orphan drug status for the management of hypereosinophilic syndrome. When given as an infusion to patients with refractory eosinophilic asthma with a history of recurrent exacerbations, mepolizumab reduced the number of blood and sputum eosinophils, had steroid-sparing effect in patients who had asthma with sputum eosinophilia despite prednisone treatment.[22]

Magnesium Sulfate

Magnesium is known to reduce smooth muscle contraction, decrease histamine release from mast cells, and inhibit acetylcholine release. In a study in pediatric patients with acute severe exacerbation, unresponsive to standard treatment, $MgSO_4$ in a dose of 40 mg/kg IV bolus, led to symptomatic improvement within a few minutes that lasted for about two hours.[23] Similarly, in adult patients with severe, acute asthma, it caused improvement in pulmonary function when used in a dose of 2 g IV, as an adjunct to standard therapy.[24] Nebulized magnesium may also improve symptoms over and above the effects of standard inhaled drugs, the most severely ill derive the most benefit.[25]

Nebulized Lidocaine

The safety and efficacy of nebulized lidocaine was evaluated in a randomized, placebo-controlled trial in 50 patients with mild-to-moderate asthma.[26] Nebulized lignocaine improved the various indicators of asthma severity, such as the FEV_1, night-time awakenings, clinical symptoms, bronchodilator use and blood eosinophil counts.

Inhaled Heparin

In a small study in 12 patients with exercise-induced asthma, nebulized heparin (1000 U/kg) prevented exercise-induced asthma without influencing histamine-induced bronchoconstriction.[27] This non-anticoagulant action of heparin is more likely to relate to the modulation of mediator release than to a direct effect on smooth muscle.

Beta-adrenergic Blockers

Some recent studies have suggested a role of beta-blockers in the management of asthma. This paradox has been likened to the beta-blocker paradox in heart failure. In a preliminary study, the safety and efficacy of escalating doses of the beta-blocker, nadolol (an inverse agonist), administered over 9 weeks to 10 subjects with mild asthma was evaluated.[28] A dose-dependent decrease in airway hyperresponsiveness to methacholine was seen in 8 out of the 10 patients after 9 weeks of nadolol treatment. Clearly, more data are needed before any conclusions can be drawn.

Steroid Sparing Anti-inflammatory Agents

There are various steroid sparing-agents, like azathioprine that have been evaluated. There is a lack of larger, well designed studies to provide evidence for its use. It cannot be recommended for clinical practice as of now.[29] Cyclosporine is another drug that has been evaluated for its steroid-sparing effect. A Cochrane review of 98 patients with severe asthma treated with cyclosporine showed a small, but significant treatment effect for cyclosporine in the terms of steroid dose reduction.[30] It is a drug with a large number of side effects, not recommended for routine use. A Cochrane review of small clinical trials showed a small, but significant treatment effect for gold in the terms of steroid dose reduction.[31] Should not be routinely used because of the adverse effects concern.

Colchicine and dapsone are two other steroid-sparing drugs. There is no reliable evidence to recommend the use of either of them in the management of steroid-dependent asthmatic patients.

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17

Immunosuppressant Drugs

Nusrat Shafiq, Samir Malhotra

INTRODUCTION

Immunosuppressant drugs are mainly used in the treatment of disorders in which autoimmunity has an important role, some malignancies and for prevention of transplantation rejection. There are four main classes of immunosuppressant drugs; glucocorticoids, calcineurin inhibitors, antiproliferative/antimetabolite drugs, and biologics (antibodies). These are briefly discussed below, particularly with reference to their role in pulmonary disorders.

GLUCOCORTICOIDS

Most aspects of glucocorticoids have been discussed in the earlier chapter on anti-asthma drugs. Their role as immunosuppressants is known since the 1960s.[1] The exact mechanism(s) behind their immunosuppressant actions is (are) unknown (Table 17.1). These actions make steroids one of the most effective immunosuppressant and anti-inflammatory drugs. Most of their effects are seen on cell-mediated immunity, they have no or little effect on humoral immunity.

TABLE 17.1: Proposed mechanisms for immunosuppressant anti-inflammatory actions of steroids

- Redistribution of lymphocytes leading to decreased lymphocytes in peripheral blood
- Transcription of various genes involved in immune processes
- Decreased activation of NF-kappa B leading to increased apoptosis of activated cells[2]
- Decreased production of IL-2 by T lymphocytes
- Downregulation of proinflammatory cytokines (IL-1, IL-6)
- Inhibition of proliferation of T lymphocytes cells
- Inhibition of activation of cytotoxic T lymphocytes
- Decreased neutrophils/monocyte-induced chemotaxis
- Decreased lysosomal enzyme release

Alone, or in combination with other immunosuppressant drugs, steroids are used in the treatment of interstitial lung diseases, vasculitides, sarcoidosis, asthma, and other allergic disorders (including drug induced). They are also used in the management of several other autoimmune disorders such as rheumatoid arthritis, other arthritic disorders, Systemic Lupus Erythematosus (SLE), dermatomyositis, psoriasis, other serious dermatological disorders, inflammatory bowel disease, many disorders of the eye, autoimmune disorders of blood, multiple sclerosis, and many other life-threatening disorders. Steroids also constitute the core management of transplant rejection. Prednisone commonly used as an immunosuppressive agent is converted to active prednisolone in the body. It is well absorbed from the Gastrointestinal Tract (GIT), conveniently given once daily in the usual dose of 1 mg/kg/day and tapered once there is clinical improvement. In many disordrers, including in post-transplant cases, it is continued life long. It should be taken with food to minimize GI toxicity. In order to mimic the circadian rhythm, administration between 7 and 8 am is recommended. Methylprednisolone is used in high doses (1 g/day IV) for three days in a month in various immunosuppressive protocols. High doses of methylprednisolone are routinely required for preventing acute graft rejection.

The most important adverse effects of steroids include hypertension, dyslipidemia, hyperglycemia, osteoporosis, avascular necrosis of bone, poor wound healing, increased risk of infections, cataract and growth retardation in children.

CALCINEURIN INHIBITORS

Calcineurin is a protein that activates T lymphocytes. Calcineurin inhibitors (cyclosporine, tacrolimus and pimecrolimus) are among the most efficacious immunosuppressant drugs (Fig. 17.1).

Cyclosporine

Cyclosporine is an 11 amino acid cyclic polypeptide obtained from fungus *Beauveria nivea*. It forms a complex with an immunophilin (cyclophilin) and inhibits T cell responses (Fig. 17.1). When administered orally it is slowly and incompletely (20 to 50%) absorbed. Food has variable effects on its absorption. The various oral preparations, which are available in the market may not be bioequivalent, hence not advisable to switch brands without expert supervision and plasma level monitoring. The absorption also depends on the presence of bile, leading to considerable interpatient and intrapatient variability. The microemulsion formulation of cyclosporine forms a microemulsion spontaneously with aqueous fluids in the GIT, making it less dependent on bile for absorption. The Intravenous (IV) formulation in castor oil needs to be diluted in 5% dextrose or normal saline before injection.

It is extensively metabolized by the hepatic CYP3A, the metabolites are eliminated by the kidneys. Its half-life is 5–18 hours with a considerable inter-individual variation. Because of this variation, toxicity and specialized use in transplant patients, monitoring of blood levels is recommended. The best time to obtain sample is just before the next dose (trough concentration) or at a designated time point after drug administration, two-hour postdose sample has been proposed as a better option.[3]

The daily doses of cyclosporine are different for transplant patients than those with autoimmune disorders. In the treatment of most autoimmune disorders, the usual initiating oral dose is 2.5–5 mg/kg/day in two divided doses, which is reduced once remission is achieved to the lowest effective maintenance dose. In most cases it is not recommended to continue treatment if there is insufficient response within six to eight weeks. The IV doses are one third of oral, given by slow infusion over two to six hours.

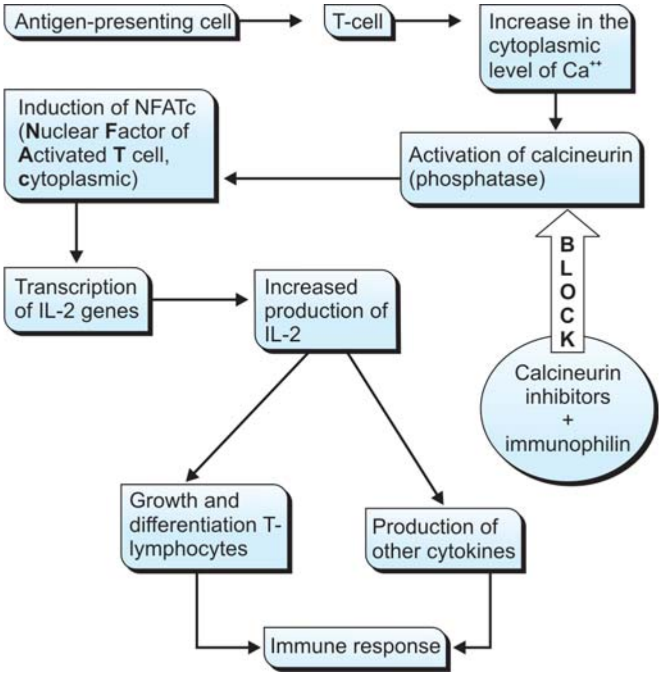
Antigen-presenting cell
T-cell
Increase in the cytoplasmic level of Ca⁺⁺
Induction of NFATc (**N**uclear **F**actor of **A**ctivated **T** cell, **c**ytoplasmic)
Activation of calcineurin (phosphatase)
BLOCK
Transcription of IL-2 genes
Increased production of IL-2
Calcineurin inhibitors + immunophilin
Growth and differentiation T-lymphocytes
Production of other cytokines
Immune response

Fig. 17.1: The calcineurin pathway and site of action of calcineurin inhibitors[4]

The pulmonary uses include refractory asthma, sarcoidosis and diffuse parenchymal lung disease. In refractory asthma (in doses of 5 mg/kg/day), it has been shown to improve lung function, decrease frequency of exacerbation, and enable reduction in doses of steroids.[5,6] Adverse effects limit its usefulness.[7] The evidence for its use in sarcoidosis and diffuse parenchymal lung disease is limited. It has also been given by inhalation in the management of acute graft rejection in lung transplantation in doses of 300 mg/day via a nebulizer.[8] One case-control study has shown aerosolised cyclosporine to improve survival among lung transplant recipients with bronchiolitis obliterans.[9] A randomized controlled trial showed that prophylactic use of inhaled cyclosporine did not have a beneficial effect on the rate of acute rejection, but improved chronic rejection-free survival and overall survival.[10]

Renal dysfunction, which may be due to arteriolar constriction, is an important complication of cyclosporine. Hypertension, hyperlipidemia, tremors, hyperuricemia, hirsutism, and gum hyperplasia are the other important adverse effects. It can also lead to GI disturbances, fatigue, hepatotoxicity, headache, hyperkalemia, hypomagnesemia, paresthesias, muscle cramps, anemia, weight gain, infections, edema, thrombocytopenia, rash, pancreatitis, neuropathy, anaphylaxis and anaphylactoid reactions, hyperglycemia, and increased incidence of infections and some tumors (particularly lymphoma, skin cancer and Kaposi's sarcoma).[11]

Because of the risk of anaphylaxis, it is recommended that patients should be "under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter."[12] In case of anaphylaxis, the infusion should be stopped and epinephrine administered.

It has a large number of pharmacokinetic drug-drug interactions. CYP3A inhibitors (verapamil, nicardipine, fluconazole, ketoconazole, erythromycin, glucocorticoids, HIV protease inhibitors and grapefruit juice) can increase its blood concentration whereas CYP3A inducers (nafcillin, rifampin, carbamazepine, phenobarbital, phenytoin, octreotide, ticlopidine, St John's wort) decrease its blood concentrations.

Because of the large number of adverse effects it also has a number of pharmacodynamic drug interactions. Sirolimus and cyclosporine potentiate each other's adverse effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) and other nephrotoxic agents lead to additive nephrotoxicity. It increases the blood levels of methotrexate, digoxin and statins. There also is the increased risk of myopathy and rhabdomyolysis with statins. Hyperkalemia may occur with the concomitant use of potassium-sparing diuretics and potassium supplements. The risk of gingival hyperplasia may be increased, if used along with amlodipine or nifedipine. It may also reduce the efficacy of live vaccines.

Tacrolimus

Tacrolimus is a macrolide antibiotic produced by *Streptomyces tsukubaensis*. It inhibits T-cell activation by inhibiting calcineurin, but acts on a different immunophilin (FKBP-12) than cyclosporine. Gastrointestinal absorption after oral administration is incomplete (20 to 25%) and variable and food (particularly high fat). It is extensively metabolized by the hepatic CYP3A4 and excreted in feces with a half-life of about 12–16 hours.

Like cyclosporine, it is used for the prophylaxis of solid-organ allograft rejection and for rescue therapy in patients with rejection episodes despite "therapeutic" levels of cyclosporine.[13]

It can be used in autoimmune diseases, but experience with its use is limited. It is currently approved in some countries for the refractory cases of myasthenia gravis, rheumatoid arthritis and lupus nephritis, if steroids are contraindicated. Tacrolimus-releasing stents are commonly used in cardiology to reduce restenosis after coronary artery stent placement.

The adverse effect profile and pharmacokinetic interactions are similar to those of cyclosporine.

ANTIPROLIFERATIVE/ANTIMETABOLIC DRUGS

Sirolimus

Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus.* After oral administration, sirolimus is rapidly, but incompletely (15%) absorbed.

Sirolimus is indicated for the prevention of organ transplant rejection in combination with a calcineurin inhibitor and glucocorticoids.[14] In patients experiencing or at high risk for calcineurin inhibitor-associated nephrotoxicity, sirolimus has been used with glucocorticoids and mycophenolate mofetil to avoid permanent renal damage.[1] It is also being evaluated in autoimmune diseases. Sirolimus-releasing stents are used to reduce restenosis after coronary artery stent placement and in peripheral arteries to reduce ischemia in severe claudication. It is well known that transplant recipients on immunosuppressant drugs are susceptible to the development of malignancies; there is some evidence to show that sirolimus, coupled with the discontinuation of immunosuppressant drugs, may not only lead to reduced incidence of malignancies, but may also cause tumor regression as seen in the case of Kaposi's sarcoma.[15]

Everolimus

Everolimus is a derivative of sirolimus and resembles it in most aspects. Its indications and adverse effects are similar to sirolimus.

Azathioprine

Azathioprine, a 6-mercaptopurine derivative, is an immunosuppressive antimetabolite drug. It is a purine analog, gets converted to a sham nucleotide 6-thio-IMP and inhibits T-lymphocytes (Fig. 17.2). Azathioprine is well absorbed from the GIT after oral administration. It is rapidly (half-life 10 minutes) metabolized to active mercaptopurine, which is further broken down to many active metabolites having longer half-lives (5 hours).

Azathioprine is used as an adjunct in autoimmune disorders, such as the interstitial lung disorders and for prevention of organ transplant rejection. Its effects may not be seen for several weeks after administration, but if there is no improvement in 12 weeks, it may be discontinued. The starting dose for the prevention of organ rejection is 3–5 mg/kg/day. For autoimmune disorders

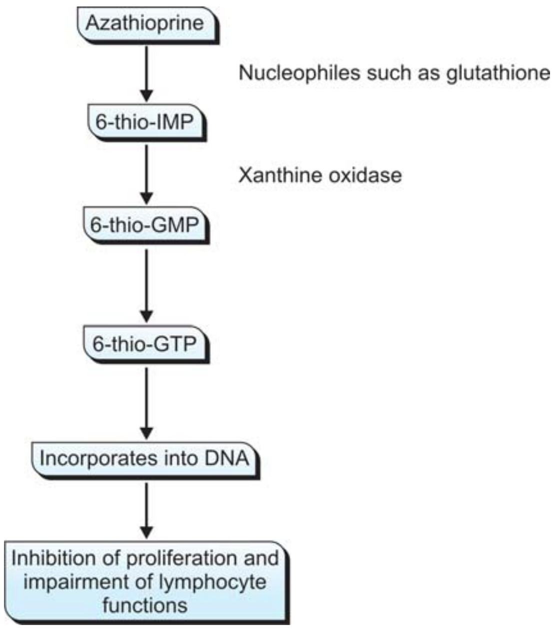
Azathioprine
Nucleophiles such as glutathione
6-thio-IMP
Xanthine oxidase
6-thio-GMP
6-thio-GTP
Incorporates into DNA
Inhibition of proliferation and impairment of lymphocyte functions

Fig. 17.2: Mechanism of the action of azathioprine

the recommended dose is 1 mg/kg/day. It is generally used orally, but may also be given by IV infusion over 30–60 minutes after dilution in normal saline or 5% dextrose. Blood counts and liver function tests should be regularly monitored and it should be withdrawn or the dose reduced if blood counts show a downward trend.

The major side effect of azathioprine is dose-related bone marrow suppression, which is generally reversible. It commonly manifestates with leukopenia, thrombocytopenia is less common, anemia is uncommon, and agranulocytosis, pancytopenia or aplastic anemia are rare. Other adverse effects are the GI disturbances, fever, rigors, rash, muscle and joint pains, pneumonitis, pancreatitis, tachycardia, hepatotoxicity (mainly cholestatic), renal dysfunction, hypotension, reversible alopecia, pancreatitis, and increased susceptibility to malignancies and infections (especially varicella and herpes simplex viruses). Rare but potentially fatal adverse effects include the occurrence of veno-occlusive liver disease, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Mycophenolate Mofetil and Mycophenolic Acid

Mycophenolate mofetil is a prodrug rapidly hydrolyzed to active mycophenolic acid. Mycophenolic acid is an immunosuppressant derived from *Penicillium stoloniferum*. It is used along with other immunosuppressants for the prevention of transplant rejection, although its use in combination with azathioprine is not recommended.[16] It is also being investigated in various autoimmune/immune-mediated inflammatory diseases, including arcoidosis, scleroderma, SLE, vasculitic syndromes (Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyangiitis, Takayasu's arteritis, and Wegener's granulomatosis), some others. It is used in doses of 2–3 g/day in two divided doses.

The most important adverse effects are GI (diarrhea, vomiting; hemorrhage and perforation) and hematologic (leukopenia, thrombocytopenia and anemia). There is an increased incidence of infections (particularly CMV sepsis) and malignancies (particularly skin cancer). Aplastic anemia and bone marrow depression may also occur and sometimes fatal.

IMMUNOSUPPRESSIVE CYTOTOXIC DRUGS

Drugs discussed in this category are cytotoxic antimetabolites used mainly as antineoplastic agents, but also possess immunosuppressive effects.

Methotrexate

It is an antimetabolite of folic acid. It acts by competitively inhibiting the enzyme dihydrofolate reductase, which is needed for the formation of tetrahydrofolate. It is rapidly absorbed from the GIT after oral, as well after intramuscular administration. Its half-life is 3–10 hours, but increases (8–15 hours) after high-dose administration. It is excreted primarily by the kidneys.

The main indications are the induction and maintenance of remission in acute lymphoblastic leukemia, non-Hodgkin's lymphomas, and solid neoplasms like choriocarcinoma. Among autoimmune disorders it is used in psoriasis, rheumatoid arthritis, asthma,[17] sarcoidosis,[18] SLE, vasculitic syndromes and others. It has steroid-sparing action in some of these diseases. It is also used to prevent graft-versus-host disease after bone marrow transplantation. The most commonly used dose is 15 mg/m^2 once or twice weekly in malignancies and 7.5–20 mg once weekly in other disorders.

Bone marrow depression (leukopenia, thrombocytopenia and anemia) and GI toxicity (oral ulcers, stomatitis, diarrhea, hemorrhagic enteritis and intestinal perforation) are the common dose-related adverse effects. Hepatotoxicity is the next important adverse effect and cirrhosis can also occur. Folinic acid is given to counter some of the adverse effects of methotrexate, paticularly on bone marrow (folinic acid rescue).

Salicylates, other NSAIDs, probenecid, and some penicillins decrease its renal excretion leading to increased chances of methotrexate toxicity. Co-trimoxazole or trimethoprim coadministration can cause severe methotrexate toxicity. Concomitant use of other drugs having bone marrow, renal or hepatic toxicity may further increase the risk. Folic acid and its derivatives may decrease its efficacy despite the fact that they are used together to reduce methotrexate toxicity.

Cyclophosphamide

It is an antineoplastic drug belonging to the class of alkylating agents and also has immunosuppressant action. It is used in the treatment of non-Hodgkin's lymphomas, many other cancers and autoimmune diseases.

Chlorambucil

It is an antineoplastic drug that belongs to the class of alkylating agents. Its immunosuppressive properties are sometimes utilized in the treatment of autoimmune disorders like sarcoidosis, amyloidosis and Behçet's syndrome. Its major adverse effects include bone marrow suppression, GI symptoms, azoospermia, amenorrhea, pulmonary fibrosis, seizures, dermatitis and hepatotoxicity.

MISCELLANEOUS IMMUNOSUPPRESSANTS

Thalidomide

Introduced many decades ago as a hypnotic, it was found to have immunomodulating actions, but its mechanism of action remains unclear. Thalidomide has been used in several autoimmune diseases like graft-versus-host disease, recurrent aphthous stomatitis in severely and terminally immunocompromised patients (HIV-associated wasting syndrome), AIDS-related Kaposi's sarcoma, treatment of the clinical manifestations of both tuberculous and nontuberculous mycobacterial infection, myelodysplastic syndrome, primary brain malignancies, sarcoidosis, Behçet's syndrome, inflammatory bowel disease, SLE, refractory rheumatoid arthritis and several others. Its major adverse effect is its teratogenic potential for which it was withdrawn in the 1960s. The other adverse effects include peripheral neuropathy, venous thromboembolism, constipation, dizziness, orthostatic hypotension and toxic epidermal necrolysis.

Leflunomide

It is an immunosuppressant antiproliferative mainly used as a disease-modifying drug in the treatment of rheumatoid arthritis. It has been tried in other arthritides like psoriatic arthritis and has been investigated in solid tumors, Crohn's disease and ankylosing spondylitis.

In conclusion, the drugs discussed in this chapter have revolutionized the area or organ transplantation and have made significant contribution to treatment of diseases that have autoimmune/autoimmune–-inflammatory components. Most of the times, several drugs are used together. Importantly, these toxic drugs having a large number of serious adverse effects since they inhibit most of the immune responses nonspecifically leading to increased susceptibility to infections and malignanices. Morever, many of these drugs are nephrotoxic, diabetogenic and suppress bone marrow. Nevertheless, it is possible to use them sometimes lifelong, relatively safely, provided proper care is taken with respect to adverse drug reactions.

Biological Agents: Interleukin-2 Receptor Antagonists

Two monoclonal antibodies, basiliximab and daclizumab exert their immunosuppressive effect by binding to the alpha chain (CD25) on the surface of activated T-lymphocytes. This binding prevents the proliferation of T-cells. **Muromonab** is a murine monoclonal antibody to the CD3 receptor on mature human T-cells **(**OKT3). It has been used as an induction therapy in transplant patients. **Alemtuzumab** has been approved for use in B-cell chronic lymphocytic leukemia, its role as an immunosuppressant is increasingly being recognized. Administration of alemtuzumab causes complete lymphocyte depletion. Alemtuzumab, when given as an induction agent along with reduced maintenance doses of immunosuppressants in lung transplant patients led to comparable early survival, rejection and infection rates as compared to conventional high-dose immunosuppression regimens.[19] **Abatacept** has been approved for the treatment of patients with moderate-to-severe rheumatoid arthritis. **Sotrastaurin** is being evaluated primarily in renal transplant patients. Some early studies have also shown efficacy in autoimmune diseases like psoriasis.[20]

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Section

4

SYMPTOM-APPROACH TO RESPIRATORY DISEASE

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Cough in the Adult

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INTRODUCTION

Coughing is an important reflex that helps protect the lungs from the aspiration of upper airway secretions and from inhaled particles and irritants. It is also an important mechanism for clearing airway secretions. When coughing becomes excessive, it potentially can be the primary symptom for a wide variety of pathological conditions. The symptom of cough is common, and it results in significant costs to the health care system. Cough is a frequent symptom for many life-threatening diseases, and it can negatively impact a patient's lifestyle and the sense of well-being. Therefore, it is vital for health care professionals to understand the etiologies and effective treatments for cough.

The format of this chapter, and its contents, are updates to material that we have previously published on the subject of cough.[1-3]

EPIDEMIOLOGY

Cough is one of the most common symptoms for which patients seek medical attention.[4] From 2001 to 2002, there were over 34 million ambulatory care visits in the US alone for a complaint of cough.[5] This makes up over 3% of all ambulatory care visits. Questionnaires estimate the prevalence of cough to be between 9% and 33% of the population in the US and Europe.[6,7] A survey in rural India reported a prevalence of cough in patients seeking medical attention to be about 3%.[8]

In 2006, over $3.6 billion were spent in the US for over-the-counter cough treatments alone.[9] Because this did not include Wal-Mart pharmacies and Wal-Mart has about 50% of the business, the real cost could be nearly $7.2 billion. If one adds to this the cost of prescription medications to treat cough, the cost of physician visits, and the lost production in the work place due to cough, the overall costs are staggering, with estimates approaching $40 billion annually.[10] In addition, there are other costs to the patient. Patients with cough are viewed by the public as being unhealthy, or having a potentially contagious disease. This in turn may result in a patient feeling isolated, embarrassed, or maligned by the society. The negative impact that chronic cough has on a patient's quality of life is well documented.[11]

PHYSIOLOGY

There are multiple cough receptors in the hypopharynx, larynx, trachea, bronchi, and probably the esophagus, that when triggered, start the cough reflux. These receptors are either chemical receptors or mechanical receptors.[12-14] Cough can be induced by stimulating the chemical receptors with stimuli such as inflammatory mediators and acid. The mechanical receptors can be stimulated by vibration and temperature. Multiple afferent nerves carry the impulse from the sensory receptors to the brainstem, where the cough response is coordinated. The major afferent nerves are c-fibers, which are located throughout the upper and lower airways, and the lungs. In addition to the c-fibers, cough can be triggered by the stimulation of vagal afferent nerves, or a group of receptors called Rapidly Adapting Receptors (RARs). The RAR are mechanoreceptors that respond to physical forces associated with lung inflation and deflation.[15]

The coughing mechanism is divided into three phases. The first phase is the inspiratory phase, which is marked by a deep inspiration. This phase is followed by the compressive phase when the glottis closes, resulting in rising intrathoracic pressure. Finally, the expiratory phase occurs with the sudden opening of the glottis. With an effective cough, expiratory velocities can reach up to 28,000 cm/sec (500 mph).[16] The most important parameter of an effective cough is the linear velocity of the moving air column in the expiratory phase. The linear velocity is determined by the expiratory flow divided by the cross-sectional area of the airways. The higher the flow and the smaller the cross-sectional area, the greater the expiratory velocity. The flow, in turn, is dependent on the initial deep inspiration in the inspiratory phase because expiratory flow rates are greatest at higher lung volumes.

PATHOPHYSIOLOGY

As mentioned above, one of the major functions of cough is to clear excessive secretions for the airway when mucociliary function is not adequate. When the cough is not adequate to serve this purpose, complications, such as gas exchange abnormalities, atelectasis, pneumonia and bronchiectasis, can occur. Clinical disorders that minimize the effectiveness of cough interfere with either the inspiratory or the expiratory phase, or both. What these clinical disorders have in common is an association with the insufficient strength of the respiratory muscles. Some conditions associated with ineffective cough are listed in Table 18.1.[1] It is estimated that a maximal expiratory pressures of less than 40 cm H_2O are associated with an ineffective cough.[17] At the bedside, an ineffective cough can be predicted if the patient is unable, or can barely cough on command.

TABLE 18.1: Conditions associated with an ineffective cough[1]

Pulmonary Disorders
- Asthma
- Bronchiectasis
- Chronic obstructive lung disease
- Cystic fibrosis
- Tracheal lesions (extrinsic compression, intraluminal masses, strictures)
- Tracheobronchomegaly

Extrapulmonary Disorders
- Paralysis/muscle weakness (cervical/upper thoracic spinal cord injuries, Guillain-Barré syndrome, amyotrophic lateral sclerosis, poliomyositis, botulism)
- Pain (rib fractures, postoperative from chest or abdomen surgery)
- Central depression of cough center (drugs, strokes)
- Upper airway obstruction (vocal cord paralysis, laryngeal masses)

BENEFITS OF COUGH

The main benefit of coughing is airway clearance. This benefit is especially important in conditions were the normal mucociliary clearance is overwhelmed such as with a pneumonia. Not only is coughing beneficial in clearing mucus from the airways, it is also important in protecting the lung from retaining inhaled particles and irritants such as the aspiration of upper airway and gastrointestinal secretions. Finally, coughing is beneficial in preventing atelectasis as might occur after intubation, general anesthesia and surgery. Cough has been demonstrated to be highly effective in cardiopulmonary resuscitation, a technique called Cough Cardiopulmonary Resuscitation (CPR). In conscious patients with asystole, profound bradycardia and ventricular tachycardia, coughing can convert the patient back to sinus rhythm.[18] Coughing can help support blood pressure and maintain consciousness in patients in ventricular fibrillation, asystole, or high-degree heart block.[19] Forceful coughing at 1 to 3 second intervals for 30 to 90 seconds is commonly employed in the cardiac catheterization laboratory in patients who develop these arrhythmias as might occur during contrast injection into the coronary arteries. Studies have demonstrated that vigorous coughing can elevate systolic blood pressures to near 140 mm Hg, compared to systolic pressures of about 75 mm Hg generated with well performed chest compressions.[19]

COMPLICATIONS OF COUGH

During the expiratory phase of vigorous coughing, intrathoracic pressures can reach as high as 300 mm Hg.[20] Therefore, it should come as no surprise that these extreme thoracic pressures can result in numerous complications. Table 18.2 lists some of the more common complications of severe coughing.[1,2,21] While coughing can be beneficial in elevating systolic blood pressure, severe coughing can also result in hypotension, most likely due to decreased central venous return that in turn can result in near-syncope or syncope. Patients with cough-induced urinary or fecal incontinence face additional embarrassment that can further worsen their quality of life and self-esteem. In the postoperative patients, severe coughing can place the patient at risk for wound dehiscence. Patients undergoing surgeries, such as hernia repair or cataract surgery should have their coughs controlled before surgery in an effort to avoid intraoperative or postoperative complications.

TABLE 18.2: Complications of severe coughing/ chronic cough*[1,2,21]

Constitutional
- Fatigue/exhaustion
- Excessive sweating
- Anorexia

Neurological
- Syncope/near syncope
- Headache
- Dizziness
- Seizure
- Stroke
- Cerebral air embolism
- Acute cervical radiculopathy

Cardiovascular
- Hypotension
- Nasal and anal vein rupture
- Brady- and tachyarrhythmias

Respiratory
- Exacerbations of asthma/COPD
- Lung herniation
- Pneumothorax
- Pneumomediastinum
- Bronchial rupture

Gastrointestinal/abdominal
- Vomiting
- Gastroesophageal reflux
- Mallory-Weiss tears
- Hernias
- Splenic rupture
- Fecal incontinence

Genitourinary
- Urinary incontinence
- Bladder prolapse
- Vaginal prolapse

Skin/ophthalmological
- Petechiae/purpura
- Disruption of surgical wounds
- Subconjunctival/intraocular hemorrhage

Musculoskeletal
- Rib fractures
- Diaphragmatic rupture
- Costochondritis
- Pulled/torn chest wall muscles

Psychological
- Depression
- Fear of serious disease
- Lifestyle changes
- Decreased self-confidence

*This table includes the most common causes in each category and is not meant to be exhaustive

CAUSES OF COUGH

Many diseases and conditions are associated with cough as a symptom. Cough can be the major symptom for disease processes that are of minor consequences, such as the common cold, or the major symptom of life-threatening conditions, such as a pulmonary embolism. A useful way to categorize the many causes of cough is to divide them up based on the duration of the cough. For example, acute cough is defined as lasting less than three weeks, subacute cough as lasting between 3 and 8 weeks, and chronic cough lasting more than 8 weeks. Table 18.3 lists the more common causes of cough, separated into these three groups.[1,2,21] One should note that several conditions, such as asthma can present as acute, subacute or chronic cough. Of this group, chronic cough contains the widest spectrum of diseases. While acute cough can be due to life-threatening conditions

TABLE 18.3: Differential diagnosis of cough*[1,2,21]

Acute Cough (< 3 weeks)
- Upper respiratory infections (viral, sinusitis)
- Allergic rhinitis
- Pneumonia
- Exacerbations of asthma and COPD
- Congestive heart failure
- Lung cancer
- Pulmonary embolism
- Acute bronchitis
- Acute environmental exposures (dusts, chemicals)

Subacute Cough (3-8 weeks)
- Upper respiratory infections
- *Bordetella pertussis* infections
- Exacerbations of asthma, COPD and bronchiectasis

Chronic Cough (> 8 weeks)
- Upper airway cough syndrome
- Asthma
- Gastroesophageal reflux disease
- ACE inhibitors
- Nonasthmatic eosinophilic bronchitis
- Chronic bronchitis
- Bronchiectasis
- Lung cancer
- Sarcoidosis
- Tuberculosis
- Psychogenic/tic cough/habit cough

*This table includes the most common causes in each category and is not meant to be exhaustive such as infections, lung cancer, congestive heart failure, and pulmonary embolism, the most common causes of acute cough are non-life-threatening conditions, such as the common cold, acute bronchitis, allergic rhinitis and the acute exacerbations of underlying conditions, such as asthma and Chronic Obstructive Pulmonary Disease (COPD).

Acute bronchitis is a condition manifested by cough, with or without phlegm, which lasts for less than three weeks.[22] However, it is a diagnosis of exclusion, as conditions that cause identical symptoms, such as pneumonia, asthma and COPD exacerbations, and the common cold, have to be ruled out. The most common cause of acute bronchitis is most likely respiratory viruses, and the routine use of antibiotics is not recommended.[22] Antitussive agents may provide some short-term symptomatic relief, and inhaled bronchodilators are sometimes used when patients have wheezing in addition to the cough. If a patient with suspected acute bronchitis does not have resolution of their cough after three weeks, an alternative diagnosis should be investigated (see subacute cough below).

The most common cause of a subacute cough is postinfectious cough, especially from infections with *Bordetella pertussis*. Subacute cough from an infection with *B. pertussis* should be considered in patients with cough-induced vomiting, and in patients with the classic whoop (a stridorous sound during inspiration that follows a prolonged episode of coughing). This condition, as well as exacerbations of asthma, bronchiectasis and chronic bronchitis should be considered when patients present with a biphasic course (cough worsens after appearing to improve).

The most common causes of chronic cough in patients with normal chest radiographs are Upper Airway Cough Syndrome (UACS) (previously known as postnasal drip syndrome), asthma, gastroesophageal reflux disease, ACE inhibitor-induced cough, nonasthmatic eosinophilic bronchitis (similar to atopic cough that has been described in Japan), and bronchiectasis. These six disorders account for nearly 95% of all the causes of chronic cough. In addition, patients often have more than one cause contributing to their chronic cough.

Work-up and Management of Acute Cough

A complete history and physical examination are most helpful in determining the cause of acute cough. Postnasal drip and throat clearing with the associated symptoms of nasal congestion, rhinorrhea and sneezing suggest an upper airway cause such as the common cold or allergic rhinitis. Symptoms of chest tightness, wheezing or dyspnea in a patient with a history of asthma or COPD suggest an exacerbation of these diseases as the cause of the acute cough. Some associated symptoms or signs should raise concern to a potentially life-threatening cause of the acute cough. Patients complaining of fever, chest pain, orthopnea or hemoptysis with their cough, or who are found to have crackles, focal rhonchi or an S3 gallop, require further testing, such as a chest radiograph looking for conditions, including pneumonia, congestive heart failure or cancer. We recommend following the diagnostic algorithm published by the American College of Chest Physicians for the work-up of acute cough[3] (Fig. 18.1).

Work-up and Management of Subacute Cough

The most common cause of subacute cough is postinfectious causes. Infections that can leave the patient with a subacute cough include viral upper respiratory infections, such as the common cold, lower respiratory tract infections from respiratory syncytial virus (RSV), and infections with *B. pertussis*. The majority of patients with cough from an uncomplicated common cold will have their cough resolve within three weeks. On the other hand, a high index of suspicion is needed to confirm a diagnosis of *B. pertussis*. While the classic "whoop" may be absent in adults, symptoms of vomiting caused by severe cough episodes suggest a *B. pertussis* infection. During the first two weeks of a *B. pertussis* infection, patients will have upper respiratory tract symptoms suggestive of a common cold, associated with an intermittent nonproductive cough, and sometimes fever. This is known as the catarrhal stage. After approximately two weeks, the patient enters the paroxysmal phase, in which the classic coughing is the hallmark. Protracted episodes of cough-induced vomiting can result in dehydration. This phase typically peaks after two to three weeks, but the cough may persist for two to three months, or longer. The last phase, called the convalescent phase, is marked by less common paroxysmal coughing. During this phase a patient may develop worsening of the paroxysmal coughing if exposed to irritants or another upper respiratory infection.

Common laboratory findings are nonspecific, but may include leukocytosis and an elevated absolute lymphocyte count (> 10,000 cells/µl).[23] Diagnosis of pertussis can be confirmed by the isolation of the organism form nasopharyngeal secretions. However, while this has a 100% specificity, the sensitivity of the culture within the first three weeks of symptoms can be as low as 15 to

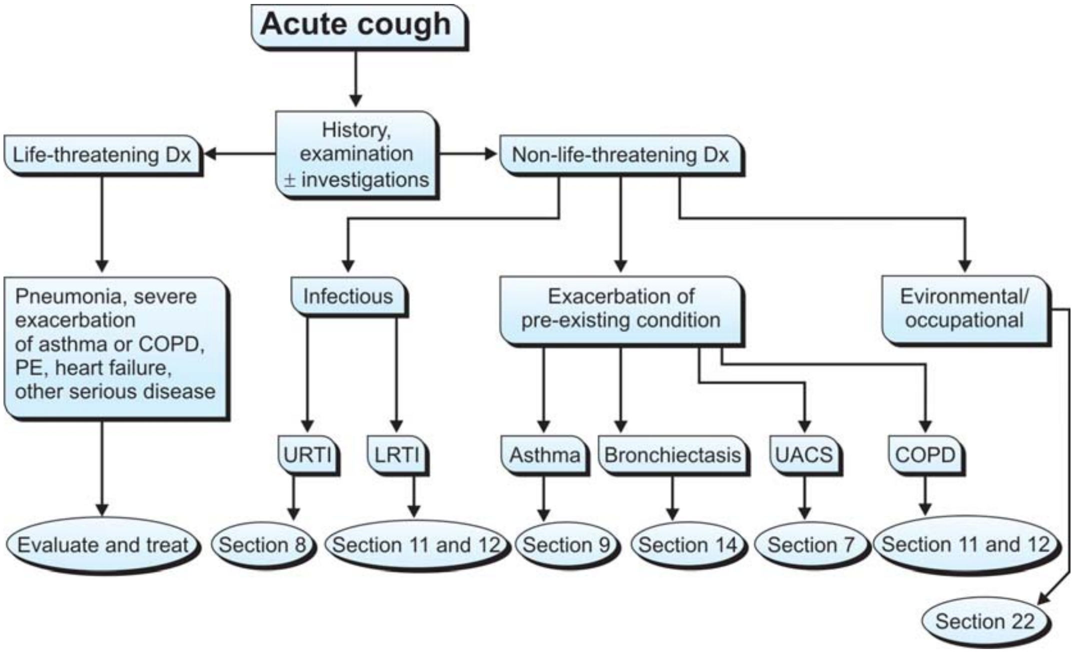
Acute cough
History, examination ± investigations
Life-threatening Dx
Non-life-threatening Dx
Pneumonia, severe exacerbation of asthma or COPD, PE, heart failure, other serious disease
Infectious
Exacerbation of pre-existing condition
Evironmental/ occupational
URTI
LRTI
Asthma
Bronchiectasis
UACS
COPD
Evaluate and treat
Section 8
Section 11 and 12
Section 9
Section 14
Section 7
Section 11 and 12
Section 22

Fig. 18.1: An algorithm for the work-up of acute cough in the adult. The sections referred in the algorithm refer the reader to the corresponding sections in the American College of Chest Physician Guideline, Chest. 2006; 129:1Suppl. *Reproduced with permission from Irwin RS, Baumann MH, Bolser DC, et al. Chest. 2006; 129(1Suppl):1-23*

45%.[24] In addition, culture sensitivity decreases with the duration of the infection.[25] Polymerase chain reaction (PCR) for *B. pertussis* appears to have a higher sensitivity, ranging from 65 to 97%.[25,26] As with the cultures, the sensitivity of the PCR decreases with the duration of the infection.[25] Direct fluorescent antibody (DFA) can provide rapid detection of *B. pertussis*, but the sensitivity and specificity are inferior to cultures and PCR. Because no single test has 100% sensitivity, the US Center for Disease Control recommends both cultures and PCR.[27] The CDC has also established guidelines for the method of collecting specimens and the method of testing.[27]

Treatment for *B. pertussis* includes antibiotics, either a microlide or trimethoprim/sulfamethoxazole[28] in the macrolide allergic patient. . While quinolones have *in vitro* activity against *B. pertussis*, studies supporting their use are lacking. Some authors also suggest the addition of oral corticosteroids.[29] If patients are treated within eight days of the onset of symptoms, antibiotics are effective at decreasing the severity of the illness, and decreasing the risk of exposing other patients. Prophylactic antibiotics are also recommended for people exposed to patients with whooping cough.

Some conditions that cause acute cough can also present as a subacute cough if there is a delay in the patient receiving medical attention. COPD and asthma exacerbations, congestive heart failure, lung cancer, and infections such as tuberculosis are examples of conditions that can present as either an acute or subacute cough. We recommend following the diagnostic algorithm published by the American College of Chest Physicians for the work-up of subacute cough[3] (Fig. 18.2).

Work-up and Management of Chronic Cough

When evaluating a patient with chronic cough, it is best to use a systematic approach such as that published by the American College of Chest Physicians[3] (Fig. 18.3). When starting with the history, the character, timing and quality of the cough are often not helpful in determining the etiology. Factors that are important include: Whether or not the patient is an active smoker; if the patient is taking an ACE inhibitor; if the patient lives in the area where tuberculosis or other fungal diseases are endemic; if the patient has a history of cancer, tuberculosis, AIDS; and if the patient has systemic symptoms such as fever, night sweats or weight loss. Other associated symptoms potentially may be helpful. For example, episodic wheezing, dyspnea, and chest tightness might suggest asthma or COPD, but wheezing alone can also be seen in patients with both asthma and UACS. Other

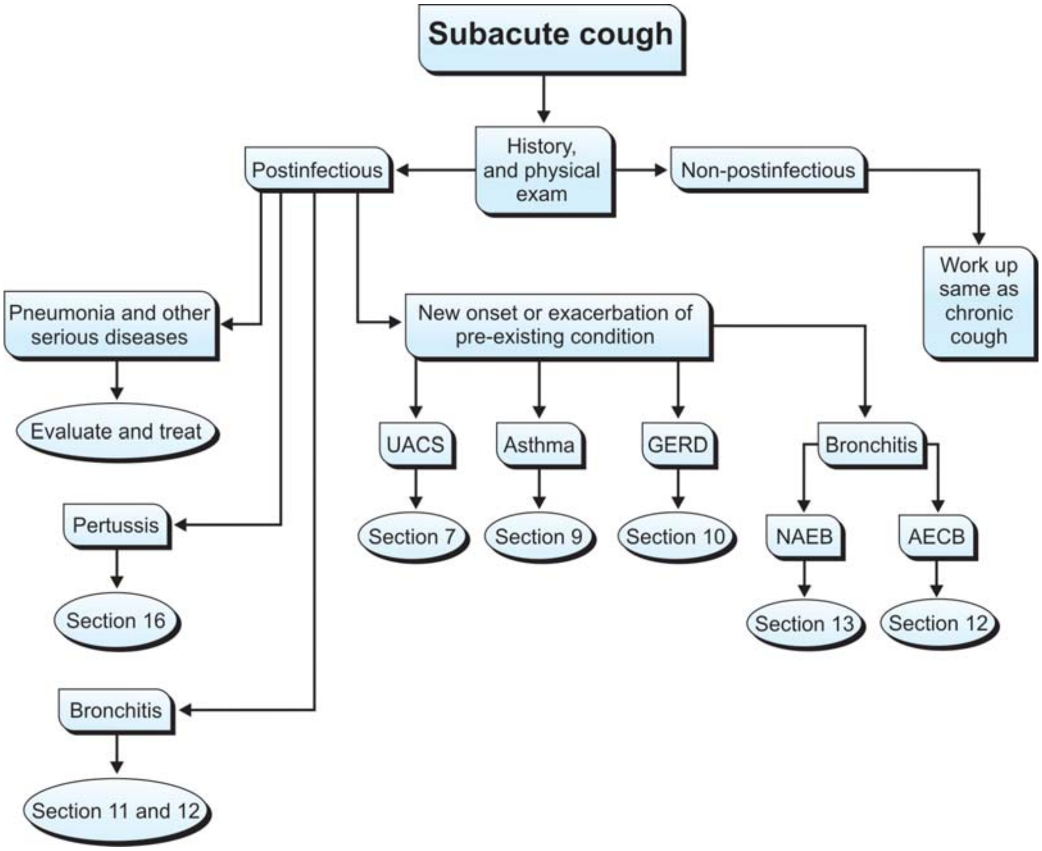
Subacute cough
History, and physical exam
Postinfectious
Non-postinfectious
Work up same as chronic cough
Pneumonia and other serious diseases
Evaluate and treat
New onset or exacerbation of pre-existing condition
UACS
Asthma
GERD
Bronchitis
Section 7
Section 9
Section 10
NAEB
AECB
Section 13
Section 12
Pertussis
Section 16
Bronchitis
Section 11 and 12

Fig. 18.2: Algorithm for the work-up of subacute cough in the adult. The sections referred in the algorithm refer the reader to the corresponding sections in the American College of Chest Physician Guideline, Chest. 2006; 129:1Suppl. *Reproduced with permission from Irwin RS, Baumann MH, Bolser DC, et al. Chest. 2006; 129(1Suppl):1-23*

potentially helpful associated symptoms and history will be discussed below with the specific conditions that cause chronic cough. If patients also describe coughing up blood, we suggest following the recommendations in the chapter on hemoptysis.

After a complete history is obtained, a thorough physical examination should be performed. While there are no specific exam findings that are pathognomonic for a specific cause of chronic cough, some findings can help in suggesting a condition contributing to the cough. For example, observing mucopurulent secretions in the oropharynx suggests an UACS due to suppurative upper airway disease, while diffuse wheezing might suggest asthma.

One of the most important tests to order when evaluating a patient with chronic cough is a chest radiograph. When the chest radiograph is abnormal and shows more than inconsequential scarring, the abnormality should be felt to be contributing to the patient's cough until proven otherwise. For example, if the chest radiograph demonstrates findings consistent with congestive heart failure, sarcoidosis or malignancy, further work-up for these conditions followed by the appropriate treatments should be preferentially pursued. One must also keep in mind, however, that an abnormality on chest radiograph may not be associated with the patient's chronic cough (e.g. solitary pulmonary nodule), or the patient may have an additional condition contributing to their cough. In these cases, further investigation, specifically investigating the common causes of chronic cough should be performed, once the conditions suggested by the abnormality have been addressed and the patient continues to complain of cough.

For patients with normal chest radiographs who are not active smokers or taking an ACE inhibitor, the differential diagnosis for chronic cough significantly narrows to one or more of the following: UACS; asthma;

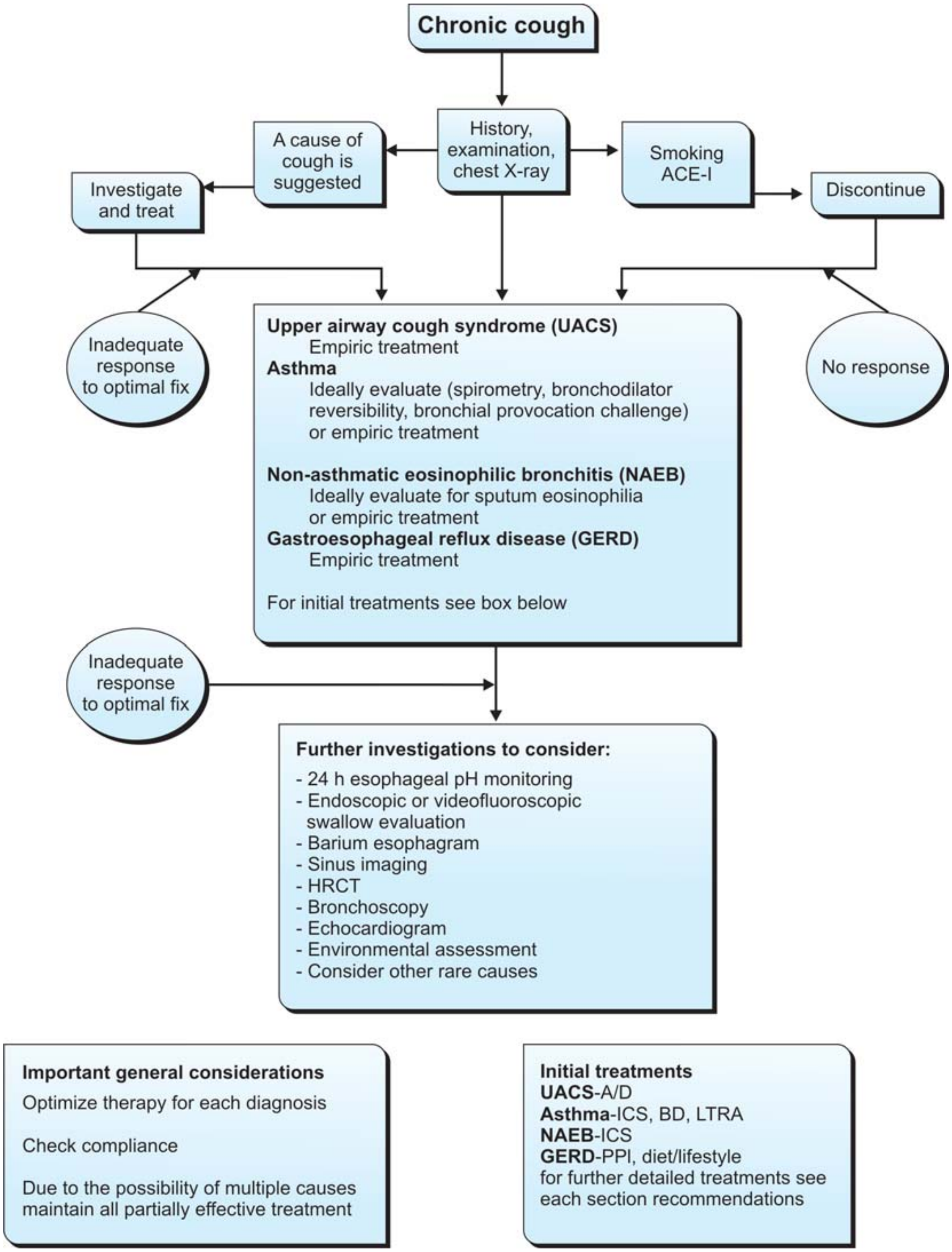
Chronic cough
History, examination, chest X-ray
A cause of cough is suggested
Investigate and treat
Smoking ACE-I
Discontinue
Inadequate response to optimal fix
No response
Upper airway cough syndrome (UACS)
Empiric treatment
Asthma
Ideally evaluate (spirometry, bronchodilator reversibility, bronchial provocation challenge) or empiric treatment
Non-asthmatic eosinophilic bronchitis (NAEB)
Ideally evaluate for sputum eosinophilia or empiric treatment
Gastroesophageal reflux disease (GERD)
Empiric treatment
For initial treatments see box below
Inadequate response to optimal fix
Further investigations to consider:
- 24 h esophageal pH monitoring
- Endoscopic or videofluoroscopic swallow evaluation
- Barium esophagram
- Sinus imaging
- HRCT
- Bronchoscopy
- Echocardiogram
- Environmental assessment
- Consider other rare causes
Important general considerations
Optimize therapy for each diagnosis
Check compliance
Due to the possibility of multiple causes maintain all partially effective treatment
Initial treatments
UACS-A/D
Asthma-ICS, BD, LTRA
NAEB-ICS
GERD-PPI, diet/lifestyle
for further detailed treatments see each section recommendations

Fig. 18.3: Algorithm for the work-up of chronic cough in the adult. The sections referred in the algorithm refer the reader to the corresponding sections in the American College of Chest Physician Guideline, Chest. 2006; 129:1Suppl. *Reproduced with permission from Irwin RS, Baumann MH, Bolser DC, et al. Chest. 2006; 129(1Suppl):1-23*

Gastroesophageal Reflux Disease (GERD); chronic bronchitis from environmental irritants such as cigarette smoke or smoke from using biomass fuels; Nonasthmatic Eosinophilic Bronchitis (NAEB); and bronchiectasis. In the US and many other parts of the world, such as southeast Asia, UACS, asthma, and GERD are the cause(s) of chronic cough in over 92% of nonsmokers who are not on an ACE inhibitor and who have a normal chest radiographic appearance.[30] Even in areas where TB is endemic, these three conditions tend to be the most common causes of chronic cough.[31] As mentioned above, these entities may coexist and the cause of chronic cough may be multifactorial. At least 25% of patients with chronic cough have more than one potential cause.[30] It is also important to realize that each of these conditions may present with cough being the only symptom (silent UACS, cough-variant asthma, silent GERD). If work-up for the common causes of chronic cough is unremarkable, one should consider less common causes that account for less than 6% of cases in patients with normal chest radiographs: Bronchogenic carcinoma, chronic interstitial pneumonia, sarcoidosis, and left ventricular failure, among others.[30]

In the initial evaluation of chronic cough in patients with normal chest radiographs, bronchoscopy has a low diagnostic yield. However, if the patient's initial evaluation is negative for UACS, asthma, NAED, and GERD, or the patient fails to respond to optimal treatment for these conditions, a bronchoscopy can yield a positive result up to 28% of the time.[1]

Below is a more detailed discussion on the commonest causes of chronic cough.

Upper Airway Cough Syndrome

In the US, UACS is the most common cause of chronic cough in immunocompetent adults. Patients usually complain of a throat "tickle" or a need to clear the throat, and nasal congestion or discharge. Symptoms may occur after a recent cold and may be accompanied by a wheeze. Approximately 20% of patients with this condition are unaware of the presence of Postnasal Drip (PND) or throat clearing (silent UACS) even though they can be heard to frequently clear their throats in front of loved ones and the physician.[32] The symptoms and physical exam findings reflective of UACS are very sensitive, but not specific, and may include the evidence of nasal discharge, drainage or cobblestoning appearance of the mucosa. The diagnosis of UACS is confirmed if rhinosinus conditions thought to be contributing to postnasal drip are treated and cough is subsequently eliminated.

PND may be a potential stimulus that irritates the afferent limb of the cough reflex in the hypopharynx and/or larynx. In association with hypersensitivity of the cough reflex in the upper airway, it is presumed that direct physical or chemical irritation stimulates the cough reflex peripherally, leading to increased central reactivity.[32] Why some patients with irritated upper airways cough, but many do not is not known. This situation is analogous to the Angiotensin Converting Enzyme Inhibitors (ACEIs)-induced cough situation. While all patients taking ACEIs have excessive amounts of substance P and prostaglandins that are thought to cause hypersensitivity of the cough reflex, it is not known why only some patients develop cough while most do not.

Several conditions cause UACS and include allergic rhinitis, rhinitis medicamentosa, environmental irritant rhinitis, perennial nonallergic rhinitis, postinfectious rhinitis (*Mycoplasma, Chlamydia pneumoniae* and *B. pertussis*), vasomotor rhinitis, allergic fungal sinusitis, bacterial sinusitis, anatomic abnormalities, and rhinitis of pregnancy.[30] Of note, chronic bacterial sinusitis may also be silent, so in patients not improving on decongestants in whom UACS is suspected as the etiology of cough, sinus imaging studies may be helpful. UACS is the principal cause of cough associated with the common cold, making it also the most common cause of acute cough.[32]

As far as treatment is concerned, there is evidence to suggest that older generation antihistamine/decongestant combination medications are more effective than newer generation relatively nonsedating antihistamines, likely secondary to their anticholinergic properties. Intranasal steroids and ipratropium nasal spray, cromolyn, and allergen avoidance are also used. For acute sinusitis, antibiotics directed at the most common organisms are recommended (see the chapter on sinusitis). Intranasal decongestants, such as oxymetazoline may be used in conjunction for symptom relief in the short term. For chronic sinusitis causing cough, a prolonged course of antibiotics (see the chapter on sinusitis) is recommended (at least 2–3 weeks), as well as older generation antihistamine/decongestants and intranasal decongestants twice daily for up to five days, along with intranasal steroids for three months. Allergic fungal sinusitis may require surgical drainage and treatment with oral antifungal agents.

Asthma

In certain patients with asthma, cough may be the primary symptom, or occasionally the only symptom.[30]

This is known as cough-variant asthma. Patients with isolated cough-variant asthma usually have baseline normal spirometry; they have airway hyperresponsiveness and the cough will resolve with asthma treatment.[30] In fact, the diagnosis of asthma as a cause of chronic cough relies upon cough resolution with asthma treatment. A negative methacholine inhalation challenge essentially excludes asthma from the differential of chronic cough. The negative predictive value of a methacholine challenge testing approaches 100% in the symptomatic patient.

Patients with cough-variant asthma respond to the same treatment as patients with the other forms of asthma and should be treated with inhaled bronchodilators, both short- and long-acting as needed, along with steroids, either inhaled, or oral as needed. Leukotriene receptor agonists may also be effective. Inhaled medications should be either a dry powder or a Metered Dose Inhaler (MDI) with a spacer. Because inhaled medications may provoke coughing, this possibility should be assessed and oral medications preferentially prescribed if this occurs. Treatment may take 6–8 weeks before maximum symptomatic benefit is achieved. Of note, if a patient's cough is refractory to inhaled corticosteroids, the presence of airway eosinophilia on induced sputum or bronchoalveolar lavage will identify patients who may benefit from more aggressive therapy.[33]

GERD

The prevalence of GERD as a cause of chronic cough has increased dramatically over the years. Studies accounted for reflux as an etiology of chronic cough in 10% of cases in 1981 and up to 36% of cases in 1998.[34] The term reflux disease is actually the preferred nomenclature over acid reflux disease because nonacid reflux can also contribute and will not respond to acid suppression therapy. Interestingly, in up to 75% of cases, there may be no associated GI symptoms.[34]

While reflux disease may cause cough by aspiration or from irritation of the upper respiratory tract irritation,[34] it most likely causes chronic cough through a vagally-mediated distal esophageal-tracheobronchial reflex mechanism.[35] Furthermore, a cough-reflux perpetuating cycle likely exists whereby cough from any cause may precipitate further reflux.

Risk factors for GERD are many and include certain medications, bisphosphonates, oral corticosteroids, inhaled bronchodilators, and theophylline, progesterone, calcium channel blockers, nitrates, anticholinergic agents, and certain narcotics, such as morphine and meperidine; obesity; smoking; vigorous exercise; alcohol; caffeine; fatty foods, chocolate, citrus juices and tomato products; prolonged intubation; lung transplantation following pneumonectomy; peritoneal dialysis; and variety of respiratory diseases such as asthma and obstructive sleep apnea.[34, 36-38] At this time, esophageal pH and impedance monitoring appears to be the most sensitive and specific test for linking acid and nonacid reflux disease and coughing in a cause and effect manner. An esophageal pH monitoring study by itself is only helpful for evaluating acid reflux, and will not detect episodes of nonacid reflux. A normal esophagoscopy does not rule out reflux disease as a cause of cough, because most patients do not have esophagitis or Barrett's epithelium. For readers interested in reading more about reflux disease in general, we encourage them to read the chapter on this topic and reference.[34]

The 2006 ACCP Cough Guideline Committee recommends empiric therapy for GERD for patients with the following clinical profile: Cough greater than eight weeks, the patient is not exposed to environmental irritants and is a nonsmoker, is not on an ACE inhibitor, and chest radiograph is normal or stable,[34] methacholine challenge is negative, cough fails to respond to a first-generation antihistamine/decongestant medication, and cough has failed to respond to systemic corticosteroids. This profile means that the following conditions have been ruled out: Asthma, UACS and nonasthmatic eosinophilic bronchitis. [34] The mainstay of treatment for reflux disease is acid suppression, prokinetic therapy, and lifestyle and dietary interventions. It is important to let patients know that they may not see improvement for two or three months after initiation of this therapy. Occasionally patients may require antireflux surgery for cases refractory to medical treatment. Failure of medical therapy can be determined by 24 hour esophageal pH/impedance monitoring while the patient continues intensive medical therapy. It is important to keep in mind that GERD may still be the cause if the patient does not respond to treatment because treatment may not be maximal or because medical therapy failed and surgery might be necessary. Up to approximately 85% of patients note improvement in their chronic cough after anti-reflux surgery.[39]

Nonasthmatic Eosinophilic Bronchitis (NAEB)

NAEB is characterized by a chronic cough, normal airway responsiveness to methacholine challenge, eosinophilic airway inflammation in induced sputum samples, and improvement in cough following corticosteroid therapy.[40] While patients usually present with normal baseline spirometry, airflow obstruction can occur if the inflammation is not suppressed. While the cough usually responds to inhaled corticosteroids, systemic corticosteroids may be necessary. The etiology of NAEB is unclear, although it may be associated with exposure to an inhaled allergen or occupational sensitizer. Whenever possible, avoidance from an offending agent is the best treatment.[40] For unclear reasons, NAEB tends to be diagnosed with greater frequency outside the US. Non-US studies have accounted for NAEB as the cause of chronic cough in up to 33% of cases, whereas some US studies have been able to prospectively report successful treatment of chronic cough without reporting a single case of NAEB.[31] It is unclear whether the prevalence is simply greater outside the US or whether it has been traditionally overlooked as a cause of chronic cough in the US. Regardless, it should be considered in all patients with chronic cough. Histologically, this disease is characterized by mast cells within the airway wall, a sign of epithelial infiltration, as opposed to the smooth muscle infiltration by mast cells that is seen in patients with asthma.[40]

Chronic Bronchitis

Chronic bronchitis is defined as a bronchial disease with cough and sputum expectoration occurring on most days for at least three months of the year for at least two years when other pulmonary/cardiac causes of a chronic cough-phlegm syndrome are excluded.[41] It is known to be one of the most frequent causes of cough worldwide.[42] It is caused by the inhalation of irritants: Tobacco, cigar, pipe smoke, passive smoke exposures, hazardous chemicals, organic dusts, cotton, wood, jute, hemp, flax, sisal, grains, manufactured fibers, oil mist, cement, silica, osmium, vanadium, welding fumes, engine exhausts, fumes of cooking fuels[41,43] and fumes from burning biomass. In India, the prevalence of chronic bronchitis among *bidi* and cigarette smokers is 8.2% and 5.9%, respectively.[44] Occupational exposure may account for up to 15% of cases. While most smokers have cough, they are not the group of patients who most commonly seek medical attention for this symptom.

Chronic bronchitis is associated with airway inflammation, mucus hypersecretion, and impaired mucociliary clearance. Additionally, the airways of patients with chronic bronchitis are thought to have heightened responsiveness, albeit, not in the range seen in asthmatics. Progressive airflow obstruction can lead to an ineffective cough due to decreased expiratory flow and impaired mucociliary clearance that can cause the retention of secretions, further aggravating the cough reflex; thereby promoting a cycle of recurrent cough.[41]

There are increased numbers of neutrophils and macrophages seen on bronchoalveolar lavage of patients with chronic bronchitis. The inflammation causes structural changes: Mucus gland hyperplasia, bronchiolar edema, smooth muscle hypertrophy, and peribronchiolar fibrosis that leads to the narrowing of the small airways.[45]

Treatment should focus on reducing sputum production and the reduction of airway inflammation by removing irritants (e.g. tobacco cessation). In patients without severe airflow limitation, cough has been shown to disappear or markedly decrease in 94 to100% of cases with smoking cessation, often within four weeks.[19] Mucolytics often do not help. Ipratropium has been shown to decrease sputum production. While anticholinergics and/or inhaled corticosteroids and long-acting bronchodilators have been shown to decrease exacerbations, antibiotics and systemic corticosteroids serve to decrease cough during severe COPD exacerbations.

Bronchiectasis

In prospective studies, bronchiectasis has caused chronic productive cough with sputum production in approximately 4% of cases.[46] Recurrent bacterial colonization and infection or bronchial obstruction causes airway injury, mediated by neutrophils, lymphocytes, and inflammatory mediators that result in the destruction of the elastic and muscular components of bronchial walls. The result is the dilation of involved airways. Some disorders predisposing patients to bronchiectasis include bronchial obstruction, pneumonia, cystic fibrosis, primary ciliary dyskinesia, allergic bronchopulmonary mycoses, rheumatoid arthritis, inflammatory bowel disease, hypogammaglobulinemia, alpha-1 antitrypsin deficiency, HIV infection, and Marfan's syndrome, among others.[46] Diagnosis is based on history, chest radiography, high-resolution chest CT scans, and the response to targeted therapy. The cough associated with bronchiectatic flares is treated with chest physiotherapy, systemic antibiotics, and drugs to stimulate mucociliary clearance.[46] There has been no proven benefit of oral steroids or long-term prophylactic antibiotics to treat chronic cough associated with bronchiectasis.

Nonbronchiectatic bacterial suppurative airway disease has also been described as a cause of chronic cough.[47] These patients will have excessive purulent secretions in their central airways and positive bacterial cultures, yet have little to no productive cough, and no radiographic evidence of pneumonia or bronchiectasis. Diagnosis is made by bronchoscopy, and patients often respond to prolonged IV antibiotics (3 weeks) after courses of oral antibiotic have been shown to be ineffective.[47]

Postinfectious Cough

The condition refers to cough that comes on following a respiratory infection and disappears with or without treatment within four weeks. It can present with transient bronchial hyperresponsiveness, and/or prolonged upper and lower airway inflammation that resolves as diagnostic and therapeutic studies are pursued.[31] It may be a consequence of *B. pertussis* infection, or may be involved in perpetuating chronic cough by precipitating GERD.

Bronchogenic Carcinoma

Bronchogenic carcinoma is most commonly due to smoking; cough is present in 65% of patients at the time of lung cancer diagnosis.[48] Chest radiography results have a positive predictive value for bronchogenic carcinoma of 36 to 38%, and markedly diminish the likelihood of lung cancer when chest radiographs are normal.[30, 49] Along with chest radiographs, chest CT scans, sputum cytology, flexible bronchoscopy are all used for diagnosis, particularly in patients for whom you have a high index of suspicion of cancer (e.g. cigarette smoker). Surgery to remove Non-Small Cell Lung Cancer (NSCLC) in patients with stage I and II disease is the treatment of choice. For patients with more advanced disease, external beam radiation and/or chemotherapy are the treatments of choice.

Newer chemotherapeutic agents like gemcytabine, can palliate the cough.[48] Localized endobronchial treatment options (e.g. brachytherapy) exist for patients with advanced disease and symptoms of dyspnea and hemoptysis. This may palliate concomitant cough; however, this type of treatment would not be an option for patients with cough alone. Some patients require narcotic antitussive agents to control cough associated with lung cancer.

ACEI-Induced Cough

The cough associated with ACE inhibitor use is typically nonproductive and described as an irritating/tickling/scratching sensation in the back of the throat. Cough has been found to be a class effect and not dose related; therefore, in patients who complain of cough who are on ACE inhibitors, switching to a different class of antihypertensives is recommended. Because angiotensin-receptor blockers are not associated with an increased incidence of cough and they have been shown to have many of the same benefits as ACE inhibitors, they are an excellent substitution choice. The incidence of cough due to ACEIs in the series of patients with chronic cough is 0 to 3% of cases and may appear within a few hours to weeks or months after initiating therapy with an ACE inhibitor.[30] Some symptomatic relief may be obtained by adding sulindac, indomethacin, nifedipine, picotamide, and inhaled sodium cromoglycate when patients are unable to come off of their ACE inhibitors; however, discontinuation of the offending medication is the preferred treatment.[50] Cough secondary to an ACE inhibitor should disappear or markedly improve within the four weeks of discontinuing the medication; however, on occasions, cough may take up to 3 months to completely resolve.[51]

Habit Cough/Tic Cough/Psychogenic Cough

The diagnosis of habit/psychogenic cough is a diagnosis of exclusion. More common causes of cough and less common causes, including tic disorders should be ruled out before labeling a patient with this diagnosis. A key to making a final diagnosis of habit or psychogenic cough requires that cough improve with behavior modification or psychotropic therapy. If a patient's cough persists despite thorough evaluation and psychiatry evaluation and behavior modification, it should be labeled unexplained cough, rather than psychogenic or habit cough.[52]

Miscellaneous Causes

A variety of unusual causes of cough are listed in Table 18.4. [53] Because the more common causes of cough can be the cause of chronic cough 50% of the time in patients with chronic interstitial lung diseases, chronic interstitial pulmonary disease should not be assumed to be the cause of the cough until the more common causes have been adequately evaluated and treated.

Endobronchial abnormalities (tumors, TB, sarcoidosis, retained sutures) occasionally cause chronic cough.[53] Bronchiolitis (nonbronchiectatic suppurative airway disease) affects the small airways and is caused by infections, toxins, systemic diseases, such as inflammatory bowel disease, drug reactions, and transplant recipients, and is another less common cause of chronic cough.[54] Because these etiologies are uncommon causes

TABLE 18.4: Uncommon causes of chronic cough*[53]

Pulmonary (airway)
- Tracheomalacia/Bronchomalacia
- Foreign bodies/Airway stents
- Tracheobronchomegaly
- Tracheobronchopathia osteochondroplastica
- Broncholithiasis

Pulmonary (interstitial)
- Lymphangioleiomyomatosis
- Langerhans cell histiocytosis
- Pulmonary alveolar proteinosis
- Pulmonary alveolar microlithiasis

Connective tissue diseases
- Relapsing polychondritis
- Scleroderma
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sjögren's syndrome
- Giant cell arteritis
- Wegener's granulomatosis

Gastrointestinal disorders
- Tracheoesophageal fistula
- Inflammatory bowel disease

*This listing is not meant to be exhaustive

of cough, one needs a strong index of suspicion based on the patient's clinical and laboratory picture.

Chronic Cough in the Pediatric Population

Unlike the adult population, a chronic cough in children less than 15 years old is defined as a cough lasting more than four weeks. A comprehensive approach for evaluating a patient < 15 years old with a chronic cough is presented in the ACCP Evidence-based Clinical Practice Guideline.[55] For patients 15 years of age and older with a chronic cough, one should follow the above mentioned guidelines for adults (Fig. 18.3).

Cough in the Immunocompromised Patient

Cough is a very common symptom in patients with compromised immune systems. The initial evaluation for immunocompromised patients presenting with an acute cough depends on the degree of their immunosuppression. HIV-positive patients with CD4 counts > 250 μl who present with acute cough are most likely to have upper respiratory infections, acute bronchitis and acute sinusitis, with less than 5% having bacterial pneumonia or *Pneumocystis* Pneumonia (PCP).[56] For patients with CD4 counts below 250 μl, upper respiratory infections and acute bronchitis still account for almost 45% of the causes, but the number presenting with pneumonia increases to over 23%, including PCP, bacterial pneumonia and TB.[56]

When considering the etiology of chronic cough in patients who are immunocompromised, it is also important to access the nature and severity of their immune defect. For instance, patients with HIV who have CD4 counts of greater than 200 cells/μl are less likely to have chronic cough secondary to *Pneumocystis* pneumonia or from other opportunistic infections. The etiology of chronic cough in these patients is the same as what would be expected in the immunocompetent patients.[57] However, in patients with severely weakened immune systems, especially when their chronic cough is associated with systemic symptoms, such as fever, weight loss or thrush, infections from *Mycobacterium tuberculosis* and opportunistic infections, such as *Pneumocystis* need to be considered.[58] A general rule to remember is as follows: If CD4 less than 200 μl, evaluate the patient for opportunistic infections. If the CD4 count is greater than 400 μl, evaluate the patient as if they had a normal immune system. For CD4 counts between 200–400 μl, the patient's clinical condition matters. If the patient is cachectic, has evidence of oral thrush, or known prior infections with opportunistic organisms, evaluate the patient for opportunistic infections. If the patient is otherwise healthy appearing, initially evaluate them as if they have a normal immune system. Although tuberculosis has been reported in all countries, it remains a highly prevalent disease in developing countries. In fact, it is estimated that approximately 1/3rd of the world's population is infected with *Mycobacterium tuberculosis*, that approximately 9 million people develop active TB each year, and approximately 1.9 million people die from tuberculosis each year.[59] Cough is a cardinal symptom of tuberculosis, and contributes to its transmission. Despite the higher prevalence of tuberculosis in the developing world, it is still not a common cause of chronic cough.[60] However, because it is highly contagious and causes significant morbidity and mortality for those infected, it should be considered in all patients with chronic cough who are at risk for tuberculosis, and patients who are immunocompromised, especially with HIV. For patients who are at high risk for tuberculosis, the World Health Organization recommends that their cough be considered "chronic" after two to three weeks and evaluation begun to rule out infections such as tuberculosis.[61] Sputum for AFB smears and culture, and chest radiograph when possible is recommended for initial evaluation for tuberculosis.

Patients who are immunosuppressed for reasons other than HIV are also at the risk of having infections, such as tuberculosis and *Pneumocystis* pneumonia as the cause of their chronic cough. Such patients include those with neutropenia; chronic disease, such as diabetes, cancer and renal failure; and patients receiving chronic corticosteroids.

Cough due to Parasitic Infections

Special attention is needed when evaluating a patient with chronic cough who resides in an area were certain fungal or parasitic diseases are endemic.[59] While this is especially true when evaluating an immunocompromised patient with chronic cough, immunocompetent patients are also at risk for these infections. For example, paragonimiasis needs to be considered as a potential cause of chronic cough in patients who live or travel in the southeast Asia, especially in Japan, Korea, the Philippines, Taiwan, and parts of China.[62] These patients should be evaluated for the presence of eosinophilia and elevated IgE levels. The chest radiograph can have various appearances, such as pulmonary nodules, cavitary lesions, lymphadenopathy, pleural effusion or pneumothorax. The diagnosis can be confirmed by identifying *Paragonimus westermani* eggs in stool, sputum, pleural fluid or in bronchoalveolar lavage.

Syngamosis is another rare cause of chronic cough. It is the result of infestation by the nematode *Syngamus laryngeus* in which the parasite lodges itself in the tracheobronchial tree of a human after the ingestion of contaminated food or water. It remains unclear if the parasite migrates from the larynx, or is spread hematogenously after absorption from the GI tract. Symptoms include cough, fever, malaise, leukocytosis and eosinophilia. While uncommon in humans, it tends to occur geographically in the Caribbean islands and Brazil.[63] Diagnosis is established by the visualization of copulating reddish-brown worms in the upper airway on bronchoscopy or in expectorated sputum.[64] Cough and other respiratory symptoms reportedly subside after the removal of parasites from the bronchial tree.

Other parasitic infections associated with a chronic chough include ascariasis,[65] leishmaniasis,[66] malaria,[67] and schistosomiasis.[68]

Treatment

Following utilization of a systematic diagnostic protocol, specific therapy has been reported to have a success rate of 84 to 98%. Therefore, because of the high probability of being able to determine the specific cause of cough and prescribe specific therapy that can be successful, there is a limited role for nonspecific therapy that has been comprehensively reviewed elsewhere.[69]

CONCLUSION

Cough is one of the most common symptoms for which patients seek medical attention. While cough is a normal defense mechanism to clear secretions and foreign material from the airways, it can also result in clinically important complications. Cough is also a common symptom for a wide spectrum of both life-threatening and non-life-threatening illnesses. Dividing cough into acute, subacute and chronic categories, based on its duration, is most helpful in constructing the lists of differential diagnoses. Once the cough is categorized into one of these groups, a systematic approach to evaluating and treating the patient has the best chance of being successful in eliminating cough.

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Hemoptysis

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INTRODUCTION

The term hemoptysis refers to the coughing of blood that emanates from the lungs or airways below the larynx.[1] It is an alarming sign for most patients and physicians, the basis of which is the fear that it represents a serious ailment.[2] In 1953, hemoptysis implied tuberculosis for the average medical student[3] and it continues to be so in the developing world;[4] however, bronchiectasis, bronchitis and bronchogenic carcinoma are now the most common causes in the developed world.[5]

Hemoptysis is the primary complaint in 8 to 15% of patients presenting to the chest clinics.[6,7] It may range from scant streaking of sputum, as often seen in chronic bronchitis, to more severe life-threatening quantities of blood that have the potential to cause significant gas exchange abnormalities.[8] It is useful to categorize the amount of hemoptysis according to the rate of bleeding. Hemoptysis is mild when there are less than 20 ml in 24 hours, moderate or submassive when 20-600 ml and massive when more than 600 ml in a 24 hour period. Gross or frank hemoptysis may be defined as the expectoration of a lesser amount than massive hemoptysis and yet more than mere blood streaking. The faster the bleeding, the greater the risk of mortality, which reaches 37% when bleeding exceeds 600 ml in 48 hours and 52% when more than 600 ml in less than 16 hours.[9-11] The rate of blood loss above 15 ml per hour substantially increase the risk of death due to asphyxiation or exsanguination.[12] These volumetric, quantitative definitions are often quoted in texts, but in practice quantification of the amount of coughed out blood is difficult. What may be more relevant and useful is a qualitative definition based on the magnitude of clinical consequences incurred by the patient with hemoptysis. The vast majority of patients with massive hemoptysis die due to asphyxiation, not exsanguination.[12] The anatomical dead space of the major airways is approximately 100-200 ml. Thus, a brisk bleed of 150 ml, for example, could lead to major airway obstruction and the rapid demise of the patient due to inability to oxygenate and ventilate.

It is important not to confuse hemoptysis with bleeding that originates from sources other than the lower respiratory tract, also referred to as "pseudohemoptysis". Patients may not be able to describe the source of their bleeding and, blood arising from the nares, oral cavity, tongue and pharynx penetrate into the larynx to stimulate the cough reflex.[7,13-15] Hematemesis, as well, may be aspirated into the respiratory tract to cause pseudohemoptysis.[15] Also, in hospitalized patients who have received broad-spectrum antibiotics and mechanical ventilation, colonization of the oropharynx by *Serratia marcescens* may produce a red pigment, prodigiosin, that can be mistaken for blood.[16] It should be kept in mind, however, that infection with *Serratia marcescens* can lead to necrotizing pneumonia, presenting with true hemoptysis. Overdose with rifamycin antibiotics can imbue tracheobronchial secretions with a reddish hue that can be mistaken for blood-tinged sputum.[17] Finally, there is also the possibility of factitious hemoptysis. In these cases, the episodes of hemoptysis are self inflicted, this may lead to an unnecessary and extensive diagnostic work-up.[18]

ANATOMY

The lungs have a dual vascular supply. The pulmonary vasculature is a low-pressure system that supplies the lung parenchyma to support gas exchange and the respiratory bronchioles. The bronchial arteries, part of the systemic vasculature, are a high-pressure system that supplies the airways, from the trachea and mainstem bronchi to terminal bronchioles, the peribronchial and perivascular connective tissue, the middle third of the esophagus, the visceral diaphragmatic and mediastinal pleura, intrapulmonary lymphoid tissue, pulmonary vessels and nerves. Bronchial arteries generally originate from the aorta or intercostal arteries. There are usually 2 to 4 bronchial arteries in total and they tend to be more numerous on the left side.[19,20] Arterial and venous communications between both vascular systems occur at the level of the terminal and respiratory bronchioles and the two systems complement each other by maintaining constant flow. The bronchial circulation is the source of over 90% of cases of hemoptysis.[21]

ETIOLOGY AND PATHOGENESIS

The source of hemoptysis depends on the location of disease. If the disease process is located within the lung parenchyma it will involve the pulmonary circulation, but if it is contained within the airways it will involve the bronchial circulation. Chronic disease processes involving the airways and parenchyma will frequently lead to increased vascularity (neovascularization, engorgement and the enlargement of the local blood supply, increased anastomoses with the pulmonary circulation) and friability/fragility in the compromised areas.[22] There are over 140 causes of hemoptysis, which have been described. For practical purposes the causes can be divided into several major categories (Table 19.1).[8,18,23-131]

Nonmassive hemoptysis accounts for the majority of cases (bronchitis being one of the most common cause), but there is a considerable overlap between the massive and nonmassive causes of hemoptysis. The most common causes of massive hemoptysis, accounting for more than 60% of cases,[132-134] are active tuberculosis, bronchiectasis, mycetoma and bronchogenic carcinoma (Table 19.2). As mentioned previously, categorizing the severity of the hemoptysis has significant implications for prognosis and further management.

Infection and Inflammation

Patients with chronic bronchitis have increased vascularity beneath the endobronchial surface. The mucosa is friable and prone to bleed, especially in the presence of bacterial or viral infections.[135] Chronic bronchitis is a major cause of hemoptysis in the United States.[136] Bronchiectatic airways are also prone to bleeding episodes due to the proliferation of bronchial vessels and precapillary anastomoses with the pulmonary circulation (Figs 19.1 and 19.2). These enlarged

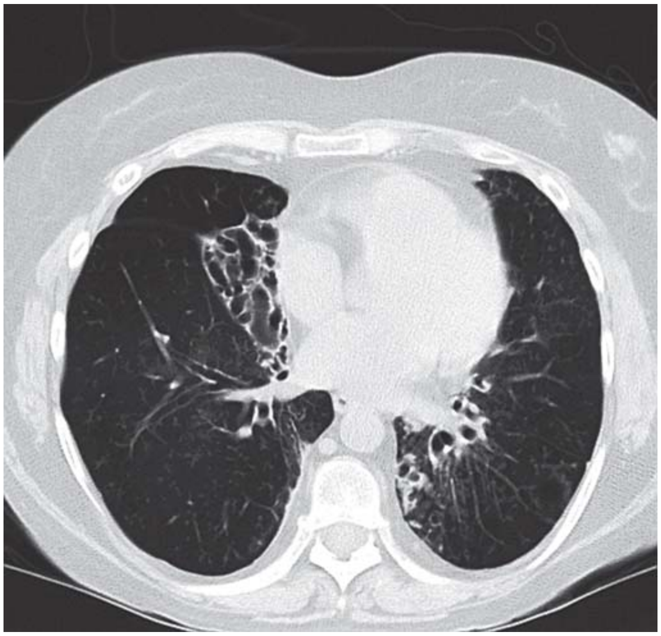

Fig. 19.1: Computed tomography of the chest showing an axial image of a patient with dysmotile cilia syndrome resulting in severe bronchiectasis

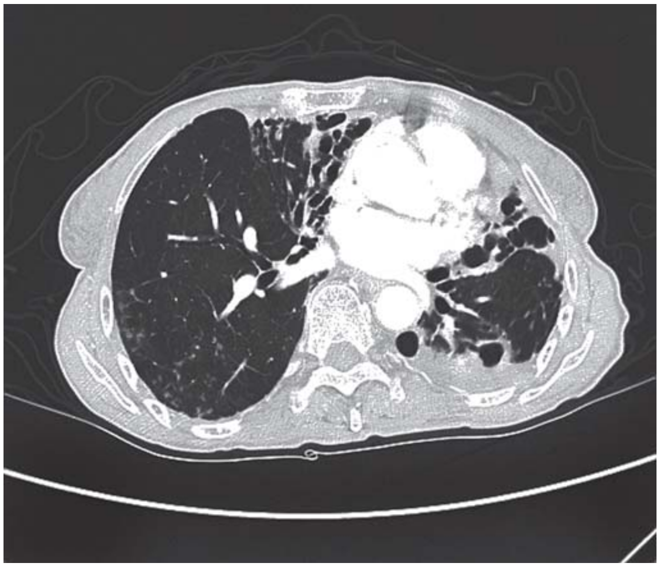

Fig. 19.2: Computed tomography of the chest showing an axial image of a patient with chronic atypical *Mycobacterium* infection and bronchiectasis

TABLE 19.1: Causes of hemoptysis*

- **Infectious and inflammatory**
  - Bronchitis
  - Bronchiectasis
  - Bacterial
    - Lung abscess
    - Necrotizing pneumonia
      - *Staphylococcus*
      - *Pneumococcus*
      - *Klebsiella*
      - *Pseudomonas*
      - *Acinetobacter*
      - *Legionella*
      - *Burkholderia pseudomallei*
  - Fungal
    - Aspergillosis
    - Coccidiomycosis
    - Histoplasmosis
    - Paracoccidiomycosis
    - Candidiasis
    - Cryptococcosis
    - Mucormycosis
    - Sporotrichosis
  - Viral
    - Influenza
  - Mycobacteria
    - *Mycobacterium tuberculosis*
    - Atypical mycobacteria
  - Parasitic
    - Amibiasis
    - Strongyloides
    - Paragonimiasis
    - Ascariasis
    - Echinococcosis
    - Schistosomiasis
- **Neoplastic**
  - Benign
    - Carcinoid
    - Polyps
    - Hamartoma
    - Lymphangioma
  - Malignant
    - Bronchogenic
    - Renal cell carcinoma
    - Breast adenocarcinoma
    - Other metastatic
    - Choriocarcinoma
    - Thyroid carcinoma
    - Melanoma
- **Cardiac**
  - Congestive heart failure
  - Mitral stenosis
  - Congenital heart disease
- **Vascular and embolic**
  - Venous thromboembolism
  - Arteriovenous malformations
  - Fat embolism
  - Pulmonary hypertension
  - Septic emboli
  - Tumor embolization
  - Thoracic endometriosis
  - Aortic aneurysm
  - Bronchial artery rupture
  - Superior vena cava syndrome
  - Dieulafoy's lesion
- **Congenital**
  - Cystic fibrosis
  - Pulmonary sequestration
  - Dysmotile cilia syndrome
  - Duplication cyst
- **Trauma**
  - Pulmonary contusion
  - Pulmonary laceration
  - Thoracic splenosis
  - Pulmonary pneumatocele
  - Tracheobronchial injury
- **Iatrogenic**
  - Central line catheters
  - Pulmonary artery catheterization
  - Tracheotomy
  - Transthoracic needle biopsy of the lung
  - Transbronchial biopsy of the lung
- **Systemic**
  - Amyloidosis
  - Goodpasture's syndrome
  - Idiopathic pulmonary hemosiderosis
  - Vasculitides and collagen vascular disease
- **Drugs and Toxins**
  - Amiodarone
  - Antiplatelet agents
  - Antithrombotic therapy
  - Charcoal lighter fluid
  - Cocaine
  - Isocyanates
  - Penicillamine
  - Trimellitic anhydride
- **Hematologic**
  - Disseminated intravascular coagulation
  - Leukemia
  - Von Willebrand's disease
  - Thrombocytopenia
  - Hemophilia
- **Miscellaneous**
  - Broncholithiasis
  - Cryptogenic
  - Foreign body aspiration
  - Hypersensitivity pneumonitis
  - Lymphangiomyomatosis
  - Gastric acid aspiration
  - Sarcoidosis
  - Factitious

* Modified from Balter MS. Hemoptysis, in Diagnosis and Treatment of Symptoms of the Respiratory Tract. Armonk, New York: Futura Publishing Company, Inc.; 1997. pp. 155-97. This table is not meant to include all causes of hemoptysis.

TABLE 19.2: Common causes of massive hemoptysis*

- Tuberculosis
- Bronchiectasis
- Mycetoma
- Bronchogenic carcinoma
- Tracheoarterial fistula
- Pulmonary arteriovenous malformation

* Modified from Balter MS. Hemoptysis, in Diagnosis and Treatment of Symptoms of the Respiratory Tract. Armonk, New York: Futura Publishing Company, Inc.; 1997. pp. 155-97.

vessels are susceptible to injury from the local inflammation and frequent episodes of infection that are the hallmark of bronchiectasis.[137]

Tuberculosis (TB) and its sequelae, such as bronchiectasis, broncholithiasis and recurrent bacterial infections continue to remain the most common causes of hemoptysis in the developing world.[4] Hemoptysis tends to develop in young, female patients with extensive disease, in cases of TB relapse, and in patients with old inactive mycobacterial disease complicated by bacterial superinfection.[138] Early pneumonia from tuberculosis may cause scant hemoptysis resulting from the necrosis of a small vessel; however, later stages of the disease may develop severe parenchymal fibroulcerative lesions that can erode into a bulging arterial aneurysm causing episodes of massive bleeding and respiratory distress (Figs 19.3 and 19.4).[139] Also, calcified lymph nodes impinging on the airway can erode into the airway lumen and cause streaky hemoptysis by disrupting vessels in the peribronchial and submucosal plexi; alternatively, they can lead to massive hemoptysis when there is a large bronchial artery in the path of this eroding calcified lymph node or broncholith.[140] Finally, expanding, thick-walled tuberculous cavities may incorporate pulmonary vessels that are prone to damage and bleeding when exposed to inflammation and mycobacteria. The vessels become ectatic and aneurysmal, as well as may rupture to cause massive hemoptysis.[139,141]

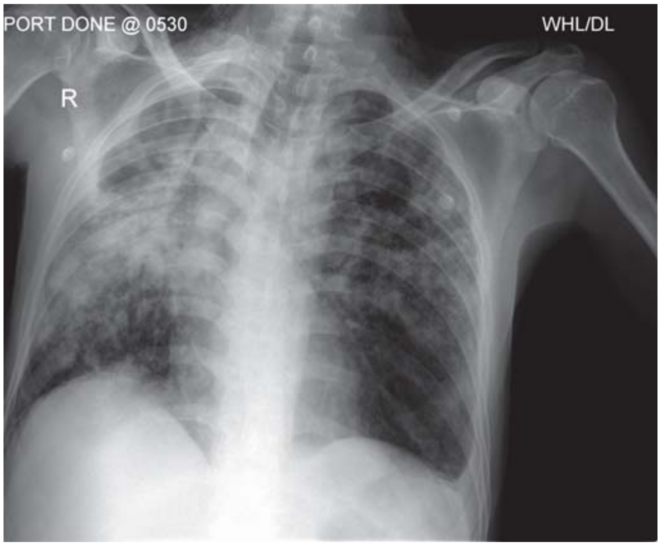

Fig. 19.3: Chest radiograph of patient with active tuberculosis

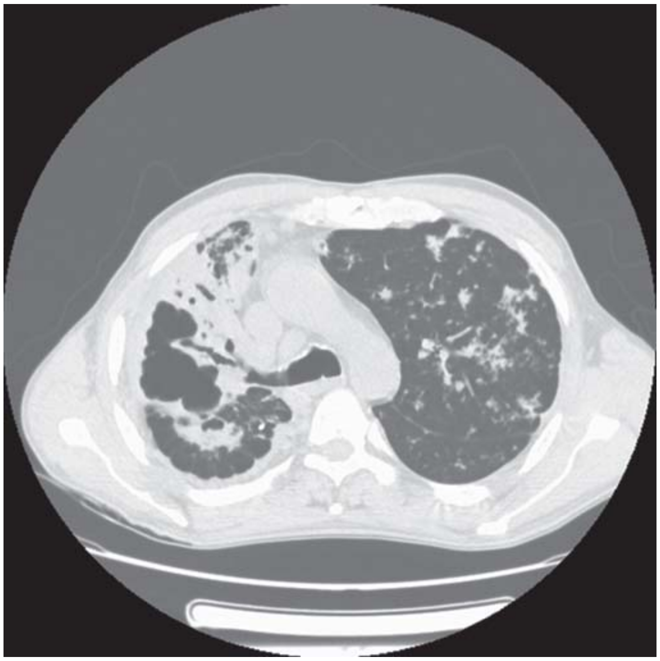

Fig. 19.4: Computed tomography of the chest showing an axial image of a patient with HIV and active tuberculosis

Cavities may develop in pulmonary parenchyma damaged by TB, sarcoidosis, vasculitis, emphysema, neoplasms, pulmonary fibrosis, lung abscess, bronchial cyst, asbestosis, ankylosing spondylitis or pulmonary infarction.[142] These pre-existing cavities may become colonized by aspergillus to form mycetomas or fungus balls (Fig. 19.5). These mycetomas are frequently complicated by hemoptysis, up to 85% of the time.[31,143] The fungus ball may cause erosion into a blood vessel by releasing anticoagulant proteolytic enzymes.[144,145]

Melioidosis caused by *Burkholderia pseudomallei* may mimic active tuberculosis. Most cases have been reported in Southeast Asia. Melioidosis, like active tuberculosis, causes protean signs and symptoms that include fever, productive cough, hemoptysis, weight loss, pleuritic chest pain and, typically, necrotizing upper lobe involvement. The disease can also be present acutely with an abrupt onset and rapidly deteriorating course.

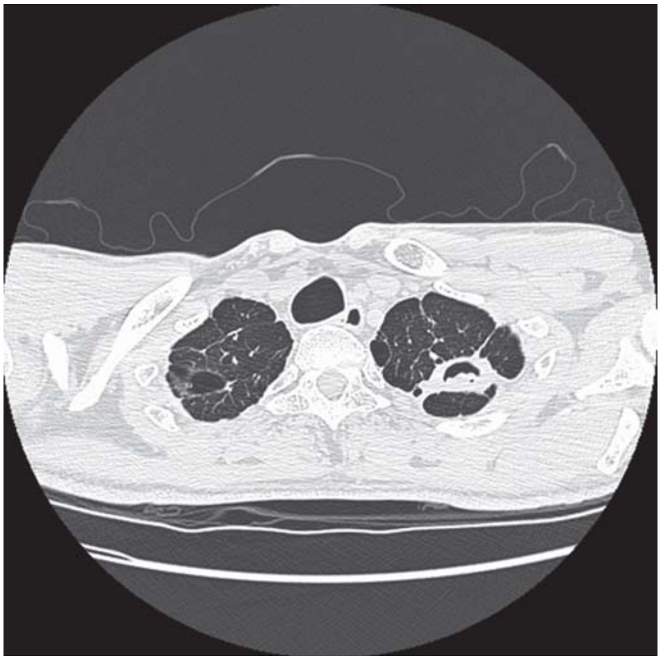

Fig. 19.5: Computed tomography of the chest showing an axial image of a patient with a mycetoma in a preformed cavity secondary to sarcoidosis

Recrudescence has been described up to 26 years after the patient had left the endemic zone.[146]

The ingestion of raw or undercooked shellfish primarily in Southeast Asia may lead to infection with *Paragonimus westermani*. The adult parasite forms cysts near bronchioles and bronchi. Hemoptysis occurs as the cysts erode into the airway.[44,45] Loeffler's syndrome is caused by different types of parasites (e.g. Ascaris, hookworm, Strongyloides) due to the migration of parasite larva through the lungs, most often one to two weeks after infection, but the incubation period will vary depending on the species of the parasite.[147] The syndrome is characterized by fever, urticaria, wheeze, dry cough and sometimes, hemoptysis. Typically, the patient has eosinophilia on a complete blood count and the chest radiograph shows migratory pulmonary infiltrates.

Neoplastic Causes

Bronchogenic carcinoma may present with hemoptysis when the tumor invades a blood vessel or becomes necrotic. Hemoptysis can be the presenting symptom in 10% of lung cancer patients,[57] typically mild to moderate.[148] Squamous cell carcinoma seems to be the most likely type of lung cancer to cause massive bleeding because of its typical central location and tendency to cavitate.[57] Squamous cell carcinoma is 10 times more likely to bleed than other types of bronchogenic carcinoma (Fig. 19.6).[57] Bronchial carcinoids are slow growing endobronchial neuroendocrine tumors that are highly vascularized and may bleed up to 30% of the time.[149,150]

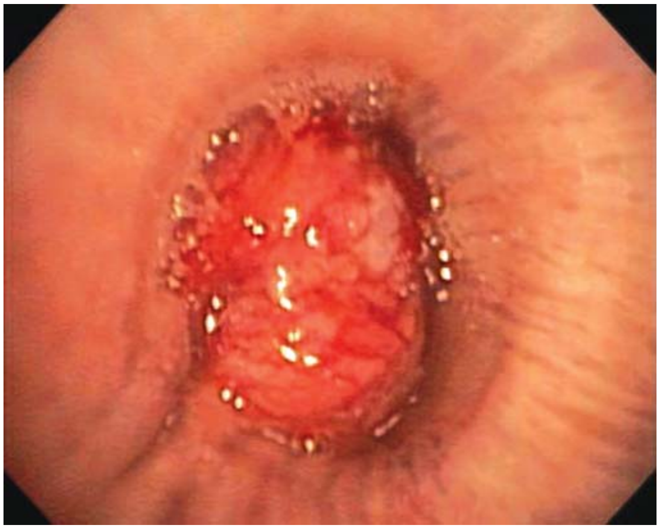

Fig. 19.6: Bronchoscopy picture showing a highly vascularized squamous cell lung carcinoma

Cardiac Causes

The elevated pressure in the pulmonary circulation that results from congestive heart failure and mitral stenosis may lead to the distension and rupture of pulmonary and bronchial veins. Significant back pressure from mitral stenosis may be transmitted to the bronchial veins, resulting in submucosal varices that are prone to rupture and bleeding.[151,152]

Vascular Causes

Venous thromboembolism can cause hemoptysis when there is the necrosis of pulmonary parenchyma due to infarction, congestive atelectasis or hemorrhagic consolidation. Venous thromboembolism can also cause hemoptysis by increasing bronchial artery blood flow through collaterals that are formed with the pulmonary circulation to bypass the embolized artery.[153,154]

Pulmonary arteriovenous malformation (AVM) is another important cause of hemoptysis that may result in profuse bleeding. The majority of hemoptysis caused by AVMs will be seen in the patients with hereditary hemorrhagic telangiectasia or Osler-Weber-Rendu syndrome. The AVMs tend to be numerous and bilateral, bleeding occurs from either rupture of a pulmonary AVM or an endobronchial telangiectasia.[7] The risk of bleeding is higher with feeding vessels of > 3 mm.[158]

Dieulafoy's lesion is another type of vascular malformation. In these lesions, there is a bronchial artery draining into a pulmonary artery causing left-to-right shunting of blood. Dieulafoy's disease of the bronchus is associated with the abnormal superficial location of this vascular anomaly contiguous to the epithelium of the bronchial mucosa. Dieulafoy's lesions can appear as sessile tumors covered by endobronchial mucosa or they may have an overlying white cap. If biopsied, these lesions may bleed profusely.[159] Disease of the bronchus is analogous to the Dieulafoy's lesion of the gastric mucosa that can present with severe upper gastrointestinal bleeding due to the superficial location of a dilated, ectopic gastric artery.

Congenital Causes

Cystic fibrosis patients are prone to develop pulmonary abscesses, recurrent pneumonias and bronchiectasis (Figs 19.1 and 19.2). Patients may subsequently present with hemoptysis, the risk appears to increase with more advanced age.[160,161] Bronchiectatic airways bleed because they have a higher degree of vascularity in the endobronchial and peribronchial circulation.[80]

Trauma

Both penetrating and blunt chest trauma can cause hemoptysis. Pulmonary lacerations, pneumatoceles and pulmonary hematomas may all be caused by blunt chest trauma. Pulmonary contusions occur when external forces are applied to the pulmonary parenchyma. Pulmonary contusions cause the disruption of the alveolar-capillary membranes, increased permeability and edema, shunting and ventilation-perfusion mismatching. Pulmonary contusions rarely cause hemoptysis since they do not tend to disrupt the pulmonary parenchyma and the bleeding is confined to the alveoli and interstitium.[84] Tracheobronchial injury is another type of traumatic injury that may occur with the sudden compression of the chest and shearing of the mainstem bronchus. Chest compression against a closed glottis can also tear the membranous portion of the cartilaginous rings and cause hemoptysis. Deceleration injuries may cause rupture at fixed points at the cricoid and main carina.[162]

Iatrogenic Causes

Rupture of the pulmonary artery by a balloon flotation catheter may complicate right heart catheterization. This complication tends to occur when there is pulmonary hypertension, a distally located catheter tip, excessive catheter manipulation, a large catheter loop in the right ventricle or advanced age.[25]

Tracheoarterial fistulas usually involving the innominate artery, are complications of tracheotomies and a cause of life-threatening hemoptysis. The fistulas are most likely to form at the stoma in low tracheotomies, at the balloon site, or at the tip of the tracheotomy tube when there is excessive angulation causing pressure necrosis. It usually takes at least 48 hours after tracheotomy to develop a tracheoarterial fistula. A sentinel bleed precedes massive hemoptysis in 35 to 50% of these cases.[91]

Transbronchial lung biopsies may cause hemoptysis in 2% of cases, the bleeding is usually mild and self limited. However, some patients are at a higher risk of more profuse bleeding, especially those with thrombocytopenia and uremia, those who are immunocompromised, or those who are on mechanical ventilation.[163] Caution should also be taken when performing transbronchial biopsies in patients with severe pulmonary hypertension [pulmonary artery systolic pressure (PASP) > 55-60 mm Hg] as they may be at increased risk for bleeding complications.[164,165]

Systemic and Immune Diseases

Diffuse alveolar hemorrhage (DAH) may occur due to capillary damage by autoimmune diseases, such as Goodpasture's syndrome; Systemic lupus erythematosus (SLE); the ANCA-associated vasculitides [Necrotizing granulomatous vasculitis (NGV), (formerly Wegener's granulomatosis)], microscopic polyangiitis; Churg-Strauss syndrome; and cryoglobulinemia (Figs 19.7 and 19.8). All of these diseases may involve the nervous system, gastrointestinal tract, skin, kidneys and joints.[166-170] Thoracic endometriosis is the cause of catamenial hemoptysis, happening within 48-72 hours of menses.[171]

Drugs/Toxins

Anticoagulants and thrombolytics may induce hemoptysis in patients with underlying chronic inflammation (e.g. chronic bronchitis), neoplastic lesions, or structural abnormalities of the lungs and airways (e.g. bronchiectasis).[172] Other, rare causes of toxin-induced DAH and hemoptysis include penicillamine, mitomycin-C, isocyanates, crack cocaine, abciximab, sirolimus, all-trans-retinoic acid and trimellitic anhydride.[120,122,173,174]

Cryptogenic Hemoptysis

Cryptogenic or idiopathic hemoptysis is the term used when no specific cause of hemoptysis can be found after

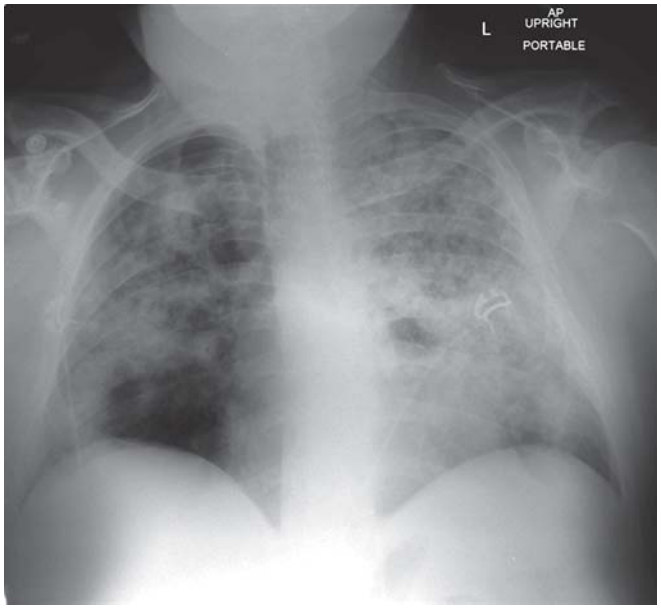

Fig. 19.7: Chest radiograph of a patient with diffuse alveolar hemorrhage in the setting of necrotizing granulomatous vasculitis

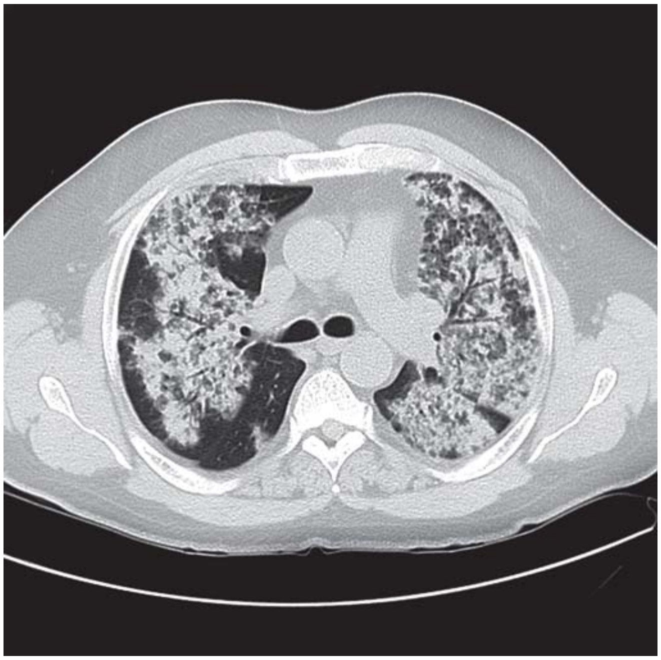

Fig. 19.8: Computed tomography of the chest showing an axial image of a patient with diffuse alveolar hemorrhage in the setting of necrotizing granulomatous vasculitis

thorough medical, roentgenographic and bronchoscopic evaluations. The incidence at referral centers is about 19%. In general, the prognosis for cryptogenic hemoptysis is favorable with the resolution of any further hemoptysis within six months of the initial evaluation. However, more contemporary data over a 6.6 year period of follow-up, has revealed that the subsequent diagnosis of lung cancer in patients with cryptogenic hemoptysis may be as high as 6%, especially among those patients who smoke and are older than 40 years of age.[124] Interestingly, it was found in a recent report from France, which described 81 patients who were labeled as cryptogenic hemoptysis, that five out of the nine patients in the cohort who presented with massive hemoptysis and required surgical intervention had a Dieulafoy's lesion as the etiology, discovered on surgical specimens. These patients were all smokers and it is postulated that the associated chronic irritation and inflammation from smoking may have participated in the pathological evolution of the ectopically located, superficial bronchial arteries seen in Dieulafoy's disease of the bronchus.[175]

Diagnostic Approach

If one excludes cryptogenic hemoptysis as a distinct diagnosis, the cause of hemoptysis can be determined in 68 to 98% of cases.[15,176] The diagnostic work-up of hemoptysis involves both standard evaluations that should be performed on most patients (Table 19.3), and specialized testing to be ordered only if indicated by the specific clinical setting (Table 19.4). After the initial evaluation, the next steps are determined by each patient's specific clinical picture.

TABLE 19.3: The initial evaluation of hemoptysis

History and Physical

- Smoking history
- Presence of cardiopulmonary disease
- History of bleeding from upper airways or gastrointestinal tract
- History of aspiration events
- Duration of symptoms
- Drugs and medications
- Travel history

Laboratory Evaluation

- Complete blood count, platelets
- BUN/Creatinine
- Urinalysis
- Coagulation studies
- Brain natriuretic peptide (BNP)

Sputum

- AFB, bacteria and fungus
- Cytology

Chest Radiograph

+/-Chest CT Scan

+/-Bronchoscopy

TABLE 19.4: List of special tests for the work-up of hemoptysis

Imaging
- High-resolution computed tomography
- CT scan with contrast
- Bronchial angiogram
- Spiral aortogram
- Pulmonary angiogram
- Magnetic resonance imaging
- Ventilation-perfusion scan
- Lower extremity venous duplex scan
- Echocardiogram

Laboratory Values
- Antinuclear antibodies
- Rheumatoid factor
- Antineutrophilic cytoplasmic antibodies
- Complement levels
- Cryoglobulins
- Anti-glomerular basement membrane antibodies
- Urine legionella and urine pneumococcal antigens
- Stool exam for ova and parasites

Pathology
- Lung or kidney biopsies

History

A detailed history and physical examination should always be performed (Table 19.3). The first step is to confirm the presence of hemoptysis and distinguish it from pseudohemoptysis. The second step is to try to quantify the volume of hemoptysis. The third step involves identifying the most likely broad category of etiology (Table 19.1). The fourth and final step is to find a specific cause of hemoptysis.

Even though not indicative of severity, the frequency, timing and duration of hemoptysis may be helpful in assessing the cause of hemoptysis. Bronchiectasis may present with recurrent episodes over the course of years.[177] Bronchogenic carcinoma causes the recurrent episodes of mild hemoptysis often developing for a few weeks.[178] The timing can also be misleading in a patient with chronic bronchitis who may subsequently develop a lung cancer. Hemoptysis coinciding with menstrual period, suggests thoracic endometriosis.[171] Exertion induced and post-coital bloody expectoration is characteristic of pulmonary congestion as seen with cardiogenic pulmonary edema.[68] Acute onset of hemoptysis, fever and chest pain suggests infection or pulmonary infarction from thromboembolism.[1]

The patient's age is another important consideration. Before the third decade of life, the likely causes of hemoptysis include acute tracheobronchitis, congenital cardiac or pulmonary disease, cystic fibrosis and infectious pneumonia. However, persistent hemoptysis after adequately treated pneumonia should raise the suspicion of an endobronchial lesion or a coagulopathy.[179] Bronchogenic carcinoma is very rare in patients younger than 40 years of age; however, germ cell tumors may lead to endobronchial metastases that may bleed. Bronchial adenoma is another consideration in the younger patient population.

Occasionally, the character of the sputum can add some useful information during the diagnostic evaluation. Pulmonary edema from passive congestion, as seen with left ventricular failure and mitral stenosis, may present with pink frothy sputum in a patient with orthopnea and paroxysmal nocturnal dyspnea. When gritty, white material is seen mixed with blood in the sputum, one should consider the diagnosis of broncholithiasis as seen in tuberculosis and histoplasmosis. Blood and pus in expectorated sputum suggest infection.

A history of hematuria should raise the suspicion of a vasculitis. NGV comes with the characteristic triad of upper and lower airway disease with rapidly progressive glomerulonephritis. SLE may cause DAH anytime during the course of the disease.[106] When the pulmonary and renal manifestations are present in a young male smoker, Goodpasture's syndrome, caused by antibasement membrane antibodies, is a strong possibility;[97] influenza infection,[180] inhalation of hydrocarbons,[181] and penicillamine ingestion should also be considered.[120] DAH may also complicate hematopoietic stem cell transplantation in 5% of allogeneic and autologous recipients, and in this setting, carries a 50 to 100% mortality rate, with a 38% six-month mortality rate for those who survive.[182]

Hemoptysis with simultaneous bleeding from the gastrointestinal tract, skin or the nose may point to an inappropriate high dose of anticoagulants or a bleeding disorder such as Disseminated Intravascular Coagulation (DIC). The latter should be suspected in a critically ill patient with bleeding, thrombocytopenia and microangiopathic anemia. Oral contraceptives, prolonged immobilization, long bone fractures and recent surgery should raise the suspicion of deep venous thrombosis and venous thromboembolism.

Tracheoarterial fistulas, though rare, should be considered in a patient with a tracheotomy and hemoptysis. Massive hemoptysis from rupture of these fistulas will have a sentinel or preceding smaller bleed in 34 to 50% of cases. The peak incidence is between the first and second week after tracheotomy, with 72% occurring within 21 days.[91] During the initial 48 hours of tracheotomy placement, bleeding can result from overly vigorous suctioning.

The travel history should be documented. Bacterial, fungal and parasitic etiologies for hemoptysis can be suspected depending on the geographical area of exposure. Tuberculosis is endemic in the developing world and should always be considered in the differential diagnosis. Melioidosis caused by *Burkholderia pseudomallei* is ubiquitous in the soil and stagnant water of Southeast Asia, as well as it can mimic the clinical presentation and course of tuberculosis.[146] Examples of fungal infections include coccidiomycosis in the Southwest of the United States, Central and South America; histoplasmosis in the Mississippi River valley, as well as in the caves of South America and Africa; and paracoccidiomycosis in the regions of North, Central and South America. Examples of parasitic infections include paragonimiasis in travelers to East Asia, Central and South America, Central and West Africa; and schistosomiasis in all of Africa, the Middle East, Southeast and Central Asia and South America.[147]

Physical Examination

While doing a physical examination, special attention should be paid to the nose, gums, pharynx and skin. The presence of telangiectasia suggests a diagnosis of Osler-Weber-Rendu disease. NGV will frequently involve the nasal passages. Ecchymoses and petechiae raise the concern for a clotting disorder or a vasculitic process. When wheezing is localized, it points to an endobronchial lesion. Stridor is more likely seen with an obstructing lesion of the extrathoracic airway or edema of the larynx. Localized crackles suggest focal airspace disease. Even though the physical examination may be helpful in determining the cause of hemoptysis, it is unreliable in localizing the site of bleeding.[6]

Laboratory Evaluation

Routine laboratory studies may be helpful in specific situations. Iron deficiency anemia may suggest idiopathic pulmonary hemosiderosis; likewise, an elevated white blood cell count in the right clinical setting may support a diagnosis of pneumonia. The urinalysis may show hematuria as seen with the pulmonary - renal syndromes. Coagulation studies and platelet counts may unmask a bleeding disorder. The Brain Natriuretic Peptide (BNP) may aid in the diagnosis of cardiogenic pulmonary edema.

Sputum Gram stain and cultures may aid in the diagnosis of bacterial pneumonia. Acid-fast bacilli smear and cultures can also be obtained from sputum. Serum anti-glomerular membrane antibodies help in the diagnosis of Goodpasture's, antineutrophil antibodies and antineutrophil cytoplasmic antibodies (ANCA) will be elevated in SLE and NGV, respectively.

Chest Radiograph

An initial posteroanterior and lateral chest radiograph should always be obtained in patients with hemoptysis. About 30% of patients with hemoptysis will have a normal chest radiograph.[183-186] The chest radiograph may sometimes reveal bilateral lesions and the source of hemoptysis will not be localized in up to 40% of patients.[6] Aspirated blood may give a false impression of being the source of hemoptysis, and bronchoscopy may reveal other areas causing bleeding that were not evident on the chest radiograph.[104,187,188] The chest radiograph may reveal radiopaque foreign bodies that can cause hemoptysis even years after aspiration. Cavities may be single or several, suggest tuberculosis and other bacterial, fungal or parasitic infections, thromboembolic events, neoplasms or NGV (Figs 19.7 and 19.8). The finding of a mass within a preformed cavity is suggestive of a fungus ball, seen with aspergillomas. Squamous cell lung carcinoma is the most likely type of lung cancer to cavitate (Fig. 19.6). Multiple nodules are seen in septic emboli, miliary TB, lung metastases and NGV. Arterio-venous fistulas may be seen as pulmonary nodules with feeding vessels. Diffuse alveolar filling, sparing the costophrenic angles and apices, is suggestive of pulmonary hemorrhage. Thick, dilated bronchi with an air fluid level may be seen in bronchiectasis. Bilateral pleural effusions, an enlarged cardiac silhouette, Kerley B lines and perihilar edema suggest congestive heart failure.

Bronchoscopy

Bronchoscopy is a very valuable tool for localizing and diagnosing the source of hemoptysis, but not all patients with hemoptysis require a bronchoscopy. Patients who may forgo this procedure include those with strong evidence of a non-neoplastic disease (e.g. congestive heart failure), those with pseudohemoptysis, those whose condition is so debilitating or so far advanced that no change in management will result from the bronchoscopic findings, and lastly those who are younger than 40 years of age with short-lived hemoptysis of less than one week in duration.[183]

Bronchoscopy will localize the source of bleeding in 93% of patients if performed within 24 hours.[187,189] However, the rate of success drops to 51% if done within 48 hours.[190] Rigid bronchoscopy is preferred in the cases of massive hemoptysis because an airway is secured and the patient is ventilated during this procedure. The rigid bronchoscope has a large lumen that allows for more vigorous suctioning and more therapeutic options than a flexible bronchoscope. Rigid bronchoscopy must be performed under general anesthesia in the operating room. Flexible bronchoscopy may be performed at the bedside, does not require general anesthesia, and can visualize up to the sixth generation of airways. However, the suctioning capacity of the flexible bronchoscope is limited and it does not secure the airway. To deal with this problem, the patient can be intubated and the bronchoscope advanced through the endotracheal tube. This ensures airway control and makes frequent removal and reinsertion of the bronchoscope possible. Alternatively, the patient could be intubated with a rigid bronchoscope for better suctioning and a flexible bronchoscope can be advanced through it for better overall airway visualization.

Bronchoscopy may also be helpful in the diagnosis of DAH. Bronchoalveolar lavage fluid that becomes progressively bloodier with each aliquot and lavage fluid containing hemosiderin-laden macrophages that number more than 20% of total alveolar macrophages are both suggestive of DAH.[191]

Computed Tomography

Computed Tomography (CT) scanning plays an important role in the evaluation of hemoptysis. It has been shown, in some studies, to be as good as bronchoscopy for localizing the bleeding, and superior to bronchoscopy at diagnosing the cause of bleeding.[192] Chest CT is superior to plain films and bronchoscopy in diagnosing bronchiectasis, post-tuberculous lesions, aspergillomas and tumors, together the most common causes of massive hemoptysis. However, CT will fail to identify localized mucosal abnormalities such as bronchitis, telangiectasias, early carcinoma, squamous metaplasia, benign papillomas and Kaposi's sarcoma.[190] Contrast administration appears to be unnecessary for making a diagnosis by CT. In addition, a large number of patients with massive hemoptysis will undergo angiographic embolization. It seems appropriate to consider a CT of the chest without contrast on all cases of massive and moderate hemoptysis.[192]

Bronchial Angiography

Bronchial angiography is an excellent method for localizing the site of bleeding in patients with active, submassive and massive hemoptysis. Abnormal bronchial arteries may be hypertrophied, tortuous, increased in size and number, as well as there may be arteriovenous shunts and aneurysms.[193] The site of bleeding can be determined angiographically in up to 90 to 93% of cases.[194] Angiography may locate a bleeding site in about 4% of cases, when bronchoscopy and other radiographic techniques fail.[189] Once a bleeding vessel is identified, arterial embolization can be performed to stop the bleeding; potential therapeutic intervention represents an additional advantage of arterial angiography (Figs 19. 9 and 19.10).

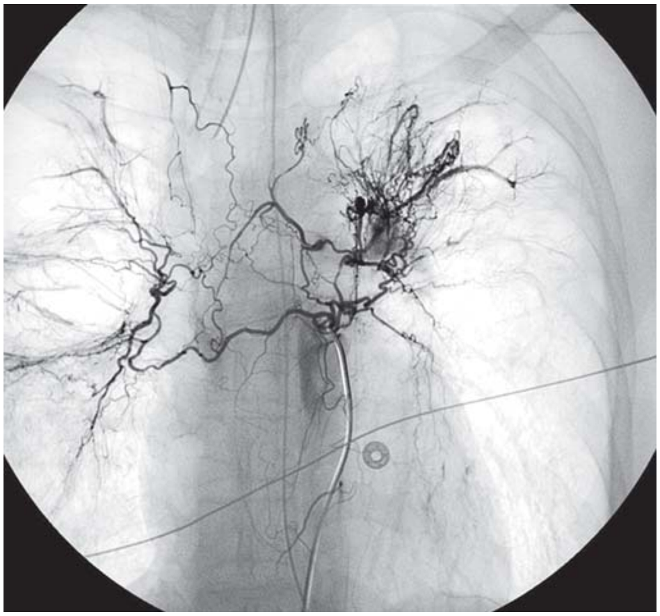

Fig. 19.9: Selective bronchial angiography showing intense neovascularization and bronchial-pulmonary anastomoses in a patient with a left upper lobe mycetoma

TREATMENT

The goals of treatment are to prevent asphyxiation due to the aspiration of large volumes of blood and to stop the bleeding. Both general supportive care and more specific definitive measures are necessary. Figure 19.11 shows an overview of the therapeutic approach to hemoptysis.

Supportive Care

Patients should be placed on bed rest; if the site of bleeding is known, the affected lung should be placed down in the lateral supine position. Mild sedation can be used to attenuate vigorous coughing that may worsen bleeding by dislodging clots; however, too much depression of cough should be avoided because an effective cough may be necessary to avoid aspiration and

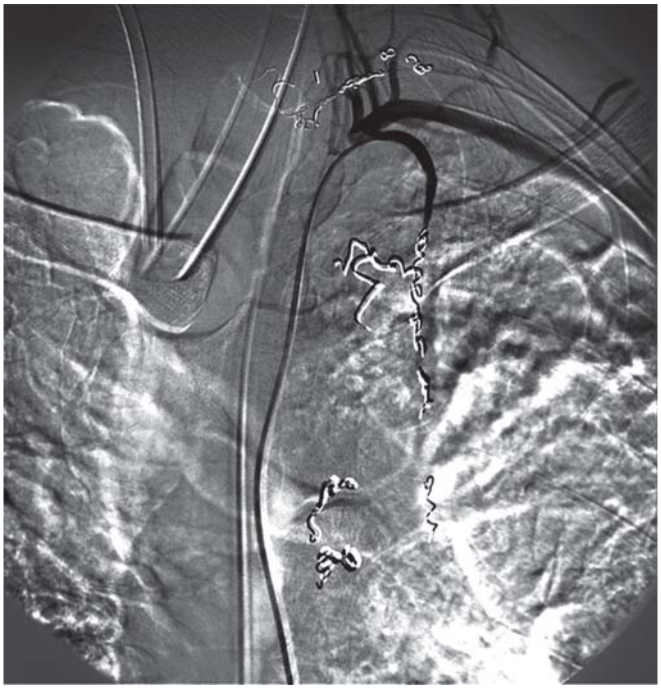

Fig. 19.10: Angiographic coil embolization of internal mammary artery and thyrocervical artery branches. Notice the acute cutoff of the contrast in the internal mammary artery after the coils

asphyxiation. Chest physiotherapy and postural drainage should be avoided.

Patients who experience rapid deterioration with worsening oxygenation may require endotracheal intubation. Whenever intubation is needed, an 8.0 mm or greater endotracheal tube should be used to allow for future bronchoscopy. Another option is to intubate with a double lumen tube and try to isolate the unaffected lung; however, these tubes have a smaller internal diameter that can be more easily obstructed by clots and secretions. They are also difficult tubes to place properly, even by an experienced anesthesiologist, are prone to migrate and lose their isolating effect.[11] Intravenous (IV) fluids and blood products should be administered as needed to reverse any underlying coagulopathy; two large bore peripheral IV lines should be placed for this end. An exception to the avoidance of anticoagulation is patients with venous thromboembolism.[195]

Definitive Care

Nonmassive Hemoptysis

For the definitive care of nonmassive hemoptysis, treatment should be targeted to the specific underlying cause. Suppurative bronchiectasis should be treated with antibiotics and a bronchodilator (e.g. β-adrenergic agonists). Similarly, an exacerbation of chronic bronchitis can be controlled with steroids, antibiotics and a bronchodilator; but most importantly, by smoking cessation. Airway lesions should be resected whenever possible. Congestive heart failure and mitral stenosis can be treated with diuretics and afterload reduction. Venous thromboembolism should be treated with anticoagulation and diuretics.

Massive Hemoptysis

Several bronchoscopic options are available to stop severe bleeding. Placement of an endobronchial balloon can be used for tamponade in all lobes except the right upper lobe where the acute angle of the right upper lobe bronchus prevents placement.[196] Placement is done with a 100 cm long four French Fogarty balloon catheter. The balloon should be positioned in a way that completely occludes the bronchus and causes distal pulmonary collapse. Smaller catheter balloons can also be used and be placed more distally in segmental bronchi. Other interventions include iced saline lavage, laser bronchoscopy,[196] application of topical epinephrine (1:20,000), thrombin, or a fibrinogen-thrombin combination.[197]

Angiographic embolization has a high success rate for the control of massive hemoptysis, being successful in 77 to 95% of cases (Figs 19.10 and 19.11).[21,189] However; there is a 16% incidence of rebleeding within one to four days so multiple procedures are frequently necessary.[21,198,199] After proper control of hemoptysis, it may be expected that 20% of patients will rebleed in the next six months,[200] and 22% within three to five years.[21] The potential complications of angiographic embolization are rare, but spinal artery embolization does occur less than 1% in experienced hands of the time, especially when a spinal artery originates from a bronchial artery.[198]

The role of surgery has decreased significantly due to the high success rate of angiographic embolization procedures. However, surgery remains the preferred treatment of massive hemoptysis a arteriovenous malformations, leaky aortic aneurysms, hydatid cysts, pulmonary artery ruptures, chest traumas, bronchial adenomas and fungus balls that have not responded to medical therapy.[198] All these situations involve either a problem not amenable to embolization, or a very likely recurrence after embolization.

The treatment of DAH generally requires intravenous corticosteroids, cytotoxic drugs and even plasmapheresis (e.g. NGV and Goodpasture's). Vasculitis-induced DAH

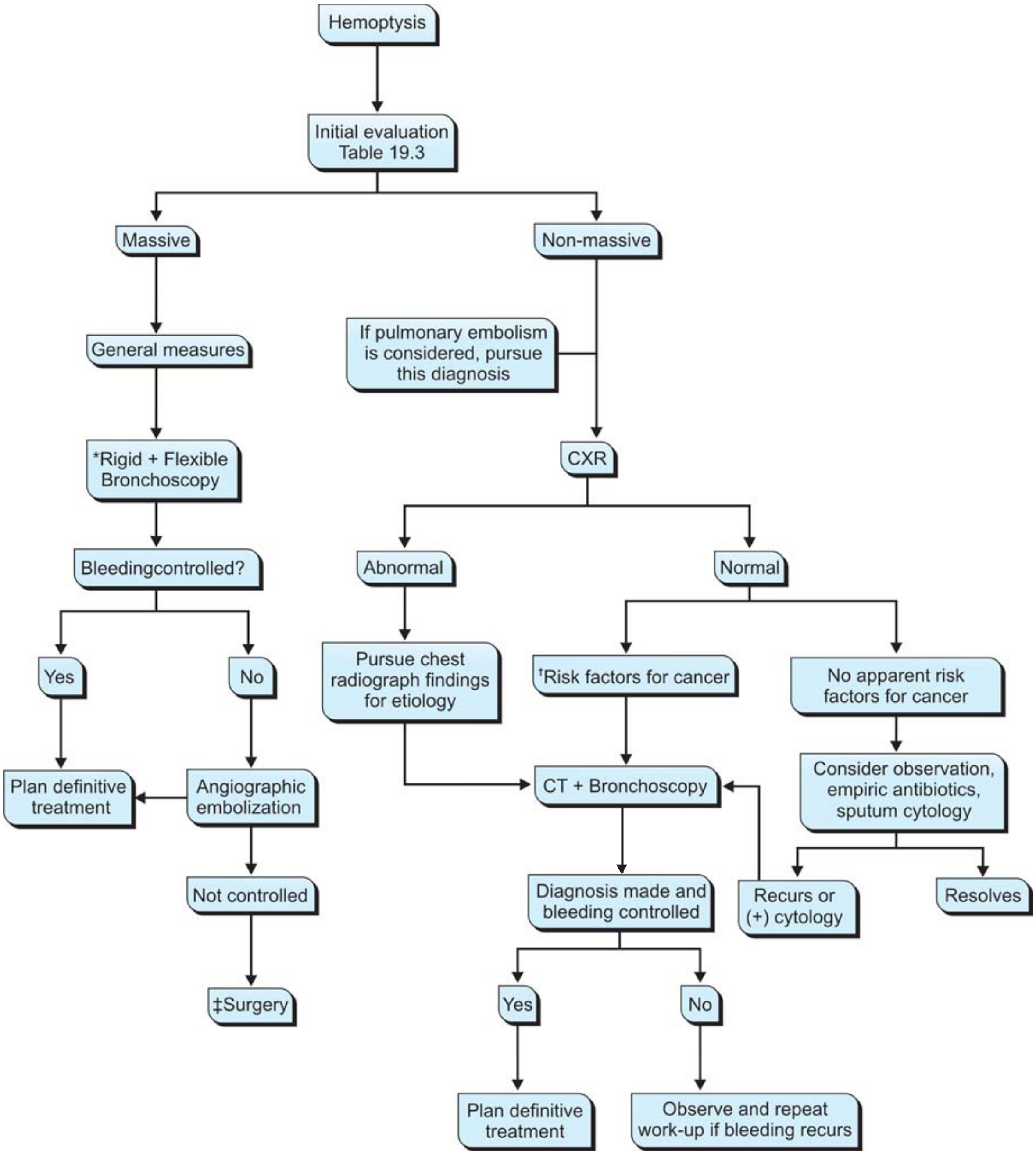
Hemoptysis
Initial evaluation Table 19.3
Massive
Non-massive
General measures
If pulmonary embolism is considered, pursue this diagnosis
*Rigid + Flexible Bronchoscopy
CXR
Bleedingcontrolled?
Abnormal
Normal
Yes
No
Pursue chest radiograph findings for etiology
†Risk factors for cancer
No apparent risk factors for cancer
Plan definitive treatment
Angiographic embolization
CT + Bronchoscopy
Consider observation, empiric antibiotics, sputum cytology
Not controlled
Diagnosis made and bleeding controlled
Recurs or (+) cytology
Resolves
‡Surgery
Yes
No
Plan definitive treatment
Observe and repeat work-up if bleeding recurs

Fig. 19.11: Proposed algorithm for the management of hemoptysis. The figure shows a proposed algorithm for the management of massive versus nonmassive hemoptysis.

*There may be situations where angiographic embolization is indicated first. †Age > 40 years old, smoker, previous cancer or other.

CXR: Chest radiograph. CT: Computed tomography.

‡Surgery may be indicated first when the etiology of bleeding is not amenable to embolization or may have a high likelihood of recurrence, see text.

will often require combined therapy. Pulmonary aspergillomas have been treated by the intracavitary instillation of amphotericin B, nystatin and sodium iodide solutions.[201,202] Local radiation of fungus balls may be an alternative for patients too debilitated or having such a poor pulmonary reserve that surgery is high risk.[203,204]

When bleeding is due to a tracheoarterial fistula, immediate measures should be taken to prevent exsanguination. One way to try to tamponade the bleeding vessel in an acute emergency consists of over-inflating the balloon cuff of the tracheotomy tube as downward and forward pressure is applied on top of the tracheotomy tube. If bleeding slows down with this maneuver, an endotracheal tube should be placed distal to the tip of the tracheotomy tube and a surgical consult should be requested emergently.[91]

In the presence of iatrogenic pulmonary artery rupture, the Swan-Ganz catheter may be withdrawn 5 cm with the balloon deflated; the balloon is then reinflated and allowed to float back to tamponade the bleeding vessel. The patient should also be intubated in the mainstem bronchus of the contralateral lung. If bleeding is controlled, patients should immediately undergo pulmonary angiography to localize the arterial tear and assess for the formation of a pseudoaneurysm. Frequently, embolization can be performed at the same time.[25]

In summary, hemoptysis is an important symptom requiring a thorough medical evaluation to determine the underlying diagnosis. The first step in evaluation is a complete medical history and physical examination. Depending on whether the bleed is massive or non-massive, subsequent evaluation and treatment may require additional radiographic imaging, flexible bronchoscopy, rigid bronchoscopy, angiographic embolization and surgery. The diagnostic tests and therapeutic interventions required will depend largely on the clinical presentation, rate of bleeding, and the availability of the proper equipment and experienced personnel.

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20

Dyspnea

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INTRODUCTION

Dyspnea is difficult, labored or unpleasant breathing that is distressing to an individual.[1] The symptom of dyspnea, often referred to as shortness of breath, is frequently described vaguely by patients and it is probably not a single sensation given the many qualitative descriptors patients use to describe it. Three distinct sensations of respiratory discomfort have been described to subcategorize dyspnea—air hunger, work and effort related, and chest tightness—and it is possible that different neural pathways underlie each.[2]

PHYSIOLOGY

The physiologic basis of dyspnea is not yet established. However, because the cardiorespiratory system is complex and regulated by complex neurophysiology, it is likely that multiple different sensory, efferent, brain stem and cortical neural pathways are involved in mediating the sensation of dyspnea.[1-3] Afferent neural pathways from all thoracic and even upper abdominal organs may potentially modulate or mediate the sensation of dyspnea.[2,4] It is not surprising that many cardiopulmonary disorders can result in dyspnea or that the intensity of the sensation can be modulated by learning, experience, and emotional and behavioral conditions.

Evidence suggests that three different types of neural receptors are involved in the genesis of dyspnea: chemoreceptors, mechanoreceptors and ergoreceptors of skeletal muscle.[5] Afferent signals from these receptors are integrated in the central nervous system, modulated by cortical input, and compared to efferent motor neuron discharge to the respiratory muscles.

Chemoreceptors detect changes in blood carbon dioxide and oxygen levels.[5] Acute increases in arterial carbon dioxide potently stimulate medullary chemoreceptors that lead to dyspnea by increasing ventilation and by mechanisms independent of ventilation as well. The effect of carbon dioxide on these central chemoreceptors is probably indirect and due to changes in pH. Consistent with this, patients with chronic hypercapnia and a compensated respiratory acidosis are less dyspneic at the same partial pressure of carbon dioxide and less sensitive to changes in carbon dioxide as well. Peripheral chemoreceptors in the carotid and aortic bodies are stimulated by decreases in the partial pressure of oxygen in arterial blood and to a lesser extent by increases in carbon dioxide and decreases in pH. Although it would intuitively seem that hypoxemia would be the main stimulus to dyspnea, this has not been supported by clinical observation or experimental evidence. Not all subjects with dyspnea have hypoxemia and not all patients with hypoxemia have dyspnea. Instead, low oxygen is not the main stimulus to dyspnea and is a much less potent stimulus than elevated carbon dioxide. Evidence suggests that, although it is not a potent stimulus, low oxygen does contribute to dyspnea mainly through its effects on increased ventilation.

Mechanoreceptors are neural receptors that detect changes in pressure, stretch and position.[5] The respiratory system has many different types of mechanoreceptors located throughout the airways, lung parenchyma, chest wall and diaphragm. Discordance between the afferent output of these mechanoreceptors and respiratory motor efferent discharge is believed to play a central role in generating the distressing sense that breathing is difficult.[2]

Ergoreceptors (also called metaboreceptors) are believed to underlie the ergoreflex.[5] This is a complex metabolic reflex that originates in skeletal muscles and stimulates ventilation. Ergoreceptors in skeletal muscle are thought to detect metabolic products of active muscle (possibly lactic acid and others) and send afferent signals that stimulate ventilation. There is high research interest in this reflex and its metabolic receptors, particularly the role of the reflex in causing dyspnea in the settings of heart failure and Chronic Obstructive Pulmonary Disease (COPD).

Differential Diagnosis of Dyspnea

The causes of dyspnea are numerous. Many diseases and disorders of the cardiorespiratory system and other organ systems can result in dyspnea. However, the causes of dyspnea can be categorized into general areas (Table 20.1). The frequency with which specific causes of dyspnea are encountered will vary with the clinical setting, the acuity of onset, and the age of the patients. For different clinical settings, it has been estimated that 75 to 92% of cases of dyspnea in an emergency department or inpatient hospital setting are due to cardiopulmonary diseases and disorders, while in the ambulatory setting that figure is 46 to 85%.[1, 6-9] Pulmonary, cardiac, psychogenic, Gastroesophageal Reflux Disease (GERD) and deconditioning disorders were the most common causes in an ambulatory clinic specializing in pulmonary diseases[9] (Fig. 20.1). Specifically for chronic dyspnea, the four most common causes were COPD, asthma, interstitial lung disease and cardiomyopathy.[8]

Disease-Specific Pathophysiology

The pathophysiologic mechanisms underlying dyspnea in asthma, COPD, cardiac disorders, GERD, psychogenic disorders and deconditioning are different and not well established.[3]

Respiratory mechanical factors, arterial blood gases and psychological factors all contribute to the genesis of dyspnea in asthma. Importantly, the severity of dyspnea in asthma does not always correlate with the degree of airway obstruction. Asthma patients with a prior history of near-fatal exacerbations have a decreased ventilatory response to hypoxia and a decreased sense of dyspnea.[10] In COPD, respiratory mechanics play an important role similar to that in asthma. However, the role of carbon dioxide and hypoxemia in the genesis of dyspnea appears

TABLE 20.1: General causes of dyspnea with selected examples*

Cardiac	
Congestive heart failure	Cardiac ischemia
Deconditioning/Obesity	
Endocrine	
Goiter	Hyperthyroidism
Diabetic ketoacidosis	
Gastrointestinal	
Gastroesophageal reflux disease	
Hematologic/oncologic	
Anemia	Lung cancer
Larynx and upper airway	
Postnasal drip syndrome (now called UACS**) due to any rhinosinus disease	
Laryngitis	
Vocal cord dysfunction	
Goiter	
Neuromuscular disease	
Amyotrophic lateral sclerosis	
Post-polio syndrome	
Mitochondrial myopathies	
Neuromuscular weakness of any cause	
Pharmacologic	
Nonsteroidal anti-inflammatory drugs	
Pregnancy	
Psychiatric	
Anxiety	
Depression	
Hyperventilation syndrome	
Pulmonary	
Asthma	
COPD	
Cystic fibrosis	
Pneumonia	
Interstitial inflammation of any cause and fibrosis	
Pneumothorax	
Pleural effusion	
Compressive lesions of the airways	
Tracheobronchial malacia	
Renal	
Metabolic acidosis	
Renal failure	
Rheumatologic	
Amyloidosis	Ankylosing spondylitis
Rheumatoid arthritis	Scleroderma
Systemic lupus erythematosus	
Vasculitis	
Vascular	
Pulmonary thromboembolism	
Pulmonary hypertension	
Right-to-left vascular shunt	

*For a more complete listing of differential diagnosis see reference 3.
**Upper airway cough syndrome.

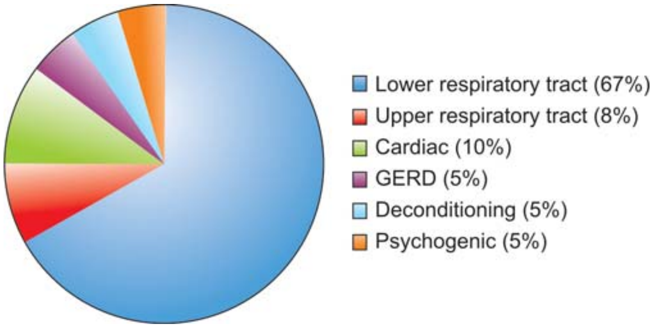

Fig. 20.1: Spectrum and frequency of the causes of unexplained dyspnea. Adapted from reference 9. In this study, 85 patients referred to a pulmonary clinic for difficult to diagnose dyspnea were evaluated. Asthma, chronic obstructive pulmonary disease, interstitial lung disease, and cardiomyopathy accounted for approximately two-third of the cases

to be greater in COPD than in asthma. Recently, for COPD, many studies have focused on the important role that dynamic hyperinflation plays in the genesis of dyspnea during exertion. The dynamic hyperinflation causes increased load on inspiratory muscles, places inspiratory muscles at the suboptimal length for effective contraction, restricts the ability of the patient to increase tidal volume (inspiratory capacity is decreased), and causes ventilation perfusion inequalities that impair gas exchange.[2] Afferent signals from mechanoreceptors and chemoreceptors reflect these distortions of muscle mechanics and changes in gas exchange. Because these are discordant with the amount of efferent motor activity emanating from the medulla respiratory center, severe dyspnea results.[2,11]

Interstitial lung diseases probably cause dyspnea by the mechanical effects of the disease on lung compliance, activation of vagal afferents, and abnormal gas exchange.[1,3] Similarly, compressing lung tissue with pneumothorax or pleural effusion and distortions of the thoracic cage by disease processes (e.g. kyphoscoliosis) probably stimulate dyspnea by the way of vagal afferents, changes in thoracic compliance, and alterations of gas exchange.

Nonpulmonary disorders cause dyspnea by mechanisms that also involve the activation of vagal afferents. Congestive heart failure probably causes dyspnea by the activation of vagal afferent mechanoreceptors in the lungs and airways and by altering gas exchange. How GERD causes dyspnea is not known, but GERD is commonly associated with respiratory symptoms and has been reported to account for unexplained dyspnea, in up to 5% of cases.[1,9,12,13] Possibly, GERD causes dyspnea by the activation of vagal afferents in the esophagus that secondarily stimulate an increase in minute ventilation to produce the sensation of dyspnea.[14] Of course, in severe GERD, the obstructive effects of laryngospasm or the aspiration of refluxate into the lungs would also be expected to contribute to dyspnea. Deconditioning can stimulate dyspnea by requiring increased minute ventilation for the task performed. Finally, there are psychogenic causes of dyspnea, such as anxiety, panic and hyperventilation. Presumably, dyspnea in these conditions is primarily due to the inappropriate cortical modulation of the neural pathways that integrate and compare the normal afferent and efferent activity driving respiration. However, hyperventilation can lead to the alterations of blood gases and these changes may secondarily contribute as well.

POSITIONAL AND NOCTURNAL DYSPNEA

Trepopnea is dyspnea that increases when one side is dependent. For example, patients with a paralyzed hemidiaphragm may complain that they cannot lie down on one side. However, trepopnea is a nonspecific finding because any asymmetric lung disease can cause trepopnea.[3] It can be seen in common diseases, such as COPD and congestive heart failure.

Orthopnea is dyspnea worse on recumbency. It is not a symptom or sign that is specific for congestive heart failure.[3] It can be seen in congestive heart failure, COPD or neuromuscular weakness. It does not reliably distinguish the cardiac causes of dyspnea from pulmonary causes.

Platypnea is dyspnea that is worsened by an upright position.[3] Classically, it is observed when there is right to left shunting of blood, either intracardiac[15] or pulmonary parenchymal.[16] For example, patients with cirrhosis can develop pulmonary arteriovenous malformations at the bases of the lungs. As these shunts become more dependent with the upright position and blood flow through them increases, right to left shunting increases when the patient is upright and this causes orthodeoxia (decrease in arterial oxygen tension when the subject goes from a recumbent position to an upright position) and dyspnea. However, the finding is not specific for right to left shunting of blood and has been reported with ileus and pericarditis as well.[3]

EVALUATING ACUTE DYSPNEA

In evaluating a patient with acute dyspnea, the first priority is to consider potentially life-threatening conditions, such as pulmonary thromboembolism, acute myocardial ischemia or infarction, congestive heart failure, cardiac arrhythmia, an acute exacerbation of asthma or COPD, pneumothorax, upper airway obstruction, pulmonary edema, and pneumonia.[1,3] A history and physical examination should be done and, based on the findings, further testing ordered as appropriate. Commonly useful tests for the evaluation of acute dyspnea include radiographic imaging, electrocardiogram, measurement of serum B-Type Natriuretic Peptide (BNP), complete blood count, arterial blood gases, spirometry or peak flow measures, and Computed Tomography (CT) angiography or ventilation-perfusion lung scanning, and echocardiography.

EVALUATING CHRONIC DYSPNEA

A systematic approach to diagnosing the underlying cause of dyspnea has been validated in a university hospital, ambulatory or pulmonary clinic.[9] In this setting, respiratory disorders accounted for approximately 75% of cases.

Evaluation begins with medical history and physical examination, concentrating on the anatomy of afferent nerves important in the genesis of dyspnea, especially the vagus nerve that subserves organs of both the thorax and upper abdomen. Also, the focus of the medical history and examination should be on the most common causes of chronic dyspnea, including asthma, COPD, interstitial lung disease and cardiomyopathy. If the initial history and physical examination are not suggestive of these most common diagnoses, additional attention should be directed to the other causes of chronic dyspnea, such as postnasal drip syndrome (now referred to as UACS) and other causes of upper airway obstruction, other respiratory disorders, evidence of deconditioning, psychogenic problems (hyperventilation), and GERD. In practice, the history and physical examination are most helpful in ruling out common diagnoses rather than establishing diagnoses. A history of wheezing or a prior diagnosis of asthma is only 50% predictive of asthma being the cause of the patient's chronic dyspnea. For another example, finding crackles on physical examination has only a modest positive predictive value for interstitial lung disease or congestive heart failure being the cause of dyspnea, but the absence of crackles essentially rules out both with 98% and 92% confidence, respectively.

The clinical impression based on medical history and physical examination is next supported by objective testing beginning with a chest radiograph. Abnormal findings on chest radiograph should be pursued as potential causes of dyspnea. The absence of findings on chest radiograph has a high negative predictive value (91%) in excluding many thoracic disorders capable of causing dyspnea.[9]

After the chest radiograph, additional objective testing is warranted to establish the cause of the patient's dyspnea. Without objective testing beyond history, examination and chest radiograph, diagnoses may be incorrect approximately 33% of the time.[1] Several tests are important in evaluating the causes of chronic dyspnea and most of them are useful because of their high negative predictive values for ruling out specific diagnoses[9] (Table 20.2). For example, spirometry is useful for ruling out COPD with 100% confidence and negative bronchial provocation studies (e.g. methacholine inhalation challenge) are useful for ruling out a diagnosis of symptomatic asthma with nearly 100% confidence.

Cardiopulmonary Exercise Testing (CPET) can be very helpful in identifying the underlying cause of dyspnea.[3,17] Observing the ventilatory responses and

TABLE 20.2: Laboratory tests useful in the evaluation of unexplained dyspnea*

Pulmonary function tests
- Spirometry with flow-volume loops
- Spirometry before and after bronchodilator
- Methacholine inhalation challenge
- Lung volumes
- Diffusing capacity
- Arterial Blood Gas (ABG)
- Pulse oximetry at rest and during exertion
- Maximal inspiratory and expiratory mouth pressures
- Cardiopulmonary exercise testing
- Hyperventilation provocation testing

Radiographic imaging
- Chest radiographs
- Chest and neck Computed Tomography (CT) scans

Noninvasive cardiovascular tests
- Blood B-Type Natriuretic Peptide (BNP)
- D-dimer
- Electrocardiogram
- Echocardiography
- Cardiac stress test

Gastrointestinal testing
- Modified barium swallow
- Barium esophagography and/or 24-hour esophageal pH and impedance monitoring

Invasive testing
- Lung biopsy
- Cardiac catheterization

*For more complete listing and suggested sequence of testing, see reference 3.

changes in gas exchange during exercise can help distinguish cardiac from pulmonary causes of dyspnea, provide evidence of deconditioning, and help identify patients with psychogenic causes of dyspnea.

Normal patients will exercise to their predicted maximum heart rate and, at that point, still have substantial breathing reserve (20 to 40%) compared to their predicted maximum minute ventilation. In cardiac disease, heart rate is maximum at a low workload, there is still substantial pulmonary reserve, the oxygen pulse (oxygen consumption divided by heart rate) is low and the anaerobic threshold is low. Distinguishing a cardiac limitation from deconditioning can be difficult with CPET unless ischemia, arrhythmias, or significant changes in blood pressure are documented by ECG and blood pressure monitoring. Typically, deconditioned patients show a low maximum oxygen consumption and low anaerobic threshold. In contrast, patients with a pulmonary limitation to exercise have a low breathing reserve and do not reach maximum predicted heart rate during exercise. They may show oxygen desaturation, show abnormalities of gas exchange, or have evidence of airway obstruction on postexercise spirometry. Patients with psychogenic dyspnea may have a normal CPET study or, with anxiety/hyperventilation syndromes, demonstrate hyperventilation at rest, but an increase in carbon dioxide as exercise first begins.

Determining the underlying cause of dyspnea depends, whenever possible, on observing that specific therapy eliminates or improves the symptom. Because causes of dyspnea may coexist simultaneously, partially successful therapy should not be discontinued as new therapeutic trials are attempted. Instead, add therapies sequentially.

TREATMENT

Specific

The best treatment of dyspnea is specific treatment directed at the underlying cause of the symptom. In one study, 76% of patients improved with specific therapy.[9] All patients with asthma, UACS, psychogenic causes, deconditioning, or GERD improved with specific therapy. Fewer patients improved with specific therapy for COPD (33%), interstitial lung disease (58%) and cardiomyopathy (78%). It is beyond the scope of this chapter to comprehensively review the treatment of even the most common causes of dyspnea. Readers are referred to the chapters that specifically focus on these diseases.

Specific therapy for obesity/deconditioning, psychogenic causes of dyspnea, and neuromuscular diseases should not be overlooked.[3] For obesity or deconditioning, both respond to diet and exercise. Consultation with a dietician and a regular, daily exercise regimen can decrease dyspnea at maximum treadmill workload, with most patients showing some improvement within three months.[3,18] For the psychogenic causes of dyspnea and hyperventilation syndromes, patients often respond to education, reassurance and breathing retraining strategies.[3,19,20] For panic disorder, many patients are helped by counseling, behavioral breathing strategies, and pharmacological intervention if necessary. For neuromuscular diseases, specific interventions designed to increase muscle effectiveness are available. In quadriplegia and potentially other diseases characterized by muscle weakness, patients may benefit from inspiratory muscle trainers aimed to increase muscle hypertrophy and strength in inspiratory muscles still innervated.[21] For patients with cervical injuries resulting in diaphragm paralysis, diaphragmatic pacing can help. Resting weak muscles with nocturnal or intermittent positive pressure mechanical ventilation may help some patients with severe muscle weakness due to diseases, such as amyotrophic lateral sclerosis or muscular dystrophy.[22]

Nonspecific

Nonspecific therapy is aimed at the symptom rather than the underlying cause of dyspnea.[3] Many nonspecific therapies for dyspnea have been proposed and these include nutritional support;[23] conditioning regimens;[24] stress reduction; teaching coping skills;[25] respiratory muscle training;[26] supplemental oxygen;[27] noninvasive or invasive mechanical ventilation; vagotomy; muscle vibration techniques; acupuncture; and pharmacotherapy[28] with narcotics, anxiolytics, phenothiazines; and furosemide. The efficacy of these various treatments has not been well established with the exception of nutritional support for patients with COPD.[23]

Some recent evidence suggests that inhaled furosemide may relieve exertional dyspnea in healthy subjects and subjects with COPD,[29-31] although the mechanisms are not clear and probably multifactorial.[32] In 20 subjects with COPD, a single dose of inhaled furosemide decreased dyspnea during exercise and exercise endurance time increased by 1.65 minutes.[32] However, the clinical role of inhaled furosemide is not yet established and awaits larger, multicenter trials.

Although benzodiazepines and opiates have roles in treating dyspnea in the terminally ill cancer patients,[33] their roles in the relief of chronic dyspnea are less clear. Benzodiazepines at low doses are prescribed by some physicians to treat intractable, chronic breathlessness, but there is very little clinical evidence to support this practice. Similarly, the use of nebulized opiates to relieve intractable dyspnea has been proposed, but most studies show no benefit.[28,34] There is more evidence supporting the use of low doses of oral opiates.[28,35] In one randomized and controlled 4-day crossover study, 48 patients who mostly had COPD as the cause of intractable dyspnea were given 20 mg of sustained release morphine per 24 hours.[36] There were documented improvements in dyspnea and improved sleep. However, the severity of a patient's baseline dyspnea was not predictive of a response to the opiates. Whether the relief may persist during treatment longer than four days is not known. It should be noted that the Global Initiative for Chronic Obstructive Lung Disease (GOLD) does not recommend the use of low dose opiates in severe COPD.[37] Because of the potential risk for respiratory depression, the use of opiates for intractable dyspnea needs to be done on a case-by-case basis with due respect for potential side effects.

In summary, dyspnea is the distressing sensation that breathing is difficult, labored or unpleasant. The symptom is nonspecific because it is caused by many cardiopulmonary disorders. The evaluation of dyspnea in a patient begins by establishing whether the symptom is acute or chronic and this is followed by a detailed medical history and physical examination. Guided by history and physical examination findings, laboratory testing then is used to establish the underlying diagnosis. For this, chest radiographs, pulmonary function tests and Cardiopulmonary Exercise Testing (CPET) are frequently helpful. In general, treatment is aimed at the specific underlying diagnosis. However, nonspecific therapies aimed at the symptom rather than the diagnosis also play a supplementary role in the relief of dyspnea.

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Wheeze and Respiratory Disease

J Mark Madison, Richard S Irwin

INTRODUCTION

Wheeze is either a symptom reported by a patient or a sign heard on the auscultation of the chest and neck during physical examination. Wheezes indicate airway obstruction somewhere in the respiratory tract and are defined as continuous musical sounds (approximately 100–1000 HZ) lasting more than 80–100 msec, but usually not more than 250 msec.[1-4] They can be inspiratory or expiratory, high or low pitched, consist of single or multiple musical tones and originate from any airway, either inside or outside of the thoracic cavity.[1-4] Stridor is a special type of wheeze and refers to inspiratory wheezing heard loudest over the central large airways of the chest and neck.

It is fundamental to understand that wheezing is a nonspecific finding that simply signifies the presence of airway obstruction, not its cause. It is not, by itself, diagnostic of any specific respiratory disease. Evaluation of the cause of wheezing begins with a medical history and physical examination and should be supplemented by diagnostic studies such as pulmonary function tests. In general, treatment of wheezing is specifically directed at the identified, underlying disease causing the airway obstruction, but nonspecific supportive therapy may be needed until definitive therapy is effective.

PHYSIOLOGY OF WHEEZE

Wheezes are caused by obstruction to airflow, but precisely how airway obstruction causes wheeze is not known.[5] Most likely, wheezes are caused by the oscillations or fluttering of airway walls and secretions in the airways. In accordance with the Bernoulli's principle describing the relationship between gas flow and pressure, air moving through an airway increases in velocity when it encounters a segment of airway that is narrowed. The higher gas velocity means lower airway pressure in that local region and, therefore, there is a tendency for the airway wall to collapse inward slightly. As the collapse increases, the worsening obstruction decreases airflow and increases pressure in the airway. Higher airway pressure in turn pushes the airway wall outward, partially relieving the obstruction and then the cycle starts again. This inward and outward movement of the airway wall happens cyclically to create an oscillatory vibration that is heard as a musical tone on the auscultation of the chest.

HISTORY AND PHYSICAL EXAMINATION

It is a common error to assume that the site(s) of airway obstruction can be reliably determined by physical examination. Determining the phase of the respiratory cycle (inspiratory vs expiratory) when wheezing is heard and noting the timbre of the wheezing (monophonic vs polyphonic) may be helpful clinically when combined with the other elements of patient evaluation, but these characteristics cannot, by themselves, be used to reliably identify the sites or causes of wheezing.

Inspiratory wheezing is neither a sensitive nor specific indicator of extrathoracic airway obstruction. It is true that extrathoracic obstruction of a large airway tends to produce inspiratory wheezing, because negative airway pressure during inspiration tends to augment the degree of narrowing as airway tissue collapses slightly inward.

However, inspiratory wheezing is an insensitive method of detecting extrathoracic obstruction since the lumen diameter must decrease to approximately 5 mm to produce stridor clinically.[6] Moreover, inspiratory wheezing is a nonspecific finding because inspiratory wheezing is frequently heard with expiratory wheezing due to intrathoracic obstruction in large or small airways such as obstruction due to asthma.[2,7] Moreover, wheezing due to asthma may sometimes be heard only on inspiration.

Expiratory wheezing by history or physical examination is neither sensitive nor specific for diagnosing asthma. Symptomatic asthma can present without wheezing and wheezing caused by other diseases can mimic the wheezing of asthma. In one clinical study, only 35% of patients referred to a pulmonary clinic for a history of difficult to diagnose wheezing ultimately proved to have asthma upon further evaluation.[8] Similarly, only 43% of patients with monophonic (see below) expiratory wheeze on physical examination proved to have asthma as the underlying cause of the wheeze.

The pitch of wheeze also does not indicate where, in the respiratory tract, the obstruction to airflow is located.[9] However, wheezing that sounds as though there are multiple different musical notes, so-called polyphonic wheezing, typically represents vibrations emanating from the large, central airways of the chest. In contrast, multiple wheezes of a single pitch (monophonic) typically reflect obstructions in the small, more peripheral, airways; however, monophonic wheezes can emanate from the vocal cords. Therefore, this distinction between monophonic and polyphonic wheezing is a general, not absolute, one and has not been studied clinically for its predictive and diagnostic accuracy.[2] Therefore, the timbre of wheezing may be helpful as additional clinical information, but should not be relied on exclusively for diagnostic decisions.

It should be emphasized that the loudness or amplitude of wheezing is not a reliable indicator of the severity of airway obstruction.[3,7,10,11] Because wheezing depends on airway narrowing and the amount of airflow, the amplitude of wheezing may be low even when there is severe obstruction present because there is very little airflow. For one classic example of this, it is an ominous finding when a patient with a severe exacerbation of asthma has a "silent chest" on physical examination.

PULMONARY FUNCTION TESTING

Spirometry and flow-volume loops can help a physician determine whether the airway obstruction causing wheeze is located in the extrathoracic upper airways, intrathoracic upper airways, or intrathoracic lower, small (< 2 mm diameter) airways.[2,3] These different regions of the airways have distinguishing physiologic characteristics that make pulmonary function testing informative when evaluating the cause of wheeze.[2,3,12,13]

Extrathoracic upper airway lesions can be located in the mouth, pharynx, larynx or extrathoracic trachea.[2,3,11,12] The word "variable" is used to describe an obstructed region of the airway that is pliable or deformable enough that the size of the lumen diameter is variable at the site of the obstruction depending on whether the patient is inspiring or expiring. Outside the thoracic cavity, the lumen diameter of the airway depends on the difference between lumen air pressure and atmospheric pressure. When a patient inspires, the airway lumen pressure becomes negative compared to atmospheric pressure and the pliable tissues of the airway collapse inward slightly (Fig. 21.1). When the patient expires, extrathoracic lumen air pressure is positive relative to atmospheric pressure and the airway wall is forced outward increasing the lumen diameter (Fig. 21.1). If there is a partially obstructing lesion narrowing the extrathoracic airway at a single point, this inward collapse during inspiration and outward movement during expiration can produce higher maximal air flows during expiration compared to inspiration. This physiology is best detected by performing flow volume loops during spirometric testing in the pulmonary function laboratory. In the presence of a variable extrathoracic lesion, inspiratory flows are limited and there is, therefore, a flow limitation or

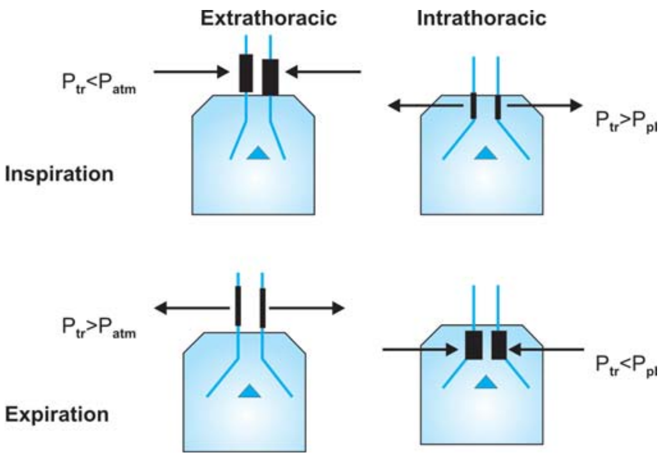

Fig. 21.1: Physiology of upper airway obstruction. Transmural pressure changes during inspiration and expiration affect the diameter of the airway lumen differently depending on whether the single site of obstruction is inside the chest cavity (intrathoracic) or outside the chest cavity (extrathoracic)

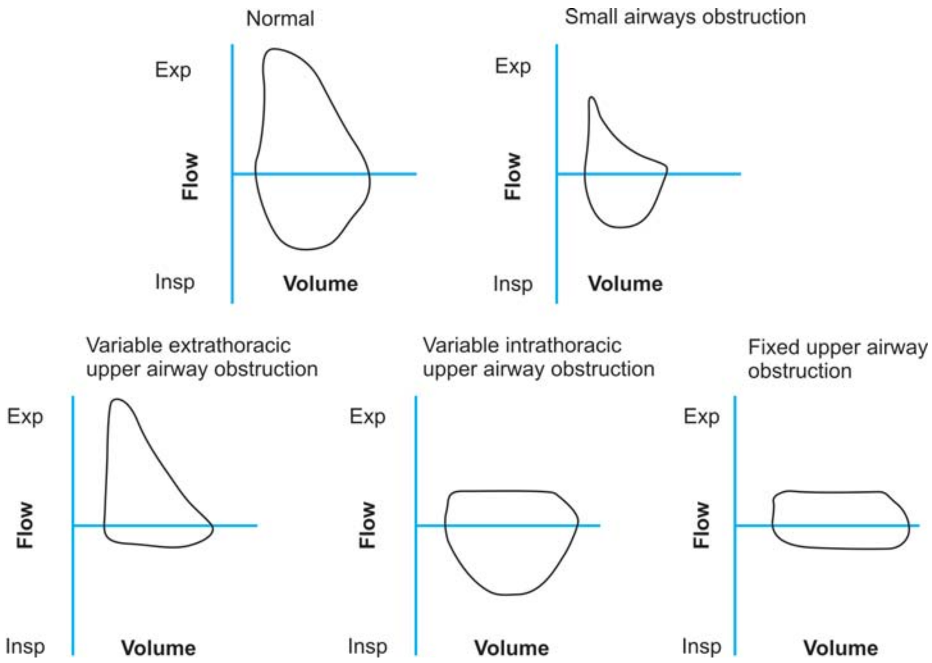
Normal
Small airways obstruction
Variable extrathoracic upper airway obstruction
Variable intrathoracic upper airway obstruction
Fixed upper airway obstruction
Exp
Flow
Insp
Volume

Fig. 21.2: Flow-volume loop configurations for airway obstruction. Flow-volume loops are useful for identifying the site of airway obstruction causing wheezing. For small, lower airways obstruction, there is a characteristic concave upward appearance on the expiratory limb of the flow-volume loop. For obstructions of the large upper airways, distinct patterns are evident for intrathoracic and extrathoracic sites of obstruction

“plateau” on the inspiratory limb of the flow-volume loop (Fig. 21.2). On the expiratory limb of the flow-volume curve, there is no corresponding flow limitation or plateau. When inspiratory and expiratory flow rates at 50% of vital capacity are compared, the ratio of the two is characteristically less than one. The patient having this pattern on the flow volume curve is said to have a variable extrathoracic upper airway obstruction.

A variable intrathoracic upper airway lesion has the opposite pattern on flow-volume loops because lumen diameter in intrathoracic airways is determined by the difference between lumen air pressure and pleural pressure.[2,3,12,13] During inspiration, pleural pressure is negative relative to lumen pressure and the pliable walls of the airways are pulled outward to increase lumen diameter (Fig. 21.1). During expiration, the opposite is true and the pliable airway walls collapse inward slightly (Fig. 21.1). If there is a partial narrowing of the airway at a single point, these differences in lumen diameter during inspiration and expiration can produce significant changes in airflow that, again, are best assessed on flow-volume loops. In the presence of a variable intrathoracic lesion, inspiratory flows may be unaffected by the presence of the lesion and so the inspiratory limb of the flow-volume loop appears normal or nearly normal. However, on expiration, when the airway diameter is smaller due to positive pleural pressure, there is a flow limitation or plateau on the expiratory limb of the flow-volume loop (Fig. 21.2). The patient having this pattern on the flow-volume loop is said to have a variable intrathoracic upper airway obstruction.

When the single obstructing lesion is “fixed” rather than variable, it means that the tissue at the site of the lesion is not pliable or deformable enough to allow significant changes in airway lumen diameter during inspiration and expiration. Therefore, the pattern on flow-volume loop is characteristically abnormal during both inspiration and expiration and there is a flow limitation or plateau on both limbs of the flow-volume loop (Fig. 21.2).

Unlike upper airway lesions, obstruction in the small intrathoracic airways is almost always at multiple scattered sites impeding airflow in a nonuniform manner. Diseases, such as asthma and Chronic Obstructive Pulmonary Disease (COPD) are among the most common causes of wheezing due to small airway obstruction. Spirometry is the main method of detecting and quantifying this airway obstruction.[14] The Forced Expired Volume in 1 Second (FEV_1) and the Forced Vital Capacity (FVC) are both reduced, but the FEV_1 is reduced out of proportion to the FVC such that the FEV_1/FVC ratio is abnormally low (less than the lower limit of predicted normal). For obstruction, an FEV_1 less than 50% of predicted, or less than 1 liter, indicates "severe" airway obstruction. The flow-volume loop of a patient with obstruction of the lower airways characteristically shows a concave upward appearance on the expiratory limb of the flow-volume loop (Fig. 21.2). Spirometry repeated after the inhalation of drugs or medications or after a treatment course can also be helpful in evaluating the causes of airway obstruction.[2,3] For example, in the presence of airway obstruction, spirometry repeated after the administration of bronchodilator or after a course of corticosteroids may reveal the presence of reversible airway obstruction consistent with a diagnosis of asthma. For another example, in the absence of airway obstruction at baseline, a nonspecific bronchoprovocation challenge test (e.g. methacholine inhalation challenge test) may reveal the presence of bronchial hyperresponsiveness consistent with a diagnosis of asthma.

It is sometimes possible to detect coexisting small and large airway obstructions by taking advantage of the fact that helium is less dense than air. Airflow in small airways, having mainly laminar flow, is unaffected by substituting less dense helium for the nitrogen in air.[2,3,15] However, in large airways, where there is much turbulent gas flow, breathing a helium-rich gas mixture allows higher rates of gas flow compared to breathing air. Therefore, if a comparison of maximal expiratory flows for breathing air versus heliox (20% oxygen/80% helium) shows significantly greater gas flow with the helium mixtures, the patient is likely to have an obstructing lesion in a large airway with turbulent gas flow as part of his/her problem.

DIFFERENTIAL DIAGNOSIS FOR WHEEZING

Because the causes of airway obstruction are multiple, it is not surprising that wheezing appreciated by history or physical examination is a nonspecific finding.[8] Any cause of airway narrowing can result in wheezing and these causes include dynamic collapse of the airways; bronchospasm; airway wall edema, thickening or inflammation; airway secretions; remodeling of the airways; distortions of airway anatomy; and any compressing or partially obstructing mass (Table 21.1). It is a common error of physicians to mistakenly assume that all wheezing is due to asthma and this pitfall in evaluation should be avoided.

TABLE 21.1: Causes of wheeze*

Extrathoracic upper-airway obstruction
Anaphylaxis
Cricoarytenoid arthritis
Epiglottitis (supraglottitis)
Hypertrophied tonsils
Laryngeal edema
Laryngocele
Malignancy
Obesity
Postnasal drip due to rhinosinus disease (now referred to as UARS)
Relapsing polychondritis
Retropharyngeal abscess
Vocal cord dysfunction or paralysis
Intrathoracic upper-airway obstruction
Benign and malignant tracheal and bronchial tumors
Foreign body aspiration
Goiter (intrathoracic)
Herpetic tracheobronchitis
Right-sided aortic arch
Tracheal stenosis postintubation
Tracheobronchomegaly
Tracheomalacia
Intrathoracic lower-airway obstruction
Anaphylaxis
Aspiration
Asthma
Bronchiectasis
Bronchiolitis
Carcinoid syndrome
Chronic obstructive pulmonary disease
Cystic fibrosis
Lymphangitic carcinomatosis
Parasitic infections
Pulmonary edema
Pulmonary thromboembolism
Tracheobronchitis

*Table adapted from Reference 3. See Reference 3 for more detailed and referenced list. UARS is upper airway cough syndrome

One clinical study examined the spectrum and frequency of the causes of wheezing among patients referred to a pulmonary clinic for evaluation[8] (Fig. 21.3). Thirty-four patients with wheezing of unclear etiology were referred to an ambulatory pulmonary clinic for further evaluation that included methacholine inhalation challenge testing. Interestingly, only 35% of these patients had methacholine challenge tests that were consistent with asthma being the underlying cause of their wheezing. The most common cause of wheeze among these patients was not asthma, but, instead, postnasal drip syndrome (46% of cases).[16] Postnasal drip syndrome (now referred to as upper airway cough syndrome or

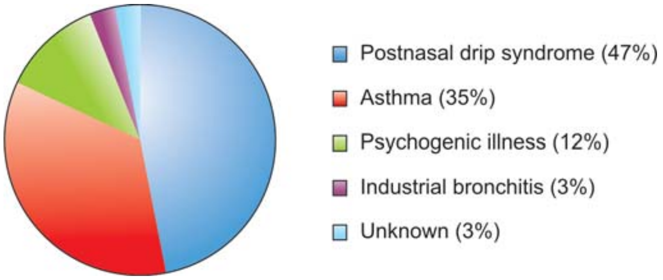

Fig. 21.3: Spectrum and frequency of the causes of wheezes. Adapted from reference 8. In this study, patients referred to a pulmonary clinic for difficult to diagnose wheezing were evaluated. Postnasal drip syndrome (now referred to as UACS) was the most common cause of difficult to diagnose wheezing among these patients. Vocal cord dysfunction syndrome is an example of a potential psychiatric illness presenting as wheeze

UACS) is a common condition and known to cause upper airway obstruction so it is not surprising that it can commonly result in wheezing.

Assessing the acuity of wheezing and the patient's overall clinical condition is an important part of the clinical evaluation and this is helpful in narrowing diagnostic possibilities, assessing the urgency of the clinical situation and planning management. For acute onset wheezing, the physician must assess the overall clinical presentation and judge whether there is a life-threatening cause of the wheezing. If so, the physician must rapidly institute specific therapy directed at the underlying disease process and support the patient until that specific therapy has had time to be effective. Obviously, not all acute or recent onset wheezing represents an urgent medical condition and that is why clinical judgment is used to assess the overall clinical presentation. It is beyond the scope of this chapter to comprehensively review the diagnosis and management of the many different diseases that cause wheezing (Table 21.1). Instead, selected diseases will be emphasized and categorized anatomically as either upper or lower airway conditions.

Upper Airway Conditions

UACS is a common cause of upper airway obstruction and therefore a common cause of wheezing.[8] The condition may be either acute or chronic and is caused by many rhinosinus diseases.[16] Acute presentations are most commonly due to the common cold. Chronic presentations can be due to allergic, perennial, non-allergic, postinfectious, environmental irritant, and vasomotor rhinitis and/or sinusitis. Consider the diagnosis when a patient describes the sensation of secretions or dripping in their throat, the frequent need to clear their throat, or frequent nasal discharge, or if patients are heard to frequently clear their throats even when they are not aware of doing it. Mucoid or mucopurulent secretions in the oropharynx or a cobblestone appearance of the pharyngeal mucosa suggest the diagnosis on physical examination.

Epiglottitis (supraglottitis) is an acute, potentially life-threatening, infection of the supraglottic region of the upper airway.[17] The infection can be caused by bacteria, viruses, or fungi, but *Haemophilus influenzae* is the most common cause. In adults, consider the diagnosis if the complaint of acute or recent onset throat pain is severe and out of proportion to the inflammation seen on physical examination of the posterior oropharynx, especially if there is respiratory distress, fever, drooling, and changed voice. Lateral neck radiographs and computed tomography of the neck can be helpful in further clinical evaluation.

Vocal cord dysfunction syndrome can cause wheeze or stridor because the upper airway is obstructed by the paradoxical adduction of the vocal cords during inspiration.[18,19] The syndrome is thought to be frequently due to emotional distress or trauma and may be difficult to diagnose when the symptoms are intermittent. It can be difficult to distinguish from asthma and, in fact, sometimes coexists with asthma.[18] An arterial blood gas may be helpful in distinguishing wheezing due to vocal cord dysfunction from that due to small airway obstruction because the alveolar-arterial oxygen tension difference would be expected to be high in asthma, but not in upper airway obstruction. Early and abrupt decreases in flow rates during inspiration on flow-volume loop can suggest the diagnosis, but usually the diagnosis is confirmed endoscopically by observing the movement of the unanesthetized vocal cords during inspiration. While initially thought to be provoked by psychogenic factors, the syndrome has also been reported in elite athletes during vigorous exercise and associated with UACS and Gastroesophageal Reflux Disease (GERD).

Laryngotracheal injury caused by endotracheal intubation is another potential cause of upper airway obstruction and, therefore, wheezing.[20] The injury can occur during the process of intubation or as a result of an endotracheal tube being in the airway for a prolonged period of time. The tissue injury can lead to obstruction in the supraglottic regions of the upper airway, at the vocal cords, or in the trachea itself. Obstructing tracheal lesions can be due to edema and/or granulation or fibrous tissues that form at the site or near the tip of the endotracheal tube. The condition is often easily missed in patients who were recently intubated for respiratory failure due to asthma or COPD. For example, in follow-up, persistent or poorly resolving respiratory symptoms can be mistakenly ascribed to the patient's underlying asthma or COPD and wheezing due to upper airway obstruction may be missed. The diagnosis should be suspected in any patient who has unexplained or persistent respiratory symptoms, especially wheezing or stridor, following endotracheal intubation. Flow-volume loops and direct endoscopic visualization of the upper airway are frequently helpful in further evaluation; comparing maximal expiratory flows during air and helium/air mixtures may uncover the large airway obstructing component as described above (see section on Pulmonary Function Testing).

Lower Airway Conditions

Asthma obstructs large and small intrathoracic airways due to bronchospasm, secretions, and inflammatory infiltration and edema of the airway walls.[21] Asthma is characterized by partially or fully reversible airway obstruction and bronchial hyperresponsiveness. Wheezing in patients with asthma may be chronic or absent during the periods of remission. It is important to again emphasize that although asthma is strongly associated with wheezing, not all patients with asthma wheeze. Patients suspected of having asthma should be evaluated with pulmonary function testing. If there is airway obstruction evident on baseline testing, then a 12% increase in FEV_1 or FVC upon the inhalation of bronchodilator (e.g. a short and rapidly acting beta-adrenergic agonist) suggests reversible airway obstruction. If there is no airway obstruction present at baseline, then nonspecific bronchoprovocation testing (e.g. methacholine inhalation challenge) is helpful in establishing the presence of bronchial hyper-responsiveness.[21] Because a positive methacholine challenge test, alone, is not diagnostic of asthma, improvement in asthma symptoms must be observed during specific treatment for asthma in order to establish the diagnosis.

COPD is a disease process consisting of varying degrees of emphysema and chronic bronchitis that leads to chronic airway obstruction.[22] Although COPD can be caused by hereditary diseases (e.g. alpha-1-antitrypsin deficiency), air pollutants from the burning of biomass fuels, and exposure to smoke from cook fires, the most common cause of COPD worldwide is tobacco smoking.[22,23] Whether tobacco is consumed by smoking cigarettes, cigars, pipes, beedi (bidi), hookahs, kreteks, or even the passive inhalation of tobacco smoke, the toxic products of tobacco combustion clearly and widely recognized to be linked to the development of COPD (chronic bronchitis and emphysema) and worldwide. The history or physical finding of wheezing in a moderate to heavy smoker should raise the possibility of COPD and prompt further evaluation for chronic airflow obstruction by pulmonary function testing. Although exceptions are frequently observed, patients with COPD typically have no, or only very small responses to inhaled bronchodilators on pulmonary function testing. However, it is important to consider that, because both COPD and asthma are common, these diseases may coexist in an individual patient.

Pulmonary edema due to congestive heart failure is a well-recognized cause of airway obstruction and wheezing—so called cardiac asthma.[24] Most likely, the airway obstruction is due to airway wall edema and peribronchial edema that narrows the caliber of the lower airways. However, some evidence suggests that bronchial hyperresponsiveness may also play a role in the airway obstruction.[3] Theoretically, any cause of pulmonary edema, whether cardiac or noncardiac, could lead to airway wall edema, airway obstruction and wheezing. When congestive heart failure is suspected as a cause of wheezing, measurement of serum B-Type Natriuretic Peptide (BNP) levels and/or echocardiography may be helpful in further evaluation.

Aspiration of secretions into the airways is common and can lead to respiratory symptoms, including wheezing, especially when the frequency and/or volume of aspiration is high.[25] The wheezing may be due to laryngeal irritation, tracheobronchitis, obstruction of airways from aspirated material, or peribronchial edema. Aspiration as a cause of wheezing should be suspected when there are predisposing factors associated with aspiration and when wheezing is associated with diffuse or multiple focal infiltrates on chest radiograph, especially in a posterior or inferior location. Predisposing factors the clinician should look for include hiatal hernia, Zenker's diverticulum, esophageal dysmotility, nasogastric feeding tubes, GERD, medications that lower esophageal sphincter pressure (e.g. calcium channel antagonists), pharyngeal dysfunction (e.g. strokes, amyotrophic lateral sclerosis), sedative use, alcohol abuse, and advanced age.[3] Diagnostic tests that can be helpful to further evaluate for aspiration include bedside swallowing evaluation, modified barium swallow, and 24 hour esophageal pH and impedance monitoring to assess for GERD.

Acute Venous Thromboembolism (VTE) may result in wheezing and can be confused clinically with the presentation of acute asthma.[26] The wheezing may be due to bronchoconstriction of small airways responding to platelet-derived mediators such as thromboxanes, serotonin and histamine. Typically, bronchospasm due to VTE is poorly responsive to bronchodilators.[26] Because the treatment for VTE is immediate systemic anticoagulation, it is important to at least consider the possibility of VTE in any patient presenting with acute wheezing, especially if there are risk factors for deep venous thrombosis.

Anaphylaxis is a systemic allergic reaction that may obstruct the upper (e.g. laryngeal edema) and lower airways (bronchoconstriction, mucosal edema, airway secretions) to produce wheezing.[27] It is typically of abrupt onset and may feature dyspnea, wheezing, urticaria, angioedema, nausea, abdominal pain, diarrhea and hypotension. It may be due to an acute allergic sensitivity to any agent, but is often due to an allergy against drugs or medications and stinging insects or due to a sensitivity to contrast agents.

Parasitic infections may also cause wheezing. Wheezing has been reported with infections due to species of *Strongyloides, Ascaris, Ancylostoma, Necator, Echinococcus, Toxocara, Schistosoma, Brugia, Dirofilaria*, and filarial species.[3] With an incubation period of 1–2 weeks depending on the species of parasite, Löffler's syndrome is seen in parasitic infections that feature the migration of parasite larva through the lungs during an acute infection. It is recognized clinically as fever, urticaria, wheeze, cough and rarely hemoptysis.[28] Laboratory findings include eosinophilia and migratory and transient infiltrates on chest radiograph. Parasites should be suspected as a cause of wheezing when there is wheeze in a patient without a history of asthma or COPD, when there has been travel or residence in an endemic area, fatigue, weight loss, fever, and infiltrates on chest radiograph.

APPROACH TO THE DIAGNOSIS OF WHEEZE

An approach to the diagnosis of wheezing uses a combination of history, physical examination and pulmonary function testing (Table 21.2). First, identify any associated symptoms or signs that might suggest specific diagnoses. Second, assess whether the wheezing is potentially life-threatening and either acute or chronic, recognize the spectrum and frequency of the causes of wheeze, and then narrow the differential diagnosis by localizing the site of the wheezing to the intrathoracic versus extrathoracic airways.

TABLE 21.2: Diagnostic tests useful in the evaluation of wheeze

Pulmonary function tests
- Spirometry
- Flow-volume loops
- Bronchodilator testing
- Nonspecific bronchial provocation testing
- Spirometry comparing air and oxygen-helium mixtures

Imaging
- Chest radiograph
- Sinus radiographs for assessing sinusitis causing UACS
- Lateral neck radiograph for assessing upper airway obstruction
- Computed Tomography (CT) of the chest, neck or sinuses
- CT angiography for assessing venous thromboembolism
- Echocardiography and other imaging for assessing cardiac function

Endoscopy
- Laryngoscopy
- Bronchoscopy

Evaluation for aspiration
- Bedside swallowing observation
- Modified barium swallow
- 24-hour esophageal pH and impedance monitoring

Blood tests
- Complete blood count and differential to assess for eosinophilia
- B-Type Natriuretic Peptide (BNP)
- D-dimer

Evaluation for parasites
- Stool for ova and parasites
- Microscopic examination of sputum and gastric washings for larva
- Serologic testing for parasites (e.g. schistosoma, strongyloides, filaria)

TREATMENT

Because the causes of wheezes are many, it is beyond the scope of this chapter to review the treatment of all the various diseases and disorders that can cause wheezing. In general, however, treatment of upper or lower airway obstructions should be specific and directed at the underlying disease.

In treating the severely obstructed patient with impending respiratory failure, supportive measures may be needed until specific therapy has had time to be effective. Supplemental oxygen should be administered and the patient's respiratory status monitored closely by clinical examination and oxygen saturation. Oral endotracheal intubation or tracheostomy may be needed to bypass critical obstruction of an upper airway and/or to support gas exchange and increased work of breathing caused by severe upper or lower airway obstructions.

For severe obstructions of the upper airway, helium and oxygen gas mixtures (40% or 80% helium and 60% or 20% oxygen, respectively) can be helpful in supporting the patient as a bridge to more definitive therapy.[29] The density of helium is low and therefore it lowers the resistance and the work of breathing when airflow is turbulent (as in the upper airways) rather than laminar (as in the lower, smaller airways).[30] In contrast, for asthma and COPD, disease processes that obstruct the small intrathoracic airways where air flow is mainly laminar, helium-oxygen mixtures may have a role, but their routine use is controversial and not currently recommended in treatment guidelines.[21,22,31]

In summary, wheezing indicates obstruction to airflow in the lower and/or upper airways. It is important for physicians to recognize that not all wheezing is due to asthma and not all asthma produces wheezes. A broad range of cardiopulmonary diseases and a variety of different infections can cause wheezing, whether the onset and timing be acute or chronic. Evaluation for the underlying cause of wheeze in a given patient, starts with a thorough history and physical examination and can be aided by additional laboratory and radiographic studies, especially pulmonary function testing. In general, treatment of wheezing should be specifically aimed at the identified underlying diagnosis. However, in the acute setting, mixtures of helium and oxygen may provide rapid, temporary relief for severe upper airway obstructions.

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Section

5

RESPIRATORY DIAGNOSIS

SK Jindal

22

History and Physical Examination

PR Gupta

INTRODUCTION

In spite of rapid advances in diagnostic tools and their wide spread availability, clinical history and physical examination continue to play an important role in assessing the medical illness of a patient. Respiratory illnesses are no exception. Optimal time required for history taking, physical examination, formulation of differential diagnosis, decision making and writing the treatment/instructions to the patients is about an hour, but in a crowded outpatient department as in India, this is usually accomplished in 5 to 10 minutes. Hence, it is necessary for every physician to acquire the necessary skills to obtain all important information in the given time to arrive at the clinical diagnosis, without missing the important points. Many a time, quick decisions regarding treatment are required on the basis of clinical evaluation alone. It is true to a great extent that the clinicians are natural bayesians and their reasoning about patients is intuitive, probabilistic, and reiterative.[1] Such subjective, context dependent reasoning is integral to clinical judgment, especially useful when diagnosing rare diseases.

HISTORY TAKING

The guiding principle to history taking is: "Listen to the patient as if he is revealing the diagnosis". Allow the patient to speak about his illness in his own words. Avoid unnecessary interruptions except when it becomes essential to seek details on certain issues. Selective open-ended questions may be asked, but avoid leading questions. Some patients describe their illness aimlessly with irrelevant details. It should be gently curtailed. When a patient is too ill to give a coherent account of his illness, history should be taken from a relative or an attendant. Begin with history of the presenting symptom. Details of time scale of each symptom is essential, whether it is progressive or static, constant or paroxysmal. Ask for aggravating or relieving factors, if any. In respiratory system, common symptoms include cough, chest pain, hemoptysis, shortness of breathing and/or wheezing. Each of the symptoms has been discussed in detail in the respective chapters.

Cough

Cough is a reflexive or deliberate explosive expiratory act. It is a physiological act, meant to clear the airways, but when it becomes troublesome, it prompts a visit to physician. Psychogenic stress may cause or aggravate cough due to organic causes.[2] Chronic maxillary sinusitis, asthma, postviral reactive airway disease syndrome and inhaled foreign bodies commonly cause persistent cough during childhood. In nonsmoker adults, asthma, postnasal drip, reactive airway disease syndrome and gastroesophageal reflux predominate, but in the elderly, asthma, cardiac failure and gastroesophageal reflux are the more common causes of cough (all may lead to nocturnal cough). Use of an angiotensin-converting enzyme inhibitor[3] causing dry cough should always be kept in mind. Smokers usually do not complain of cough, but when it is associated with excessive sputum, blood or dyspnea, it may point to an underlying disease, i.e. Chronic Obstructive Pulmonary Disease (COPD) or bronchogenic carcinoma.

History should cover the duration and characteristics of cough, whether dry or productive of sputum or blood, provocative factors, such as cold, smoke, change of posture or eating, and accompanying symptoms to find out the likely causes, i.e. running nose and sore throat (postnasal drip); fever; chills and pleuritic pain chest (pneumonia); heartburn (gastroesophageal reflux); weight loss and night sweats (chronic infection or tumor); choking sensation and difficulty in swallowing while eating or drinking (aspiration).[4]

Sputum

A patient having productive cough should be asked regarding the time course, amount, character, viscosity, taste and color of the sputum. Early morning sputum in smokers suggest chronic bronchitis, but if it occurs while going to bed, it suggests bronchiectasis or lung abscess. Most children and adult females usually do not spit and swallow their sputum, but its presence should be assessed by the sound of their cough. It is usually not possible to measure the exact amount of sputum, but can be assessed from the number of spits, spoonfuls or cupfuls. Sputum may be very foul smelling in lung abscess or bronchiectasis.

It is better to inspect the sample of sputum as the patient may not be able to describe its exact character, viscosity and color. Sputum may be serous (pulmonary edema, bronchioalveolar carcinoma), mucoid (chronic bronchitis/COPD, asthma) or mucopurulent/purulent (bronchiectasis, lung abscess, pneumonia). Viscous sputum is often difficult to expectorate (asthma). In anaerobic infections, sputum is foul in taste and smell. Sputum is yellow, green or brown in bronchopulmonary infections, green if it contains eosinophils, golden yellow or green in bronchobiliary fistula, rusty in pneumococcal infections, red currant jelly type in *Klebsiella pneumonia*, anchovy sauce colored in ruptured amoebic liver abscess, and black in coal workers pneumoconiosis. Sputum may contain brown or black casts in recovery phase of asthma or Allergic Bronchopulmonary Aspergillosis (ABPA).[5]

Hemoptysis

Hemoptysis is coughing out blood from respiratory tract, mainly the lungs. Mild hemoptysis, often seen as blood streaking, is a common symptom. Lungs have been provided with a dual blood supply namely the low-pressure pulmonary arteries (95%) and the high-pressure bronchial (systemic) arteries (5%). Hemoptysis mostly originates from the later except in the cases of trauma or erosion of pulmonary arteries or inflammation of pulmonary capillaries. Efforts should be made to differentiate true hemoptysis from hematemesis, epistaxis or bleeding from oral cavity by asking the patient about the temporal patterns.[6] Hematemesis generally follows nausea, vomiting or retching; in epistaxis, the patient feels sensation of postnasal drip or bleeding from nares without coughing, but hemoptysis follows coughing. The type of blood can also help to detect the source (bright red often mixed with frothy sputum in hemoptysis versus the dark black, often in clumps and mixed with food, in hematemesis).[6]

History should cover its onset (sudden, recurrent or cyclical), duration, provoking factors (exertion, change of position, exposure to cold, smoke or allergens) and amount (streaking or massive). Hemoptysis is seldom a solitary event. Associated symptoms may provide clue to the cause of hemoptysis, i.e. chest pain (pulmonary embolism), dependent edema, orthopnea and paroxysmal nocturnal dyspnea, fever and cough (pneumonia), weight loss (TB or cancer), bloody nasal discharge (Wegener's granulomatosis), hematuria (Goodpasture's syndrome, Wegener's granulomatosis), and bleeding from other sites or easy bruising (coagulopathy). Enquire about the risk factors as it may provide the likely etiology, i.e. Human Immunodeficiency Virus (HIV) infection or use of immune-suppressant drugs (TB and fungal infections), long-standing smoking history (lung cancer) or a recent history of immobilization, travel for long distances, surgery, pregnancy, cancer or use of oral contraceptives (pulmonary thromboembolism).

Chest Pain

Chest pain is a common complaint, but patient's perception may vary. To some, it is a warning of potential life-threatening illness, they may seek repeated consultations even when the symptom is trivial. Others, including those with serious illnesses, may tend to ignore. However, a physician should never discard the symptom without exploring its etiology. Chest pain may have its origin from disorders of chest wall, pleura, lungs, heart/great vessels, esophagus and subdiaphragmatic structures (Table 22.1).

History of chest pain should include its duration, location (including radiation to other areas, if any) and character, i.e. heaviness, tearing, burning, stabbing, sharp needle like, urge to eructate or merely a discomfort. Precipitating factors, such as physical or psychological stress, respiratory efforts, coughing or swallowing, and relieving factors (such as leaning forward) should be enquired. Associated symptoms like cough, dyspnea,

TABLE 22.1: Common causes of chest pain

	Causes	*Likely character of chest pain*
Pulmonary	Tumors	Mostly dull aching in character
	Pneumonia	Often pleural in character
	Pulmonary embolism/infarction	Central, sharp and sinking in character
Pleural	Pneumothorax	Sharp, stabbing in character, worse on coughing
	Hemothorax	
	Effusion/empyema	
	Pleuritis	
	Tumors	
Cardiovascular	Myocardial ischemia/infarct	Central, sharp and sinking in character, radiating to left arm
	Myocarditis	Mostly dull aching in character
	Pericarditis	Sharp, stabbing in character
	Dressler's syndrome	Sharp, stabbing in character or dull aching
	Dissecting aortic aneurism	Sharp, tearing in character
	Mitral valve prolapsed	Mostly dull aching in character
Esophageal	Spasm	Central lower chest and sharp in character
	Rupture	
	Esophagitis/ulceration	
	Neoplasm	Mostly dull aching in character
	Achlasia	Burning in character
	Diverticula	
	FB	Sharp, stabbing in character
Gastrointestinal	Liver abscess	Sharp and throbbing in character
	Pancreatitis	Sharp, stabbing, radiating to back
	Whipple's disease	Mostly dull aching in character
Chest wall	Skin lesions/herpes zoster	Sharp and sometimes throbbing in character
	Breast lesions	Mostly dull aching in character
	Musculoskeletal lesions	Often with cough, dyspnea and fever
	Infection/tumor in spine/rib	Localized and sharp
	Trauma	Often pleural in character, local tenderness
Mediastinal	Tumors	Mostly dull aching in character
	Inflammation	Central and sharp in character
Referred pain	Abnormalities of subdiaphragmatic structures	Boring in character, no local tenderness
Miscellaneous	Subdiaphragmatic abscess	Sharp and throbbing in character
	Psychoneurosis	Always severe, worse in presence of attendants

palpitation, syncope, diaphoresis, nausea, vomiting, fever and chills, weakness, malaise and weight loss should be asked for. Leg pain and swelling may point to deep vein thrombosis and pulmonary thromboembolism.

Dyspnea

Dyspnea is an unpleasant or uncomfortable awareness of breathing. In most situations, it occurs due to an imbalance between neurological stimulation and the mechanical changes that occurs in the lungs and the chest wall, the resulting mismatch of ventilation and its demand.[7] A variety of scaling methods have been used to quantify dyspnea, i.e. Borg Category Scale, Visual Analogue Scale and American Thoracic Society Scale, but none can be universally applied to all the patients.[8] For epidemiological purposes, the one suggested by the Medical Research Council is quite useful.[9]

A host of pulmonary, cardiac or other disorders may lead to dyspnea. History should cover its duration, onset (sudden or insidious), severity and exacerbating or relieving factors like exertion or rest, supine or sitting position and exposure to cold, dust, smoke or allergens. Associated symptoms may provide useful clue to the cause of dyspnea, i.e. chest pain (pulmonary embolism, myocardial infarction), dependent edema, orthopnea or paroxysmal nocturnal dyspnea (cardiac failure), wheezing (asthma), fever or cough (pneumonia), black stools or heavy menses (anemia) and weight loss (TB or cancer). A patient with psychogenic dyspnea is symptomatic more often during rest than on exertion.

Upper Respiratory Tract Symptoms

A brief history of upper respiratory tract symptoms, more particularly running of nose, itching, sneezing, congestion, discharge of blood or blood mixed secretions or blocked nose, should always be obtained while assessing a patient for respiratory illness. These symptoms may point to specific respiratory (asthma) or systemic illnesses (sarcoidosis, Wegener's granulomatosis, etc.).

General Symptoms

Once the assessment of the respiratory symptoms is over, the patient should be asked for the presence of general symptoms and those pertaining to other systems. Presence of fever, loss of appetite, weight loss or anemia signifies serious illness. History of associated urinary symptoms, dysphasia, joint pain and skin lesions may point to an important systemic illness. Symptoms pertaining to cardiac and neuromuscular diseases may unravel the cause of respiratory illness, particularly of dyspnea.

HISTORY OF PREVIOUS DIAGNOSIS AND TREATMENT

Most patients visit a pulmonologist only after consulting their family physician. It is always worthwhile to ask the patient about the details of such consultations, investigations already done, diagnosis made, treatment offered and the outcome thereof. Often, a correct diagnosis is missed for want of time and skill, but even if a diagnosis is made, the treatment may be wanting in the terms of drugs, dosages and compliance. Past history of incorrect or irregular treatment of tuberculosis (TB) may have resulted in drug failure (and drug resistance), relapse, bronchiectasis, aspergilloma or chronic necrotizing pulmonary aspergillosis.[10] Drugs taken for other illnesses may be responsible for the current illness, e.g. busulphan causing pulmonary fibrosis, ACE inhibitors causing cough, aspirin and Nonsteroidal Anti-inflammatory Drugs (NSAIDs) causing asthma, and so on.

Past Medical History

Past medical history of the patient, many a times, gives an important clue to the etiology of the current illness. Ask about childhood illnesses like fever, cough and cold, more so, if it is recurrent, as these may end up in asthma, COPD or bronchiectasis during adult life. History of wheezy bronchitis in childhood may unravel the diagnosis of asthma in adults. Chest injuries in past (particularly those with hemothorax) may end up in frozen chest. History of recurrent loss of consciousness in the past may point to lung abscess. Surgery or pregnancy in recent past suggests pulmonary thromboembolism. Indeed, history of infections, trauma, surgery, malignancies or prolonged bed rest in past, all may provide important clue to the diagnosis of the current illness.

Important lifestyle diseases that may have impact on respiratory system include diabetes mellitus and obesity. Also assess for allergy to food, drugs and/or dust, as this may give an important clue to the diagnosis of rhinitis/asthma. At times, comparison of the recent chest radiograph with the old may provide great diagnostic value.

Personal History

Patient's lifestyle and personal habits like smoking or alcohol consumption, along with the details of the quantum, frequency and its duration, are integral parts of a good history-taking. Exposure to pets and animals may be responsible for serious or recurrent respiratory illness. Present or past occupational exposure to organic dust like bagasse or hay or inorganic dust like silica, coal or asbestos may some times help to unravel the diagnosis in most difficult situations. History of extramarital or promiscuous sexual practices may point to the coexisting HIV and acquired immunodeficiency syndrome (AIDS) or other infections.

THE PHYSICAL EXAMINATION

After the history-taking, the clinician has already some idea regarding the likely diagnosis and what to expect of the physical examination. However, a systematic approach to physical examination is always rewarding and may obviate the need of unnecessary investigations at a later stage. This includes a general physical and respiratory system examination as well as a quick review of other systems. For details regarding the methods of examination, the reader is referred to various books on clinical methods in medicine.[11-13]

General Physical Examination

Always begin by examining the general appearance of the patient, breathing pattern and the recording of vital signs, such as the rate, rhythm and character of pulse and respiration, blood pressure and temperature. An anxious look indicates acute illness while the presence of fatigue and cachexia point to a chronic disease or malignancy. A plethoric appearance may be seen in polycythemia, most commonly as a result of chronic lung disease or Superior Vena Cava (SVC) obstruction (Fig. 22.1). Look at the tongue, soft palate and the nail beds for cyanosis, anemia or polycythemia, at fingers for clubbing, at face, neck, hands and feet for edema; and at neck for any lymphadenopathy or abnormal pulsations/fullness of veins. Look for nicotine stains on the intertriginous surfaces of the second and third fingers (in cigarette or *bidi* smokers) or the palm (in *chillum* or *hookah* smokers). Note down wheeze, stridor or voice abnormality, if any.

Breathing Pattern

Breathing pattern should be observed throughout the clinical examination. Normal breathing is quiet with a frequency of between 12 and 18 per minute. An increased respiratory rate (tachypnea) is seen in the presence of anxiety, anemia, asthma, restrictive lung diseases, pulmonary artery hypertension and hypoxia of any etiology. A slow respiratory rate (bradypnea) may be attributed to decreased respiratory drive as a result of drug overdose or lesions of the central nervous system. Use of the accessory muscles of respiration or pursed lip breathing, which indicate severe illness, should be recorded. Noisy breathing indicates the narrowing of central airways, such as from carcinomatous lesions of vocal cord or trachea, or intrinsic lesions of vocal cords like palsies. When such obstruction is severe, the sound assumes a musical note on inspiration, occasionally during expiration also. This is called as croup or stridor. Wheezy breath sound, audible to unaided ears, are produced by the narrowing of intrathoracic airways, e.g. in asthma. Periodic breathing patterns, including Cheyne-Stokes and Biot's breathing, are usually associated with left heart failure and disorders of the central nervous system. In Kussmaul breathing, the depth of respiration is increased more than the rate. This pattern most often occurs in severe metabolic acidosis, but may be seen in an anxious person. The resultant hyperventilation in the latter may lead to respiratory alkalosis, weakness, dizziness and muscle cramps (tetany).

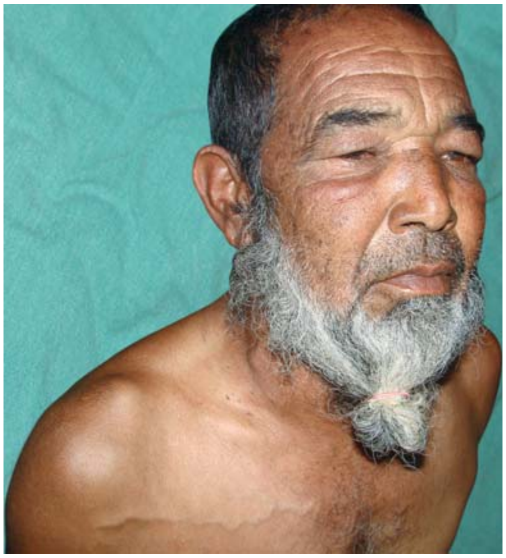


Fig. 22.1: Plethoric appearance of face in a patient with superior vena cava obstruction

Cyanosis

Cyanosis is the bluish discoloration of the tongue and the soft palate (central, when it mostly reflects arterial hypoxemia) or of nail beds and lips (peripheral, when it may reflect arterial hypoxemia due to low blood flow). Methemoglobinemia or sulfhemoglobinemia also causes bluish discoloration of the tongue and the soft palate, the nail beds or the lips. Severe chronic hypoxemia, pulmonary or cardiac, responsible for central cyanosis (Table 22.2) is often associated with polycythemia.

TABLE 22.2: Common causes of cyanosis

Pulmonary	*Cardiac*	*Others*
Pneumonia	Pulmonary edema	Central apneas
Atelectasis	Congenital heart disease	High altitude
Asthma/COPD	Pulmonary thromboembolism	
Interstitial lung diseases	Decreased cardiac output	
Pulmonary AV fistulas		

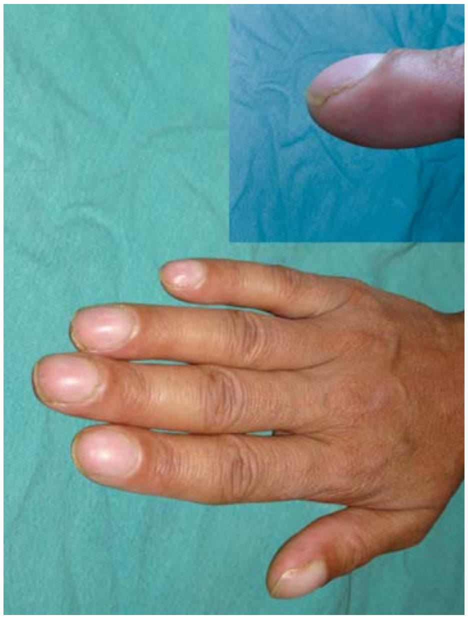


Fig. 22.2: Clubbed fingers. Insert showing the same in side profile. Note the convexity of nail and the loss of the normal angle between the base of the nail and the adjacent dorsal surface of the finger

Peripheral cyanosis (often with edema) affecting face, neck (and sometimes the upper limbs) may indicate SVC obstruction, and that of lower limbs, the inferior vena cava obstruction. In carbon monoxide poisoning, the organs are discolored as cherry red.

Clubbing

Clubbing is characterized by the diffuse bulbous enlargement of the terminal phalanges (Fig. 22.2). Early changes consist of thickening of the fibroelastic tissue of the nail bed, which can be detected by the loss of the normal angle between the base of the nail and the adjacent dorsal surface of the finger. This finding is demonstrated best when the finger is viewed from the side. Finger clubbing can occur in various pulmonary, cardiac and abdominal diseases (Table 22.3). Rarely clubbing may be congenital (familial) in origin. With time, it may progress to Hypertrophic Pulmonary Osteoarthropathy (HPOA). At this stage, the patient may complain of bone or joint pains.

Lymphadenopathy

Lymphadenopathy is abnormal enlargement of lymph glands (> 0.5 in size) at neck, axilla, groin and other external or internal sites. Note down the number, size, consistency and fixity of the lymph nodes to each other, the underlying tissues or to the overlying skin. Large fixed masses indicate metastasis, while firm and matted nodes may point to tuberculosis. Lymph nodes in Hodgkin's lymphoma are classically described as large, soft and rubbery in character.

Miscellaneous Physical Findings

Upper respiratory tract (nasal cavity, nasopharynx, nasal sinuses, oropharynx and the larynx) needs to be examined sequentially, this may help clinch the diagnosis, e.g. discharging nasal lesion in Wegener's granulomatosis. Thyroid gland should also be examined to detect abnormality in its shape, size and consistency. Other lesions that may provide clue to the underlying respiratory pathology include skin lesions, such as erythema nodosum in sarcoidosis and TB (Fig. 22.3), malar rash in systemic lupus erythematosus, dermatomyositis, subcutaneous nodules in metastatic carcinoma, eye lesions (phlyctenular conjunctivitis) in TB (Fig. 22.4), Horner's syndrome in lung cancer, iridocyclitis in TB and sarcoidosis, chemosis in SVC obstruction, hypercapnia and flapping tremors in type II respiratory failure.

Examination of the Chest

Examination of the chest is traditionally done with the help of inspection, palpation, percussion and auscultation in that order, but some physicians combine inspection with palpation. It is best done in the sitting posture with arms at the side.

Inspection

Appearance, shape and size of chest: Normal chest is bilaterally symmetrical and elliptical in cross-section.

TABLE 22.3: Common causes of clubbing

Pulmonary	*Cardiac*	*Enteric*
Tumors of lung	Congenital heart disease	Cirrhosis liver
Mesotheliomas	Bacterial endocarditis	Ulcerative colitis
Suppurative lung diseases		Coeliac disease
Idiopathic pulmonary fibrosis		Crohn's disease

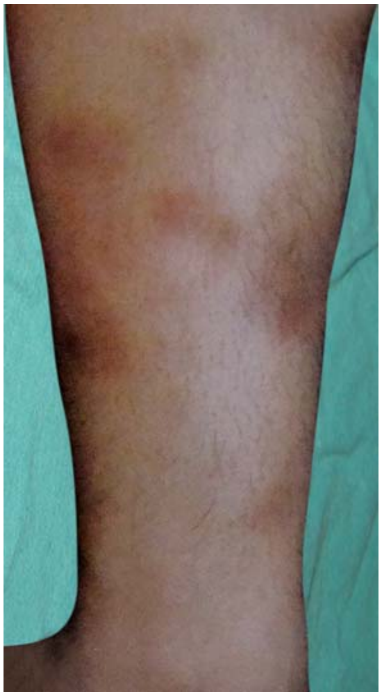


Fig. 22.3: Erythema nodosum. Note the coppery red and raised skin lesions

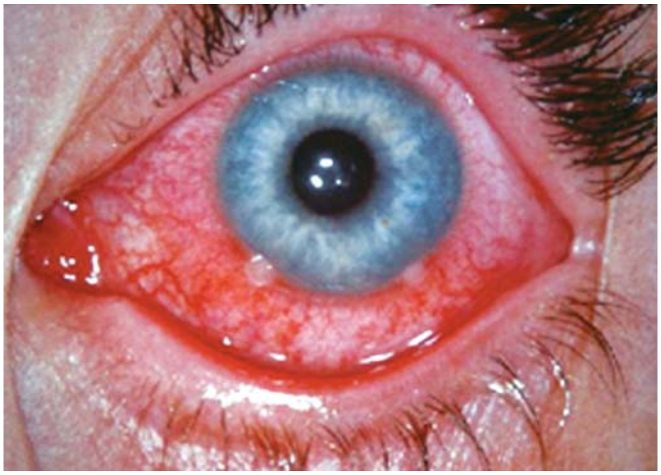


Fig. 22.4: Phlyctenular conjunctivitis

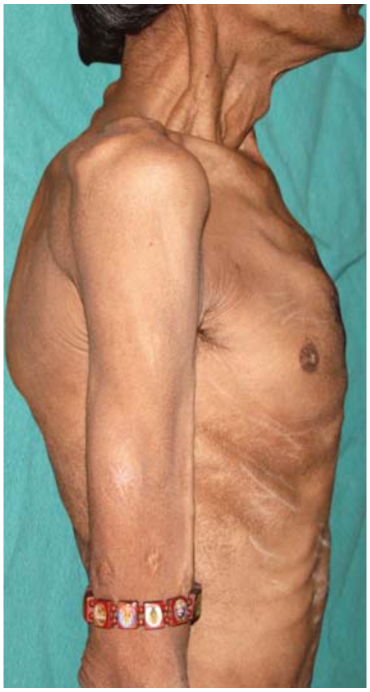


Fig. 22.5: Pectus carinatum (Pigeon chest)

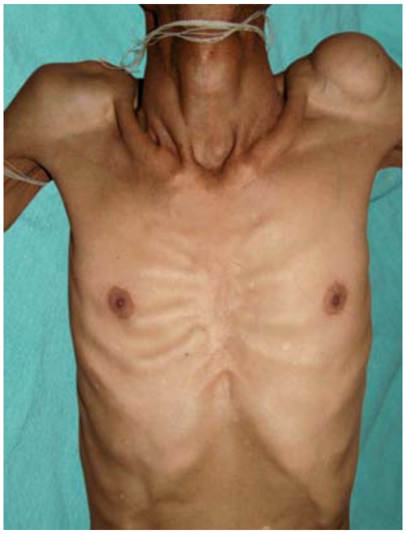
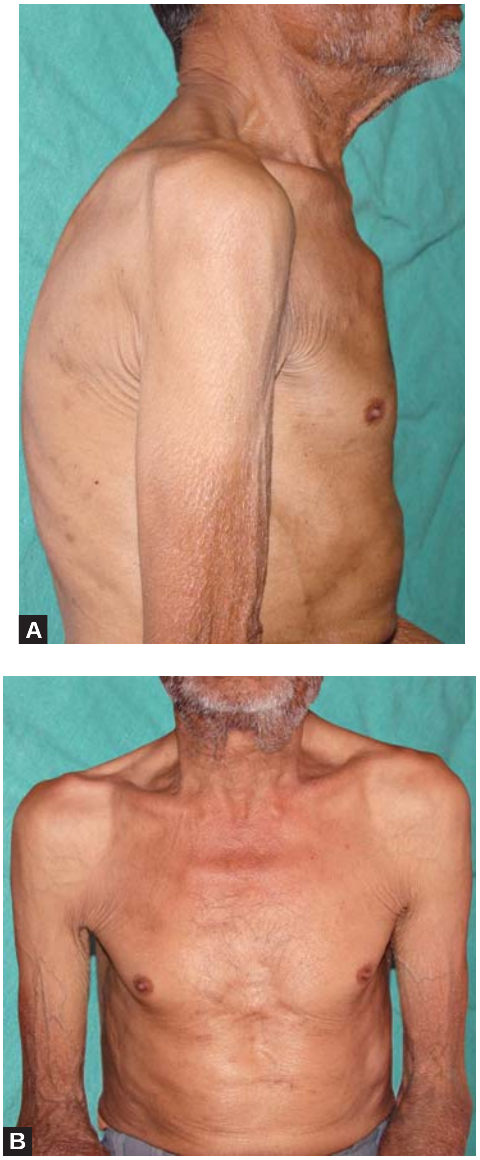


Fig. 22.6: Pectus excavatum (Funnel chest)

Observe it for any scar, injection mark, stains or lumps as a consequence of disease or trauma. Its shape may be distorted by the disease of ribs, vertebrae or the underlying lungs, pectus carinatum or pigeon chest [localized prominence of sternum and adjacent ribs (Fig. 22.5)], pectus excavatum or funnel chest [localized depression of sternum and adjacent ribs (Fig. 22.6)], kyphosis (forward bending), scoliosis (lateral bending), kyphoscoliosis, flattening (decreased AP diameter), hyperinflation or barrel shaped [increased AP diameter (Figs 22.7A and B)]. Also, look for muscle wasting, if any.

Movements of chest wall: Normally, the two sides of the chest move equally. Decreased or absent movements on one side may indicate disease of chest wall, pleura or of the lung on that side. Symmetrical decrease in the movement of chest wall occurs in emphysema, asthma



Figs 22.7A and B: Barrel-shaped chest

and end-stage diffuse pulmonary fibrosis. Intercostal recession (In-drawing of intercostals spaces) indicates severe upper airway obstruction (laryngeal or tracheal tumor). Inward movement of lower ribs on inspiration (instead of normal outward movement) occurs in emphysema and asthma. Observe for use of alae nasi (pneumonia in childhood) or accessory muscles of respiration (emphysema).

Palpation

Gently begin palpating the part of the chest showing obvious swelling on inspection, or at the site where the patient complains of pain to detect: Inflammatory edema (fractured ribs, cellulitis, infected cysts or tumors), air (subcutaneous emphysema), pus (abscess, empyema necessitans) or nodules (purpura, sarcoid nodule, metastatic nodule). Assess the position of trachea in suprasternal notch and of cardiac impulse at the lower chest wall. Displacement of these structures indicate shift of the mediastinum. Same side shift occurs in collapse or fibrosis, contralateral shift in effusion or pneumothorax. Vocal fremitus is detected by placing the ulnar side of hand, over the patient's chest wall when the patient narrates "one, two, three" or "ninety-nine." It may be done along with vocal resonance at the time of auscultation. A rub or rhonchus may, at times be palpable.

Percussion

Compare the degree of resonance over the equivalent areas on the two sides of chest and then focus on an area of interest to detect the generalized or localized abnormality. Always note for area of tenderness, if any. Different character of percussion note may point to the likely underlying pathology (Table 22.4). Topographical and tidal percussion has practically lost its value in modern clinical practice.

In general, the side of chest, which moves less is pathological (or "more pathological" than the other side). A stony dull percussion note indicates pleural effusion, more so, if the breath sounds and vocal resonance are decreased. A dull note with increased bronchial breath sounds and bronchophony indicates consolidation, but dull note with shrunken chest and decreased breath sounds indicate atelectasis. Hyper resonant note indicates pneumothorax, more so when the chest appears fuller and the breath sounds/vocal resonance are decreased or absent. Pulmonary tumors cause dullness when peripheral, and abut the chest wall, or in the presence of collapse of a lobe or a lung.

Auscultation

Breath sounds: Listen to lung sound for their character and quality on the two sides, on all the lung fields using

TABLE 22.4: Types of percussion note and likely etiology

Type of note	*Underlying object/pathology*
Tympanic	Hollow viscus, pneumothorax
Hyper-resonant	Pneumothorax
Resonant	Normal lung
Impaired to dull	Consolidation/collapse/fibrosis
Stony dull	Effusion/empyema

the diaphragm of stethoscope. Normal vesicular breath sounds (low frequency rustling sound) are best heard at the lung bases throughout inspiration, but a more high pitched sound is heard in early expiration. When the vesicular breathing is blowing in character and loud in mid-expiration, it is called as bronchovesicular. In a normal person, such a breath sound may be heard over either lung apex. Bronchial breathing is a high-pitched blowing sound of higher intensity, heard during inspiration and expiration and separated by a brief pause. It may be normally heard over the trachea or the larynx, but when heard over the chest, usually as a result of consolidated lung, it is abnormal. It is heard due to the increased transmission of high-pitched breath sounds through the chest wall as the solid lung acts as a bridge between the patient's airways and the chest wall. On the contrary, breath sounds are decreased in intensity when fluid (effusion), air (pneumothorax) or atelectasis interferes with the transmission of sounds from airways to the chest wall.

Adventitious sounds: Normal lung fields are devoid of any extra sounds, but extra sounds may be heard in disease states. These include wheezes, crackles and pleural rub. Wheezes are continuous, high-pitched sounds, often musical in character, which arise from air moving in the narrowed airways, e.g. in asthma. They are more marked during expiration and usually associated with prolonged expiratory time. Continuous, but low-pitched sound may be heard at a localized area (rhonchus) such as obstruction of a large airway by a tumor. Crackles are discontinuous, "popping" or bubbling sounds. Coarser, gurgling sounds are caused by secretions in the larger airways, heard during inspiration, as well as expiration. Finer crackles are usually heard during early inspiration. They are commonly heard in the presence of restrictive lung disorders such as the pulmonary edema and pulmonary fibrosis. They may be produced due to sudden opening of the small airways. Rub is a localized cracking or rubbing sound, often associated with chest pain, heard during both inspiration, as well as expiration (to and fro character). It may at times, be felt by the palpating hand. It indicates pleural inflammation. Exclude extraneous or false sounds that may occur due to the movement of stethoscope on skin, hair or clothing, or due to muscle twitching (shivering due to cold).

Vocal resonance: It is the audible perception of the transmitted vibrations from the vocal cords over the chest as the patient narrates "one, two, three" or "ninety nine." Compare each point on one side with the corresponding point on the opposite side. It is increased in the presence of consolidation. The spoken sound may be perceived as if spoken directly into the listener's ear, bronchophony. At times, even when a patient whispers, the sounds may be clearly heard, whispering pectoriloquy. Vocal resonance is decreased (or absent) in the presence of atelectasis or pleural effusion. In the latter, the spoken sound may be perceived as nasal or bleating in character, egophony.

Systemic Examination

Examination of other systems provides vital clues in the assessment of a patient with respiratory illness. Certain skin lesions are an essential part of the pulmonary disease, for example, erythema nodosum in TB and sarcoidosis; Kaposi's sarcoma in AIDS; larva migrans in Loeffler's syndrome; metastatic nodule in lung carcinoma; and "Mat" telangiectasia in Osler-Weber-Rendu disease. Skin lesions may also manifest as the complication of management, e.g. Stevens-Johnson syndrome in a patient of TB on antitubercular treatment, or be a part of a systemic disease having pulmonary manifestations, such as lupus pernio, flashy papules and erythema nodosum in sarcoidosis, malar rash and discoid lesions (often accompanied by telangiectasia, atrophy and scarring) in systemic lupus erythematosus. Besides, certain primary skin diseases like erythema multiforme may have pulmonary complications.

Examination of the joints may show symmetrical arthritis of small joints (rheumatoid arthritis) or large joints (Behçet disease). Examination of cardiovascular system may unravel cor pulmonale complicating the hypoxemia of pulmonary diseases or unravel the underlying pericardial, myocardial, endocardial or valvular lesions of the heart or aneurysmal lesions of vessels that complicate the respiratory diseases. Similarly, examination of abdomen may reveal advanced cirrhosis that leads to hepatopulmonary syndrome, while neurological examination may reveal the signs of metastatic brain lesion in an otherwise occult lung cancer.

Bedside Measurement of Lung Functions

Measurement of forced expiratory time had been used to detect the presence of airway obstruction in a patient at bedside.[14] The length of time taken to walk a known distance is a simple test of lung function.[15] Peak expiratory flow measurements and oxymetry can also be considered as an essential component of initial clinical and physical assessment.

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23

Microbiological Approach to Respiratory Infections

Pallab Ray

UPPER RESPIRATORY TRACT INFECTIONS

Bacterial infections of the upper respiratory tract vary from benign pharyngitis to life-threatening epiglottitis. Infections can be divided into syndromes involving the nasal cavity and its extensions, including the sinuses, the middle ear and the associated tissues.

Normal Flora of the Upper Respiratory Tract

The upper respiratory tract is colonized with a host of organisms. The paranasal sinuses are normally sterile. The anterior nares are colonized by staphylococci, micrococci and corynebacterium species.[1] Continuous evaporation of tear draining into nasal cavities raises the salt concentration locally, favoring colonization by salt-resistant staphylococci, including *Staphylococcus aureus*. The nose is the primary site of carriage of *S. aureus* in nearly a third of the healthy population. The nasopharynx has a more complex flora comprising of resident and transient flora. The resident flora comprises of streptococci (viridans group), *Neisseria* species, members of family *Enterobacteriaceae* and anaerobes, including *Bacteroides* species and *Fusobacterium* species.[2] Additionally, all individuals are transiently colonized by one or more potentially pathogenic bacteria that include group A streptococcus (less frequently groups B, C and G), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis* and *Moraxella catarrhalis*.

The Common Cold

Common cold is an upper respiratory syndrome caused by a variety of viral pathogens. The significance of common cold originates from the sheer frequency of these illnesses in the general population. Although generally mild and self-limited, these illnesses are associated with an enormous economic burden both in lost productivity and in expenditures for treatment.

Etiology

Rhinoviruses cause approximately one half of all colds. More than 100 serotypes and short-lasting serotype specific immunity results in repeated infections with seasonal predominance in the community. Other important pathogens include the coronaviruses and Respiratory Syncytial Virus (RSV). Influenza, parainfluenza and adenoviruses are often associated with cold-like symptoms though these agents primarily cause lower respiratory or systemic symptoms. Recently identified causes, though uncommon, include metapneumovirus, detected in 2001,[3] and bocavirus, a human parvovirus discovered in respiratory secretions in 2005.[4]

Laboratory Findings

Routine laboratory studies are not helpful for the diagnosis and management of the common cold. A nasal smear for eosinophils may help to differentiate allergic rhinitis from a viral etiology. A neutrophilic predominance in nasal secretions is rather characteristic of uncomplicated colds and does not necessarily indicate bacterial superinfection. Though it is possible to establish the viral etiological agent of common cold by culture, antigen detection and molecular or serologic methods, the lack of therapeutic relevance generally precludes the necessity of the same. Bacterial cultures or antigen detection is indicated only when group A *Streptococcus* (GAS), *Bordetella pertussis*, or nasal diphtheria is suspected. The isolation of other bacterial pathogens is not an indication of bacterial nasal infection.

Pharyngitis

Acute pharyngitis classically presents as sore throat, fever and pharyngeal inflammation characterized by redness and edema, frequently with vesicles or ulcerations.[5] It affects all age groups though children are more frequently affected with higher incidence during winter and spring in temperate climates and transitional seasons in tropical climates. Besides pharyngitis as a primary entity, sore throat and pharyngeal erythema may be associated with systemic disorders, such as the acute retroviral syndrome, or part of a more generalized upper respiratory tract infection.

Etiology

Most cases of acute pharyngitis are due to viral infections, and are usually benign, self-limited illnesses. Viruses account for up to one half of all cases, often associated with other signs or symptoms of upper respiratory tract infection.[6] All viruses implicated in upper respiratory tract infections have been implicated in causation of pharyngitis. Adenovirus is considered as the most common viral cause of pharyngitis, reported in 12 to 23% of cases.[7] Other respiratory viruses that cause pharyngitis include rhinoviruses, coronaviruses, enteroviruses, influenzavirus A and B, parainfluenza viruses, RSV, coronaviruses, Human Metapneumovirus (hMPV), and human bocavirus.[8] Human Merpesviruses, such as Epstein-Barr Virus (EBV), Herpes Simplex Virus (HSV), Human Immunodeficiency Virus Type 1 (HIV-1) and human cytomegalovirus have been infrequently reported to cause pharyngitis.

A child in the age group of 5 to 15 years suffers from an average of seven episodes of sore throat in a year, of which six are viral and one is streptococcal.[9] *Streptococcus pyogenes*, also known as Lancefield GAS or Group A Beta Hemolytic Streptococcus (GA-BHS), is the commonest bacterial etiological agent of highest concern because of its associated nonsuppurative sequelae, acute rheumatic fever and post-streptococcal glomerulonephritis. Group A streptococcus is responsible for approximately 10 to 15% of cases of pharyngitis in adults[10] and 15 to 30% of cases in children.[9,11] Developing countries have reported a recent trend of emergence of streptococcus group C and G in pharyngeal carriage and infection.[12] *Arcanobacterium haemolyticum* is a rare cause of bacterial pharyngitis, especially in adolescents and young adults.[13] *Fusobacterium necrophorum*, a gram-negative, nonspore-forming anaerobe, is a bacterial cause of sore throat in about 10% of cases of pharyngitis, distinctive by its frequent recurrences.[14] *Corynebacterium diphtheriae* is a cause of pharyngitis and diphtheria in countries without adequate coverage of primary immunization.[15,16] Rare causes of bacterial pharyngitis include *Neisseria gonorrhoeae* in sexually active adolescents and young adults, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*.[7]

Diagnosis

Pharyngitis is one of the most common causes for seeking medical attention. Differentiation of bacterial etiology from viral is important for the substantially higher morbidity of the former, serious nonsuppurative sequelae associated with GAS infection and to avoid unnecessary antibiotic therapy in viral cases. In GAS pharyngitis, the risk of development of rheumatic fever or post-streptococcal glomerulonephritis is directly proportional to the delay in the institution of therapy. Symptoms, such as conjunctivitis, coryza, oral ulcers, cough and diarrhea suggest a viral cause. On the other hand, abrupt onset, presence of tonsillar or pharyngeal exudates, tender anterior cervical lymphadenopathy, and fever are more commonly associated with GAS infection. Many clinical prediction rules have been proposed to help differentiation GAS from viral pharyngitis. Scoring systems use clinical and epidemiologic pointers to a quantitative probability that favors GAS over a viral etiology.[17] The clinical predictive efficacy of these scoring protocols are limited by extensive overlap of the signs and symptoms of many viral causes of acute pharyngitis with those of infections caused by GAS. Consequently, the Infectious Disease Society of America, the Committee on Infectious Diseases of the American Academy of Pediatrics, and the American Heart Association recommend guidelines that include confirmation of GAS infection by Rapid Antigen Detection Test (RADT), throat culture, or both.[18] In contrast, the guidelines issued by the Centers for Disease Control and Prevention and the American College of Physicians–American Society of Internal Medicine suggest empirical treatment based on a pharyngitis score alone with or without microbiologic confirmation.[19]

The differences in these guidelines have been debated, and empirical therapy based on these clinical prediction rules has been implicated in the overuse of antibiotics for treatment of pharyngitis.[17] A study of the effectiveness of these strategies concluded that microbiologic confirmation was the most effective and least expensive when all factors were considered.[20]

Confirmation of GAS by throat swab culture on sheep blood-agar plate is the most widely accepted practice for diagnosing streptococcal pharyngitis. Selective streptococcal media, less often used, inhibit contaminating normal flora and increase the sensitivity and specificity of culture for GAS,[21] with the attending risk of inhibiting other bacterial etiologic agents. Specimens should be obtained from bilateral tonsillar surfaces and the posterior pharynx while avoiding the mouth and other surfaces of the pharynx. The major disadvantage of culture for the confirmation of GAS pharyngitis is the time period of 24 to 48 hours required for accurate detection. Rapid antigen detection tests have become widely available and the sensitivity and specificity compares well with those of culture. Rapid results help in timely treatment, help to reduce the spread of GAS and antibiotic abuse in viral pharyngitis, and, most importantly, minimize suppurative and nonsuppurative sequelae of GAS. Newer assays use molecular biology methods to detect DNA specific to GAS by chemiluminescence or real-time Polymerase Chain Reaction (PCR), but are restricted because of the need to batch specimens and the specialized equipment required. On a properly collected specimen, the sensitivity of RADTs is 70 to 90% compared with culture, with a specificity of approximately 95%.[22] A negative RADT result, in a child with high index of suspicion for GAS infection, should be confirmed by culture.[23] Culture on either standard blood-agar plate or selective streptococcal media will isolate both group C and G streptococci; however, identification needs further characterization and serogrouping. *Arcanobacterium haemolyticum* also grows on standard blood-agar or selective streptococcal media, but may take as long as 72 hours to grow as small and dry colonies.

Confirmation of pharyngitis, caused by other bacterial agents, requires high degree of clinical suspicion and use of specific media and techniques. If diphtheria is suspected, the laboratory must be informed so that tellurite containing selective and differential media, not routinely used, are used for isolation. Recently, multiplex PCR has been used for the identification of *Corynebacterium diphtheriae* and to differentiate toxin producing from nontoxigenic strains.[24] *Fusobacterium* pharyngitis demands special technique for the isolation of anaerobic bacteria. The diagnosis of pharyngitis caused by *N. gonorrhoeae* is confirmed by culture on selective gonococcal media like modified Thayer-Martin medium.

Pharyngitis caused by *M. pneumoniae* or *L. pneumophila* requires serologic testing demonstrating rising titers in paired, acute and convalescent, serum samples; however, PCR and culture are commonly used in addition to serology for research purposes in advanced laboratories. The diagnosis of EBV infection is also confirmed by serology, by a heterophile antibody test (Monospot® or Monoslide®) or detection of immunoglobulin M antibodies to EBV viral capsid antigen. Common respiratory viruses that cause pharyngitis can be identified by either viral culture of a nasopharyngeal swab or molecular detection techniques such as PCR or reverse transcriptase-PCR.

Acute Laryngitis

Acute laryngitis is a not-so-uncommon clinical condition, usually mild and self-limiting. The symptoms include recent onset of hoarseness or a husky voice often associated with dry cough.[25] Similar symptoms are frequently associated with an upper respiratory tract infection, rhinorrhea and sore throat.

All the major respiratory viruses have been known to cause laryngitis, the commonest being parainfluenza virus in one-fifth of the cases. Less frequent agents include the rhinoviruses, influenza virus, the parainfluenza viruses, coronavirus, adenovirus and human metapneumovirus.[26,27] Bacterial respiratory infections have been associated with acute laryngitis. Hoarseness is often associated with acute streptococcal pharyngitis and diphtheria, the latter especially in the developing world. Tubercular laryngitis is a frequent association with tubercular lung infection.[28] The possible etiologic roles of *Moraxella (Branhamella) catarrhalis* and *H. influenzae* in acute laryngitis has been suggested, but remains to be proven. Uncommon causes of acute laryngitis include herpesviruses, parvovirus B19, mucosal candidiasis, *Coccidioides immitis, Cryptococcus neoformans, Sporothrix schenckii,* and group G betahemolytic streptococci in normal and immunocompromised patients.[29] Hoarseness may also be noted as a component of other laryngeal infections such as croup, acute epiglottitis or supraglottitis.

Acute Laryngotracheobronchitis (Croup)

Croup is a childhood viral infection of the upper and lower respiratory tracts resulting in inflammation in the subglottic area and manifesting as dyspnea with characteristic stridor on inspiration. The term “croup” is derived from an Anglo-Saxon word “kropan” or the old Scottish term “roup,” which meant “to cry out in a shrill voice.”

Etiology

The predominantly viral etiology of croup has been established with recent molecular diagnostic techniques, including Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), with the parainfluenza type 1 virus causing one-fourth to one-third of cases followed by parainfluenza type 3 as the second most common agent. Other agents, less frequently incriminated include the influenza virus, rhinoviruses, enteroviruses, bocavirus, adenoviruses, hMPV, *M. pneumoniae*, human coronavirus and measles virus.[30]

Diagnosis

The diagnosis of croup is primarily clinical and epidemiological. Identification of the specific viral agent is usually unnecessary, and obtaining respiratory tract swabs and secretions is more likely to augment the child's respiratory distress than yield clinically relevant information.

Otitis Externa

Infection of the external auditory canal (otitis externa) resembles those of skin and soft tissue elsewhere and the microbial flora of the external auditory canal resembles flora of skin elsewhere, predominantly composed of *Staphylococcus epidermidis*, *S. aureus*, corynebacteria, and *Propionibacterium acnes*.[31] Otitis externa may be subdivided into acute localized otitis externa, acute diffuse otitis externa, chronic otitis externa and malignant otitis externa, and the causative organisms include those of the normal skin flora and *gram-negative bacilli,* particularly *Pseudomonas aeruginosa*.

Otitis Media

Acute otitis media (AOM) is an acute illness characterized by inflammation of the mucosa lining the middle ear with exudation. Otitis Media with Effusion (OME) is characterized by fluid in middle ear without signs of acute inflammation of the middle ear mucosa.

Microbiology

The bacteriology of otitis media documented by the cultures of middle ear effusions obtained by needle aspiration has implicated the importance of *S. pneumoniae* and *H. influenzae* in all age groups, but more recent studies, since the introduction of the pneumococcal conjugate vaccine in developed countries, suggest that *H. influenzae* may replace pneumococcus as the most frequently isolated pathogen of AOM in children.[32] *S. pneumoniae* is the most important bacterial cause of otitis media in most parts of the world. Otitis media caused by *H. influenzae* is associated with nontypeable strains in majority of patients whereas *H. influenzae* type b causes 10% of cases, which are frequently severe and accompanied by bacteremia or meningitis.

M. catarrhalis has been isolated from approximately 10% of children with AOM[33] and is usually associated with a mild form of disease. Most strains produce beta-lactamase and are resistant to penicillin G, ampicillin and amoxicillin. *S. aureus*, including methicillin and multi-drug-resistant strains, is an uncommon cause of AOM. During the preantibiotic era, GAS was a frequent cause of severe AOM, frequently complicated by mastoiditis and often associated with scarlet fever, but the entity has become rare in the last two decades. Chronic suppurative otitis media cases frequently yield *P. aeruginosa*, *S. aureus* and *aerobic gram-negative bacilli* on culture.[34]

Viral infection is frequently the initial event in the development of acute otitis media.[35,36] Respiratory viruses have been isolated from one fourth of middle ear fluids of children with AOM. Respiratory syncytial virus, influenza virus, enteroviruses, coronaviruses and rhinoviruses were the most common viruses.[36] Combined viral and bacterial infections are frequent and may be more severe than bacterial infection alone.[35]

Mastoiditis

Most cases of AOM with fluid in the middle ear space is associated with inflammation of the mastoid air cells. Clinically significant mastoiditis has been rare since the introduction of antimicrobial agents. Infection in the mastoid usually follows middle ear infection. The bacteriology of mastoiditis is the same as that of AOM, including *S. pneumoniae* and *H. influenzae* as the major pathogens. Patients with prolonged perforation of the tympanic membrane may have invasion of organisms from the ear canal, including *Pseudomonas* spp. Polymicrobial flora is commonly isolated from the cases of chronic mastoiditis in developing countries.[37] Cultures for bacteria from ear drainage fluid must be taken with care to distinguish fresh drainage fluid from material in the external canal. The canal must be cleaned and fresh pus, free of contamination from external canal, obtained. If the tympanic membrane is intact, tympanocentesis should be performed to obtain material from the middle ear.

Sinusitis

Sinusitis may be classified as acute or chronic. Because most cases of acute bacterial sinusitis are secondary to viral infection of the upper respiratory tract or allergic inflammation, nasal inflammation is commonly associated justifying the commonly used term as rhinosinusitis. The preferred term is acute community-acquired bacterial sinusitis.[38,39]

Microbiology

The paranasal sinuses are sterile under normal conditions, unlike the nasal passages, which are heavily colonized with bacteria. Reliability of knowledge of the microbiology of acute community-acquired sinusitis is dependent on proper specimen collection. The nasal cavity is heavily colonized with commensal flora that easily contaminates specimen from the paranasal sinuses. Reliable specimens of sinus secretions have been obtained by puncture of the maxillary antrum, to reduce the risk of nasal contamination. To further discriminate true infection from contamination, quantitative methods have been used to enumerate the microbial load. Attempts have been made to define infection as a bacterial load of 10^4 Colony-Forming Units per Milliliter (CFU/ml) of aspirated material.[39] Cultures obtained from the middle meatus adjacent to the sinus ostia collected by swab or aspiration via an endoscope have been compared to those obtained by sinus aspiration. This is associated with a high risk of contamination of the endoscope while negotiating through the nonsterile anterior nasal cavity. Most studies using endoscopic middle meatal culture in adult patients show a sensitivity of approximately 80%, a specificity of 90%, a positive predictive value of 80 to 90%, and a negative predictive value of 80 to 90%, with maxillary sinus aspiration considered the gold standard.[40]

In community-acquired bacterial sinusitis, *S. pneumoniae* is the most frequently isolated organism, followed by nontypeable *H. influenzae* and *M. catarrhalis*. Streptococci, *S. aureus,* and anaerobes are isolated less frequently.[41] In children, *M. catarrhalis* is isolated with a greater frequency than in adults. Widespread immunization with pneumococcal conjugate vaccine, in several countries, has diminished the frequency of *S. pneumoniae* with a consequent shifting of the serotypes[42] and a relative increase in the isolation of *H. influenzae*.

Viruses have been infrequently isolated from patients with acute sinusitis. This may reflect the delay in the timing of sampling, done after the patient has been symptomatic for a week, when the viral infection may have waned or overshadowed by secondary bacterial pathogens. Respiratory viruses, such as adenovirus, parainfluenza and rhinovirus have been recovered from approximately 10% of sinus aspirates. Fungi have long been recognized as important pathogens in selected patients with acute or chronic sinusitis.

Nosocomial sinusitis is a frequent complication, particularly in critical care setting affecting between 7.7 to 32% of patients.[43] Nasal intubation has a risk factor for this infection. Gram-negative organisms, including *P. aeruginosa* and *S. pneumoniae* are frequently isolated in patients with nosocomial sinusitis.

Epiglottitis

Acute epiglottitis is a cellulitis of the epiglottis and adjacent structures leading, in some cases, to sudden airway obstruction. *H. influenzae* type B is the most frequent pathogen isolated from epiglottis in pediatric patients and in up to one-fourth of adult patients.[44] Other agents occasionally implicated include *S. pneumoniae*, staphylococci and streptococci.[45] The role of viruses in epiglottitis, other than possibly herpes simplex infections (rarely) has not been established.

LOWER RESPIRATORY TRACT INFECTIONS

Acute Bronchitis

Acute bronchitis refers to a clinical syndrome distinguished by a relatively brief, self-limited inflammatory process of large and mid-sized airways, not associated with pneumonia on chest radiograph.

Microbial Etiology

Acute bronchitis is most commonly caused by a wide range of viruses. Approximately 10% of cases are attributed to bacterial pathogens, including *M. pneumoniae, C. pneumoniae,* and *B. pertussis*. The relative prevalence of different pathogens varies according to age, season and the reliability of the diagnostic methods used. Molecular tests, contrary to conventional culture, identify a wider range of viral pathogens, especially in adults, that include RSV, adenovirus, hMPV and parainfluenza viruses.[46] Influenza A and B viruses are commonly associated with winter outbreaks of acute bronchitis.[47] Coronavirus, rhinoviruses, echovirus, coxsackievirus and strains of Severe Acute Respiratory Syndrome (SARS), can cause acute bronchitis. Bacteria contribute to a minority of cases and the agents include *M. pneumoniae*, *C. pneumoniae*, *B. pertussis* and *Bordetella bronchiseptica*.[47,48]

Diagnosis

Etiologic diagnosis depends on laboratory confirmation. Rapid antigen detection in nasopharyngeal swabs is relatively sensitive for influenza virus and RSV. Identification of other viral pathogens (RSV, hMPV, coronaviruses and parainfluenza viruses) requires tissue culture or RT-PCR assay. Diagnosis of *M. pneumoniae* depends on demonstrating specific IgM in serum or PCR. *B. pertussis* diagnosis can be made by serology, PCR, or culture. *C. pneumoniae* is difficult to diagnose and requires PCR or serology.

Bronchiolitis

Bronchiolitis, variously named as "acute catarrhal bronchitis," "interstitial bronchopneumonia," "spastic bronchopneumonia," "capillary or obstructive bronchitis," and, more commonly, "wheezy bronchitis" and "asthmatic bronchiolitis", is the most common acute viral lower respiratory tract illness occurring during the first two years of life.

Etiology

Respiratory syncytial virus is the cause of about two-third of the cases of bronchiolitis.[49,50] Other viruses include hMPV, the parainfluenza viruses, influenza, rhinoviruses, human non-SARS virus, coronaviruses and human bocavirus.

Viral agents of upper respiratory tract infections, rhinoviruses and enteroviruses, also are commonly isolated from specimens from children with bronchiolitis. Role of these viruses as primary agents causing bronchiolitis or as coinfecting agents is uncertain.

Diagnosis

Laboratory determination of the specific etiology of bronchiolitis usually is unnecessary and therapeutically irrelevant. Rapid virologic diagnosis may be epidemiologically useful for the implementation of appropriate infection control procedures or, in selected cases with high-risk conditions or severe illness with influenza or RSV, for determination of specific antiviral therapy. The specific agent of bronchiolitis can be identified by viral isolation from a nasal wash using shell vial culture techniques. Rapid viral antigen techniques, including immunofluorescent assays, optical immunoassays and enzyme immunoassays are technically nondemanding, cost effective and rapid.[51] These assays are available for RSV, parainfluenza viruses, influenza viruses, and hMPV and many of these commercially available antigen assays allow the simultaneous detection of multiple agents.

The use of molecular diagnostic assays, including RT-PCR has enhanced the sensitivity and specificity of the detection of the respiratory viruses associated with bronchiolitis,[51,52] but they are expensive, and are not usually easily available in developing countries.

Acute Pneumonia

Pneumonia, designated by Sir William Osler as the "Captain of the Men of Death." is among the top ten most common causes of death among all age groups in the United States, the sixth leading cause of death in those 65 years or older, and the single most common cause of infection-related mortality.[53] An understanding of the pathogenesis of the disease, evaluation of relevant data from a careful history and physical examination, recognition of common clinical patterns of infection, and information from the microbiology laboratory all aid in narrowing down the possible etiologic agents of pneumonia, thereby allowing reasonable therapy to be selected empirically.

Acute Community-Acquired Pneumonia

A long list of bacterial, fungal, viral and protozoal agents may cause pneumonia. *Streptococcus pneumoniae* is undoubtedly the commonest cause of acute community-acquired pneumonia in developing countries, accounting for one-half of the cases though reliable reports of its actual prevalence are not available.

Acute Respiratory Infections (ARI) are leading causes of high morbidity and mortality in infancy and childhood in developing countries. Such respiratory infections are reported to kill 4 million children every year worldwide, while in India, they account for 14.3% of deaths during infancy and 15.9% during early childhood.[54,55] Of all upper and lower respiratory tract diseases, pneumonia is the most important cause of death accounting for about 3 million deaths in children worldwide. In United States alone, pneumonia rank as the sixth leading cause of death while in India, it is the number one killer disease.[56] Annually 94 out of every 1,000 Indian children develop pneumonia and account for 12 to 15% of deaths.[57]

Pneumonia is a disease caused by a wide variety of microorganisms and has a spectrum of severity that ranges from mild illness to severe disease associated with a high mortality rate. *Streptococcus pneumoniae* is the commonest pathogen though the relative incidence is rapidly coming down with the implementation of pneumococcal vaccination in developed nations. An estimated 3 to 38% of cases of acute community-acquired pneumonia are caused by *H. influenzae*.[58] In developed countries, the use of the *H. influenzae* conjugate vaccine has decreased the incidence of invasive disease caused by *H. influenzae* type B, with a consequent increased incidence of invasive disease, including pneumonia caused by nontypeable strains.[59]

Classically, *S. aureus* has accounted for 2 to 5% of acute community-acquired pneumonia cases[60] commonly in older adults and in those with influenza. Although pneumococcus still represents the most common etiologic agent, staphylococcal disease occurs with a higher frequency than that noted in non–influenza-related, community-acquired pneumonia. In 2002 many cases of community-acquired pneumonia caused by *S. aureus* were described in France.[61] Acute Respiratory Distress Syndrome (ARDS) was a frequent complication of infection and mortality rates were higher than in patients with pneumonia caused by *S. aureus* without the Panton-Valentine Leukocidin (PVL). Similar disease patterns have been described in the United States with these strains of Community-Acquired of Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA).[62] These CA-MRSA pneumonias are associated with severe pneumonia with mortality rates of 29 to 60%. CA-MRSA pneumonia has therefore become an important entity to consider in the right clinical setting.

Aerobic gram-negative bacteria and mixed aerobic and anaerobic infections cause most of the remaining cases of acute community-acquired pneumonia. Gram-negative rods may cause 7 to 18% of pneumonia cases. *Klebsiella pneumoniae, P. aeruginosa* and *Enterobacter* species are the most often isolated organisms.[63] Gram-negative bacilli are particularly important pathogens in older adults, especially those with chronic underlying disease and those who are bedridden and recently hospitalized. *Pseudomonas* infection should be suspected in patients with pulmonary comorbidities and recent hospital stays.

Indian investigations have reported *S. pneumoniae* and *H. influenzae* as the most commonly involved organisms in community-acquired pneumonia.[64,65] In a study from Shimla,[66] 70 cases of CAP were studied by culture of sputum, blood and pleural fluid and IgM Enzyme-Linked Immunosorbent Assay (ELISA) for *M. pneumoniae*. An etiological agent was identified in 53 (76%) cases of which 41 (77%) were monomicrobial and 12 (23%) had a mixed etiology. *Streptococcus pneumoniae* was the commonest (36%) agent followed by *K. pneumoniae* (22%), *S. aureus* (17%) and *M. pneumoniae* (15%). The role of *M. pneumoniae* in the causation of CAP has been variably reported from various studies in India. One study from Delhi[67] showed evidence of *M. pneumoniae* infection in 36% (10% definitive and 26% probable) of 62 adults studied using IgM ELISA, Gelatin Particle Agglutination Test (GPAT) and antigen detection by immunofluorescence; another study from same place has shown *M. pneumoniae* responsible for 27% of 62 children with CAP.[68] There was evidence of *Chlamydia pneumoniae* in 6% of the children with CAP. From the South, incidence of *M. pneumoniae* have been shown to be 24% amongst children with CAP in Manipal[69] and 30% amongst children with CAP from Vellore.[70] The serological evidence of *Legionella pneumophila* infection was reported in 60 hospitalized cases of CAP.[71]

Legionella species are the most important water-related pulmonary pathogens in the United States with regard to mortality and morbidity. The importance of *Legionella* species in causing pneumonia has varied greatly in different geographic areas, with incidences ranging from 2 to 30%.[72] *Moraxella catarrhalis* has also been identified as a cause of pneumonia.[73] The overall incidence of disease caused by this bacterium is low, but it is an important pathogen in older adults with COPD and various forms of immunosuppression.

Pneumonia is the second or third most common reason for hospitalization in people who are 65 years old and above; and represents a major cause of morbidity and mortality. In some series, pneumonia represents the leading cause of death in this population. In general, the cause of community-acquired pneumonia in the older population follows the general trend of infection in younger populations. *S. pneumoniae* is the predominant organism, accounting for more than half of the cases. *H. influenzae*, mostly nontypeable, is the second most common agent; accounting for up to 10% of episodes.[74] The incidence of other aerobic gram-negative bacilli in causing pneumonia in older adults is variable because the criteria for diagnosis of true pneumonia versus colonization vary. Increased oropharyngeal colonization with aerobic gram-negative bacilli has been documented in the older population. Colonization is an outcome of debility, prior use of antibiotics, decreased activity, diabetes, alcoholism, and incontinence and is thought to be a risk factor of development of pneumonia caused by these organisms.[75] Older adults are at greater risk for infection with group B streptococci, *M. catarrhalis* and *Legionella* species, although the overall incidence of these agents in the older population is relatively low.[73] Polymicrobial infections and pneumonia due to aspiration occur more frequently in older adults.[76] With the development of sensitive nucleic acid amplification tests, the role of viruses as a cause of pneumonia is being more clearly defined.[77] Recent studies have suggested a viral etiology in 15 to 29% of all patients hospitalized with pneumonia with significantly more viral infections noted in the older age groups (median age of 76).[77,78]

Influenza is consistently the most commonly isolated virus usually followed by RSV, human metapneumovirus, parainfluenza virus, enterovirus and coronavirus.

The cause of community-acquired pneumonia in patients with AIDS has changed significantly since the beginning of the epidemic. *Pneumocystis jiroveci (carinii)* remains the most frequent AIDS-defining opportunistic pneumonia in the United States and the rest of the world, although Highly Active Antiretroviral Therapy (HAART) and effective prophylactic strategies have more than halved the incidence of *P. jiroveci* pneumonia and its associated mortality. Bacterial pneumonia has a ten times higher incidence in HIV-positive versus HIV-negative cohorts.[79] The rate of invasive pneumococcal disease may be three times greater in HIV-infected patients than in non–HIV-infected controls.[80] *H. influenzae* and *S. aureus* are also important pathogens.[80,81] A variety of other bacteria have been implicated, including *Rhodococcus equi, Escherichia coli, Serratia species* and *P. aeruginosa.* Infections with *Pseudomonas* are associated with the late stages of disease with *Mycobacterium tuberculosis,* nontuberculous mycobacteria, *C. neoformans* and cytomegalovirus playing important roles as etiologic agents.[82]

Health Care-Associated Pneumonia

An increasing number of patients present to hospital services with pneumonia following contact with various types of the health care institutions, resulting in a blurring of the distinction between community-acquired and nosocomial pneumonia. Health care-associated pneumonia now represents a new syndrome, a hybrid of community-acquired pneumonia and hospital-associated pneumonia.[83] Patients with a history of hospitalization within 90 days prior to developing pneumonia; patients attending hemodialysis clinics; patients receiving intravenous therapy, wound care, or chemotherapy at home; and residents of long-term care facilities or nursing homes are the most likely involved. *S. aureus,* including MRSA; aerobic gram-negative bacilli, including *P. aeruginosa*; and mixed aerobic-anaerobic pathogens associated with aspiration have been most commonly reported.

Atypical Pneumonia Syndrome

Atypical pneumonia classically presents with a mild respiratory tract illness followed by pneumonia with dyspnea and cough without sputum, an atypical chest X-ray and a negative routine culture of sputum specimen. Atypical pneumonia in its typical form is rarely encountered today. *M. pneumoniae, C. pneumoniae, L. pneumophila*, and respiratory viruses are the most significant causes of atypical pneumonia. Other agents, such as *Chlamydophila psittaci, Francisella tularensis, M. tuberculosis* and *Coxiella burnetii* may also cause atypical pneumonia. In patients with AIDS, *Pneumocystis* and nontuberculous mycobacteria should also be included. The difficulty in identifying the various etiologic agents associated with atypical pneumonia has made estimates of incidence difficult. *M. pneumoniae* may account for 10 to 30% of cases of community-acquired pneumonia.[84] *C. pneumoniae* has emerged as an important cause of atypical pneumonia and may account for approximately 6 to 20% of community-acquired pneumonia cases.[85] Of the viral agents associated with atypical pneumonia in adults, influenza A and B, adenovirus types 3, 4, and 7 (especially in military recruits), human metapneumovirus,[77] RSV (especially in older adult and immune-suppressed patients), and parainfluenza virus are the most common.[78,86]

Aspiration Pneumonia

The bacteriology of aspiration pneumonia reflects the flora of the oropharynx, and presence of periodontal disease. Anaerobic bacteria alone are involved in half of cases[87] and in combination with aerobes in other cases.[88] *Bacteroides* species, *Porphyromonas species*, *Prevotella melaninogenica, Fusobacterium species* and anaerobic gram-positive cocci are the predominant anaerobes isolated. In community-acquired aspiration pneumonia, *Streptococcus species* and *H. influenzae* are the most common aerobic isolates.[87] *M. catarrhalis* and *Eikenella corrodens* may also be involved. In contrast, gram-negative bacilli (including *P. aeruginosa*) and *S. aureus* are the most commonly isolated aerobes from nosocomial aspiration pneumonia, including ventilator-associated pneumonia.[87]

Nosocomial Pneumonia, Hospital-acquired Pneumonia, Ventilator-associated Pneumonia

Nosocomial pneumonia is the second leading type of nosocomial infection and accounts for 13 to 18% of all such infections. It is the leading cause of infection-related deaths in hospitalized patients with an attributable mortality of 33 to 50%.[89] Higher mortality rates have been observed when patients are bacteremic or have pneumonia caused by *P. aeruginosa* or *Acinetobacter* species. Ventilator-associated pneumonia (VAP) has been accepted as an important subcategory of nosocomial pneumonia.

Approximately 60 to 75% of cases of nosocomial pneumonia are caused by aerobic gram-negative bacilli, with members of the family Enterobacteriaceae (*K. pneumoniae, E. coli, Serratia marcescens, Enterobacter* species), *Acinetobacter* species and *Pseudomonas* species accounting for the majority of these. *Staphylococcus aureus* causes 13 to 40% of nosocomial pneumonia and appears to be more common in burn units, in patients with wound infections, and in patients recently ventilated after neurosurgery or head trauma.[90] MRSA and Multidrug-resistant (MDR) organisms now play major etiologic roles. In contrast to its prominent role in community-acquired pneumonia, *S. pneumoniae* causes only 3 to 20% of nosocomial pneumonias in most studies and is associated with infection developing early in the hospital course. Anaerobic bacteria have been isolated in up to 35% of the cases of nosocomial pneumonia, although usually less than 5% of infections are thought to be caused by these organisms. They play a role when aspiration is likely to have occurred. Pneumonia caused by *Legionella* species may occur sporadically or as part of outbreaks.

Pleural Effusion and Empyema

Microbiology

In the preantibiotic era, *S. pneumoniae* accounted for 60 to 70% of cases, *Streptococcus pyogenes* for 10 to 15% of cases, and *S. aureus* for 5 to 10% of cases. *S. pneumoniae* more recently accounts for less than 10% of cases and many infections are mixed, with anaerobes present in up to 75% of empyemas as sole organisms or in combination with other aerobic or facultative organisms.[91,92] Bartlett and Finegold found that pleural empyema was caused by aerobic bacteria in 24%, anaerobic bacteria in 35%, and both aerobic and anaerobic bacteria in 41% of 83 medical service patients without prior antibiotic therapy or surgical procedures.[93] The most common anaerobes isolated include the *Bacteroides fragilis* group, *Prevotella species, Fusobacterium nucleatum,* and *Finegoldia species.* Recently, there has been a shift from conventional pathogens to the *Streptococcus anginosus* group in community-acquired empyema in patients with comorbidities.[93] Hospital-acquired empyemas include more staphylococcal infections and gram-negative organisms.

Predisposing factors and associated comorbidities are important pointers to the most likely pathogens. Pneumonia continues to be the most frequent predisposing factor in the development of empyemas. Otherwise healthy adults with pneumonia, the most common bacteria causing empyema are *S. aureus* and *S. pneumoniae.* The incidence of a parapneumonic effusion in hospitalized patients is estimated to be 40%. Empyema caused by *S. aureus, S. pneumoniae* or *H. influenzae* has been common in children. Most cases of *S. aureus* empyema result from *S. aureus* pneumonia with a tendency to cause cavitation, most often seen in older hospitalized patients with underlying medical problems. In developing countries, tuberculous effusions are common, and they can be secondary to a primary infection or more frequently occur as a reactivation tuberculosis. Factors predisposing to aspiration, such as altered mental status, alcoholism and periodontal disease, are common in patients with anaerobic infections of the pleura. Many of these cases tend to be polymicrobial. In addition to anaerobes, viridans group streptococci, aerobic gram-negative bacilli, and occasionally *S. aureus* have been recovered. Pleuropulmonary actinomycosis can result from aspiration leading to a chronic pulmonary infection with chest wall involvement. Nocardia infections occur more frequently in patients with underlying conditions, such as organ transplantation, malignancy, diabetes mellitus, Acquired Immunodeficiency Syndrome (AIDS) and long-term use of steroids. Pleural effusions can develop in up to 50% of patients with nocardiosis.

Laboratory Diagnosis

Aspirated pleural fluid should be sent to the microbiology laboratory for a Gram stain and for aerobic and anaerobic cultures. Using conventional methods achieve a bacterial diagnosis in approximately 60% of pleural fluid samples.[94] The low detection rate may be due to prior antimicrobial use frequent in developing countries. Antigen detection test by latex agglutination test or Immunochromatographic Test (ICT) for the detection of *S. pneumoniae* antigen is rapid, highly sensitive and not affected by prior antibiotic therapy.[94]

Pleural tuberculosis can be diagnosed by acid-fast stain microscopy of pleural fluid in only 18 to 23% of patients, but cultures of pleural fluid and histologic examination of pleural biopsy specimens permit the diagnosis in up to 95% of patients. Radiometric culture increases the speed of diagnosis in patients with pleural tuberculosis. Three other diagnostic tests are available to help establish the diagnosis of tuberculous pleural disease—tests for Adenosine Deaminase (ADA) and interferon-gamma and the polymerase chain reaction assay. In one study, pleural fluid ADA levels above 40 U/L were found in 99.6% of patients with tuberculous pleurisy.[95] Assay of interferon-gamma needs evaluation in developing countries where the disease is more prevalent. Two tests for *M. tuberculosis* nucleic acid are commercially available and nucleic acid amplification tests require rigorous standardization to prevent nonspecific results common with this technique.

Bacterial Lung Abscess

Microbiology

The predominant organisms responsible for lung abscess are bacteria, specifically mouth anaerobes that are normal flora in the gingival crevices.[96] Studies using rigorous sample collection techniques that avoid contamination with oral flora combined with reliable anaerobic culture methods have shown that anaerobes are found in about 90% of lung abscesses and are the only organisms present in about half of cases. The most frequently isolated anaerobes are *Peptostreptococcus spp*. (now probably identified as *Finegoldia magna*), *Fusobacterium nucleatum* and *Prevotella melaninogenica*.[97] Abscesses usually contain multiple anaerobe species, usually three to four per culture specimen; microaerophilic streptococci and viridans streptococci often are present as well.

Lung abscess occasionally may be caused by *S. aureus*, enteric gram-negative rods such as *Klebsiella spp*., *P. aeruginosa*, *Burkholderia pseudomallei* (melioidosis), *Pasteurella multocida*, GAS, *H. influenzae* types B and C, *Legionella spp*., *R. equi*, *Actinomyces spp*., and *Nocardia* spp. Oropharyngeal colonization with *P. aeruginosa,* other aerobic gram-negative rods and, less often, *S. aureus* is a common event in hospitalized patients, particularly patients who receive ventilatory support. These bacteria are important pathogens when lung abscess or necrotizing pneumonia develops during hospitalization and may produce infection as the sole pathogen or as one component of a mixed flora infection involving other aspirated oropharyngeal organisms. In patients with impaired cell-mediated immunity (AIDS, transplantation immunosuppression), opportunistic pathogens, such as mycobacteria, *Nocardia*, *Aspergillus*, and *Rhodococcus,* are important causes of cavitary lung lesions. In patients with impaired host defenses caused by granulocytopenia (leukemia, chemotherapy), aerobic bacteria (*P. aeruginosa*, *S. aureus*) and fungi, including *Aspergillus* and Zygomycetes, are important pathogens.

Diagnosis

Sputum Gram stains in these patients show many neutrophils and mixed flora, with many morphologically different bacteria; routine cultures usually grow normal respiratory flora. Because expectorated sputum is contaminated by oral flora containing large numbers of anaerobes, special techniques for obtaining lower tract specimens are necessary to confirm the role of anaerobes. These techniques include transtracheal aspiration, transthoracic aspiration, protected brush fiberoptic bronchoscopy, bronchoalveolar lavage with quantitative cultures,[98] and empyema fluid obtained by thoracentesis. Blood cultures rarely are positive in anaerobic lung abscess. Patients without the classic presentation and patients with secondary lung abscess should have stains and cultures of expectorated sputum for aerobic bacteria, mycobacteria, fungi, and, in some instances, parasites.

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24

Systematic Approach to Interpretation of Plain Chest Radiographs*

D Behera

INTRODUCTION

In this chapter, various diagnostic methods used for the diagnosis of different lung diseases will be discussed. Important diagnostic tools include: Radiology, pulmonary function testing, bronchoscopy, bronchoalveolar lavage, thoracoscopy biopsy of various kinds, cytological methods and hematological investigations. Some of the microbiological and skin testings will be dealt with in chapters on specific diseases.

RADIOLOGY AND IMAGING

Chest Skiagram

Roentgenographic examination of the chest is an integral part in the diagnostic evaluation of all types of lung diseases. In fact, in the absence of a plain chest skiagram, workup of any lung disorder is not complete. While chest skiagram itself is not diagnostic of a particular disease, in correlation with clinical history, it provides important clues to the possible etiology and hints at whether any further diagnostic method is necessary or not.[1-11] After clinical examination, it is the first investigation of choice in any lung disease. Anatomical localization of pulmo-nary lesions is possible most of the time, and always an attempt should be made to collect this information. A lateral view is most often necessary for this purpose for recognizing various segments and lobes although posteroanterior views are good enough (Figs 24.1 to 24.7).

Posteroanterior (PA) View

The standard PA views are taken, when the X-rays pass through the body in a posteroanterior direction with the

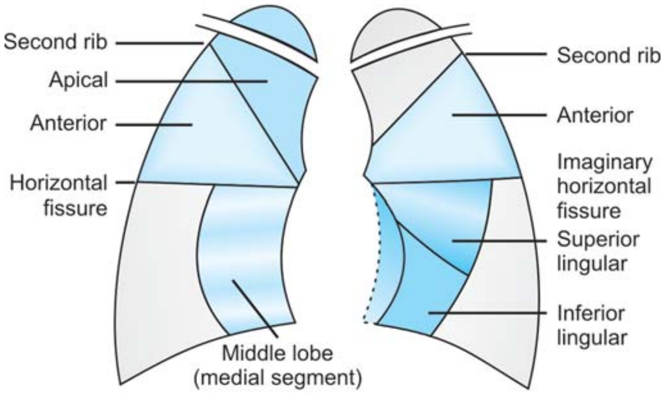
Second rib
Apical
Anterior
Horizontal fissure
Middle lobe (medial segment)
Second rib
Anterior
Imaginary horizontal fissure
Superior lingular
Inferior lingular

Fig. 24.1: Posteroanterior view of the chest skiagram showing different segments of the lungs on both sides. Note that there is no horizontal fissure on the left side. For convenience, however, an imaginary horizontal fissure is drawn. The medial most point is the hilum on the either side

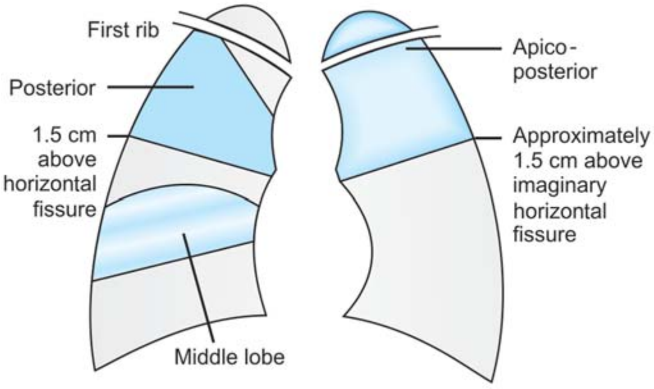
First rib
Posterior
1.5 cm above horizontal fissure
Middle lobe
Apico-posterior
Approximately 1.5 cm above imaginary horizontal fissure

Fig. 24.2: Posteroanterior view of the chest skiagram showing the posteior segments on either side. Right middle lobe is also shown

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*D Behera. Textbook of Pulmonary Medicine. Systematic Approach to Interpretation of Plain Chest Radiographs. 2nd edition. New Delhi: Jaypee Brothers Medical Publishers; 2010. pp. 134-64.

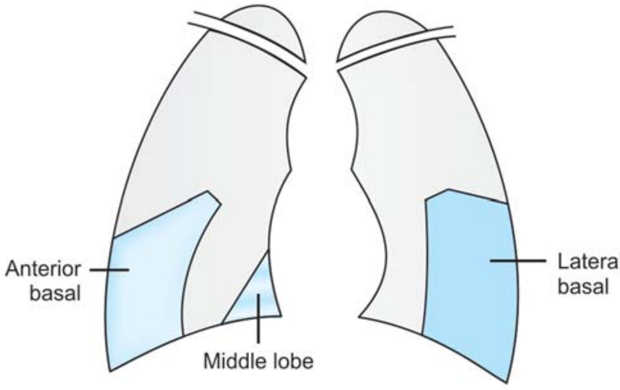

Anterior basal
Middle lobe
Lateral basal

Fig. 24.3: Basal segments of lower lobes as seen in PA view of chest skiagram

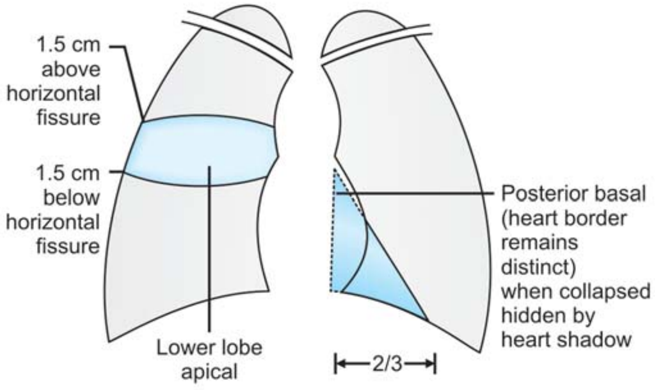

1.5 cm above horizontal fissure
1.5 cm below horizontal fissure
Lower lobe apical
2/3
Posterior basal (heart border remains distinct) when collapsed hidden by heart shadow

Fig. 24.4: Apical and posterior basal segments of lower lobes on either side on PA view

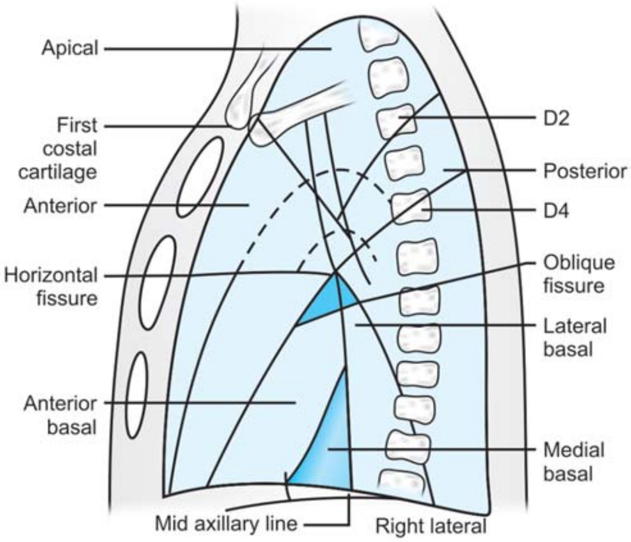

Apical
First costal cartilage
Anterior
Horizontal fissure
Anterior basal
Mid axillary line
Right lateral
D2
Posterior
D4
Oblique fissure
Lateral basal
Medial basal

Fig. 24.5: Right lateral view of the chest skiagram showing different segments of the right upper lobe and lateral and medial basal segments of lower lobe (right). Note the position of oblique fissure. It starts 1.25 cm behind the costophrenic angle and passes through the hilum to touch the body of D4 vertebra. Horizontal fissure is represented by a horizontal line drawn from the hilum

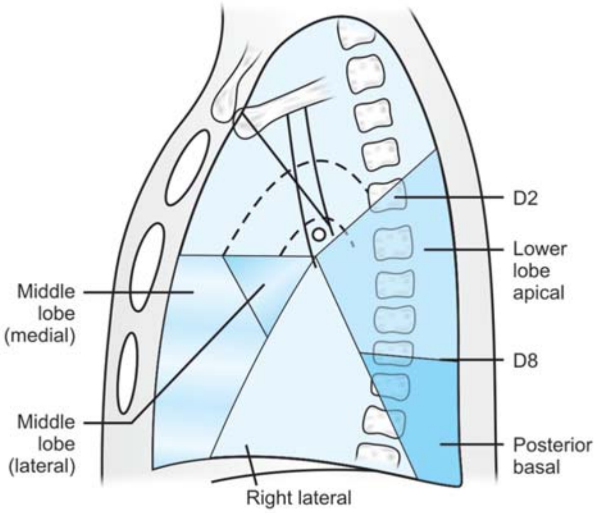

Middle lobe (medial)
Middle lobe (lateral)
Right lateral
D2
Lower lobe apical
D8
Posterior basal

Fig. 24.6A: Right lateral view of the chest radiograph showing segments of middle lobe and apical and posterior basal segments of lower lobe

patient facing the film cassette. The X-ray tube is placed at a distance of 6 feet. Although the standard technique is to use 60 to 80 kVp, many centers now use the high voltage technique using 120 to 350 kVp. The advantage with the latter technique is that the roentgenographic density of the bony thorax is reduced with an overall improvement in the quality of other structures, particularly the pulmonary vasculature and the mediastinum behind the heart. However, the disadvantage of this method is that the visibility of calcium is diminished. Proper positioning of the patient and the timing with

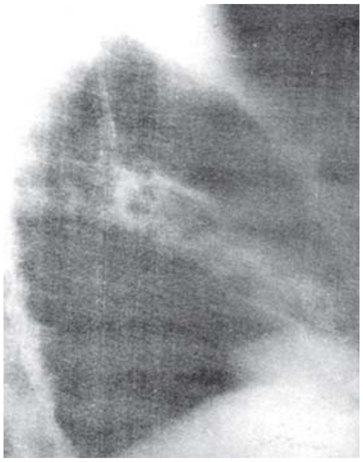


Fig. 24.6B: Cavity in the right middle lobe

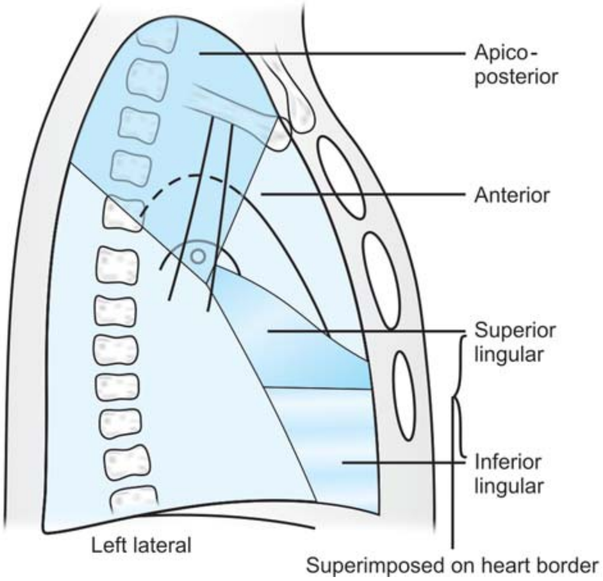


Fig. 24.7: Left lateral view of the chest skiagram showing segments of the left upper lobe including the lingular segments

phase of respiration (in full inspiration or TLC) is important for a better quality of PA film.

Anteroposterior (AP) View

This view of the chest radiograph is used when the patient is sick and cannot be moved into the radiology department—the so-called "portable X-rays". Such roentgenograms are technically inferior because of the patient's supine position, short focus-film distance and the inability in most patients to achieve a full inspiration. The mediastinal structures and the heart appear enlarged because the cassette lies at the back of the patient, and the heart is further away from the film and nearer to the X-ray tube.

Lateral View

These chest radiographs are particularly helpful in localizing a mediastinal or pulmonary lesion in its appropriate anatomical compartment. It differentiates a chest wall or cutaneous lesion from that in the lung. Small lesions in the retrocardiac or retrosternal areas or in the curvatures of the diaphragm hidden in the PA films are better seen in a lateral view. However, the lateral film is less easy to interpret than a PA film, as the two lungs and the mediastinum are superimposed one upon the other. The particular side to be X-rayed remains nearer to the film, i.e. in a left lateral view the left side is nearer to the film.[6,7]

Apicogram

Apicogram or the apical lordotic view is taken for the better visualization of the lung apices, which tend to be obscured on the standard PA projections by the upper ribs and the clavicles. The patient assumes a lordotic position arching the back, so that the nape of the neck rests on the top of the cassette, and the X-ray beam remains horizontal. The same view can be taken in an immobile patient in a modified technique. Superior mediastinum and the thoracic inlet can also be better delineated by this method. The minor fissure is better identified in the suspected cases of atelectasis of the right middle lobe in this view.

Oblique View

These skiagrams are infrequently used in respiratory workup. A standard anterior oblique view is obtained with the anterolateral wall of the chest placed against the cassette at an angle of about 45 degrees and the hands are held in extension above the head. Similarly the posterior oblique views are taken. These skiagrams are helpful in demonstrating pleural and pulmonary shadows close to the chest wall, pleural plaques in asbestosis and sometimes suspected rib pathology.

Lateral Decubitus Films

For this view, the patient lies on one side and the X-ray beam is oriented horizontally. The technique is particularly helpful in detecting small pleural effusions. Fluid collections as little as less than 100 ml can be detected by this method, whereas those taken in erect posture usually do not show pleural effusion of less than 300 ml. A more refined technique can detect fluid as little as 3 to 5 ml. The lateral decubitus view is also helpful to demonstrate the shifting of air fluid level in a cavity or to demonstrate a freely moving intracavitary loose body as a fungus ball or mycetoma in a tubercular cavity. Another usefulness of this roentgenography is to demonstrate air trapping, characteristic of endobronchial foreign bodies particularly in infants and young children.

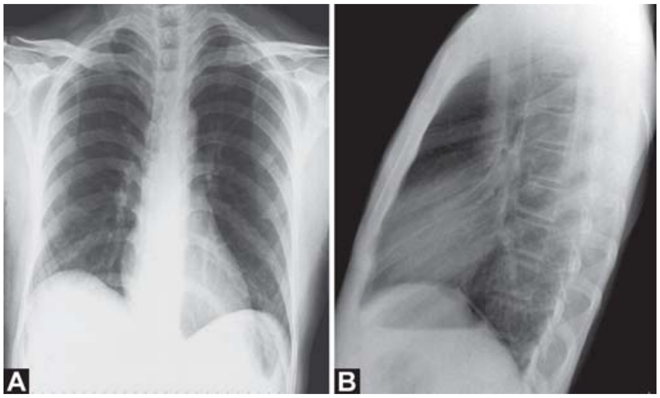
Expiratory Skiagrams

These are used (i) to investigate local or generalized air trapping; or (ii) to detect small pneumothoraces. When air trapping is generalized as in bronchial asthma or emphysema, there is little change in the lung density because of symmetrical diminution in the excursion of both diaphragms. However, localized air trapping (bronchial obstruction or lobar emphysema), the expiratory X-ray reveals restricted ipsilateral diaphragmatic elevation, a shift of the mediastinum to the contralateral side and a relative absence of the density change in the involved segment. In small pneumothoraces, when the visceral pleural line is not visible on the standard inspi-ratory films, an expiratory film may show the line more clearly. This is because of the volume of air in the pleural space being relatively greater in relation to the volume of the lung during expiration, which provides the better separation of the pleural surfaces, and the relationship of pleural line to the overlying ribs change during this maneuver.

Digital radiography is a recently introduced technique when the skiagram can be acquired digitally and can be stored like the data in a computer. The picture can be retrieved later. Further areas of particular interest can be studied more thoroughly.[11]

Fluoroscopy

Fluoroscopy or screening of the chest is helpful to visualize diaphragmatic excursions in cases of elevated diaphragms, and to distinguish a mass, particularly in the mediastinum whether it is pulsatile or not. In addition, this procedure is used more frequently now a days for transbronchial biopsy and percutaneous aspiration of lung or mediastinal masses for cytological examination. Loculated or deep-seated lung abscess, empyema or pleural effusions can be easily aspirated under fluoroscopic guidance. This is also used conveniently for other purposes like bronchography, pulmonary angiography and barium swallow examination of the esophagus.



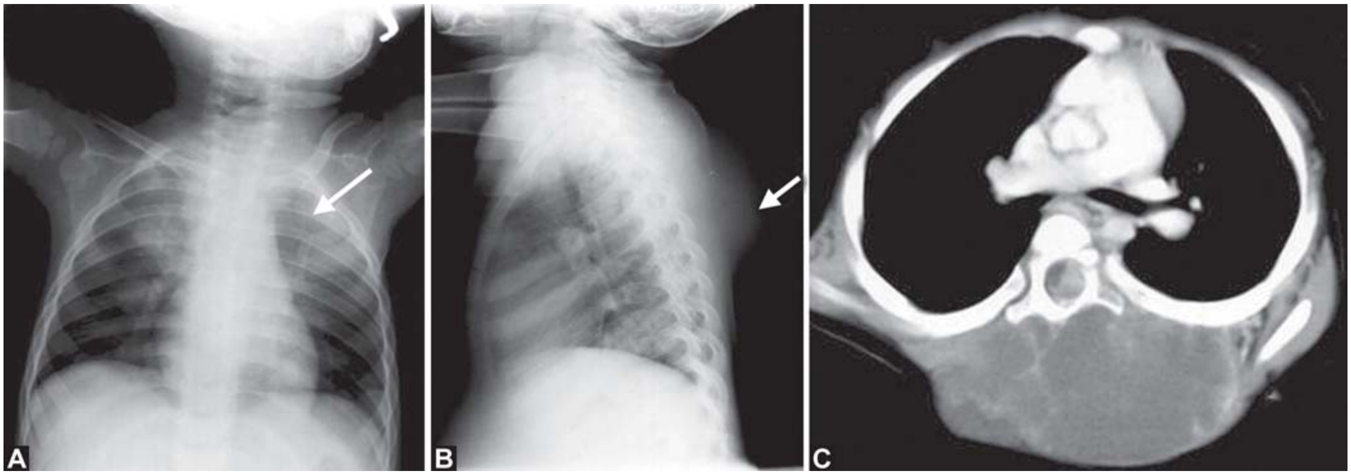
Figs 24.8A and B: Normal chest X-ray

Reading a Chest X-ray

Normal X-ray

The reading of a standard PA film should proceed in a systematic manner so that no abnormality can be missed. It is always better to read such a film together with a radiologist, a practice most often very helpful. A suggested scheme of reading a chest X-ray is as follows:

First identify the quality and centering of the film. Neither an overpenetrated nor an under penetrated film is good (Figs 24.8A and B). One may then start looking at the extrapulmonary sites like the soft tissue shadows (Figs 24.9 to 24.11), including the breast shadows, skin and sub-cutaneous tissue thickness, bony cage, supraclavicular areas, scapulae and the areas below the diaphragms. The clavicles and ribs are to be looked for any abnormality (Figs 24.12A and B).



Figs 24.9A to C: Note the external shadow while studying X-ray – also corresponding CT scan showing the external shadow

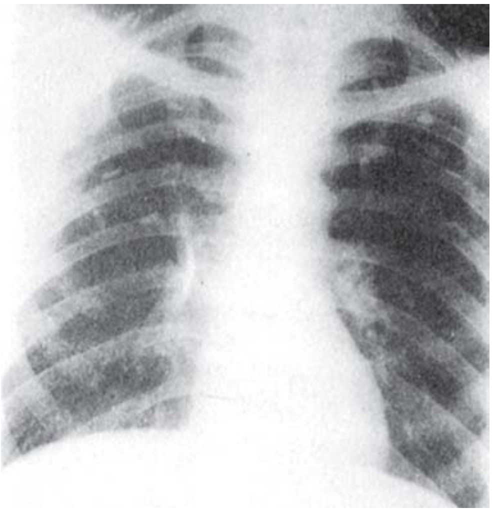


Fig. 24.10: Cysticerci in the soft tissue of the chest wall

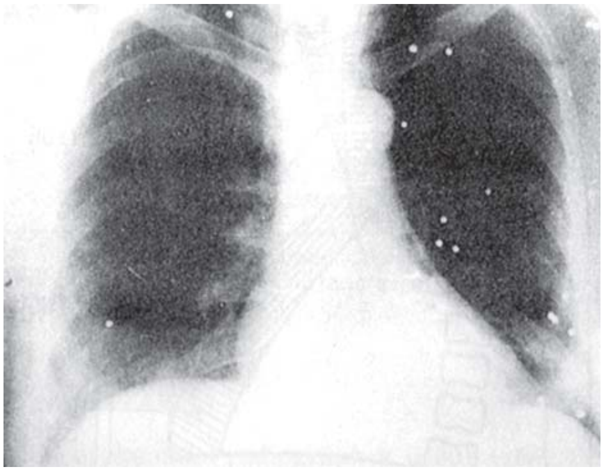
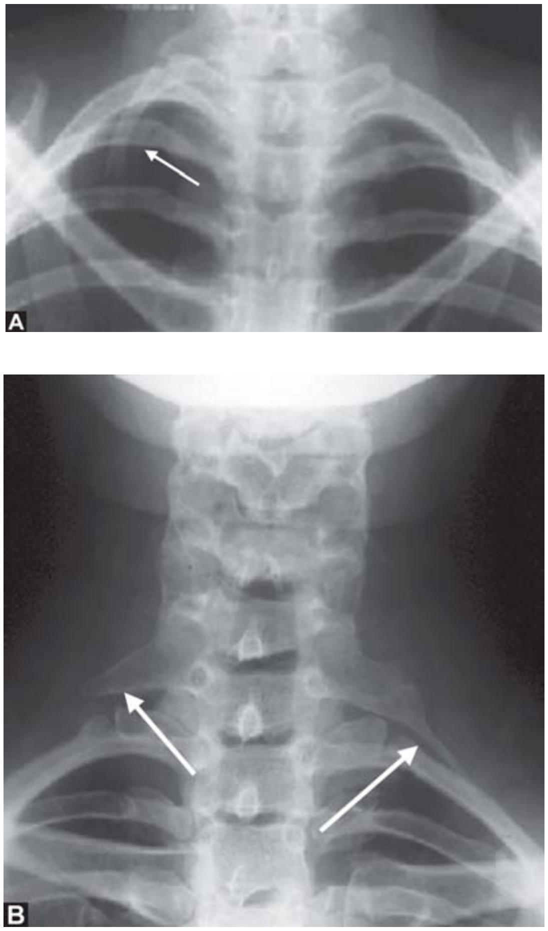


Fig. 24.11: Multiple bullets in the chest wall



Figs 24.12A and B: Cervical ribs

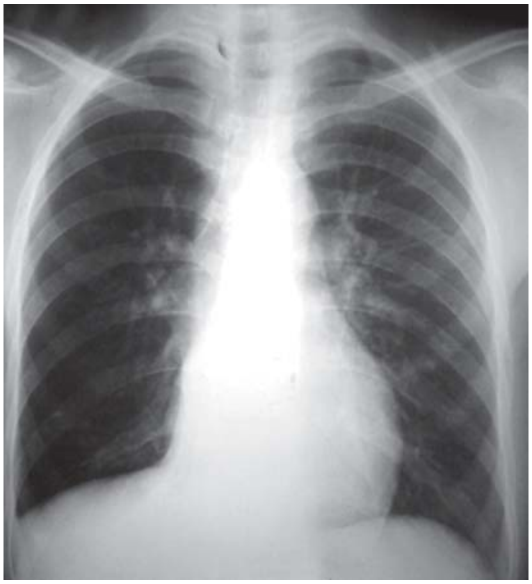


Fig. 24.13: CXR—Flattening of right dome of diaphragm—right subpulmonic effusion

The levels of both the diaphragms and their contour are to be studied and compared. Normally the right diaphragm is higher than the left and lies at the level of the sixth rib anteriorly (Figs 24.8 and 24.13).

The mediastinum is an important area, which is liable to be misread/over read. The tracheal and bronchial shadows can often be seen. The left pulmonary artery lies above the left main bronchus at the level of the seventh rib and is higher by one rib space than the right (at the level of eighth rib), which overlaps the right bronchus intermedius. The dimensions of both the arteries are to be measured. Normally, the maximum diameter is less than 17 mm. The aortic knuckle is a prominent structure on the left side. The cardiac size and its borders are then to be looked for. Normally, the right border of the heart does not extend beyond the spinal column. The Cardiothoracic Ratio (CT Ratio) is normally less than 50%. An attempt should always be made to look behind the heart, if necessary by taking a more penetrated or a left lateral view. Thus, any abnormality in the mediastinum can be picked up. The spine should always be examined carefully for any evidence of destruction, secondaries or cold abscess. Normally, the spine and the left lower lobe vessels are just visible through the heart shadow. The lung parenchyma is divided into three radiological zones. Upper zone is the area lying between the apex and the second intercostal space; the mid zone between the second and the fourth space; and the lower zone extends from the fourth space downwards. Any abnormality in each of these zones on either side should be noted very carefully.

Various deviations from the normal skiagram and few other abnormalities that can be seen are shown in Figures 24.14 to 24.34.

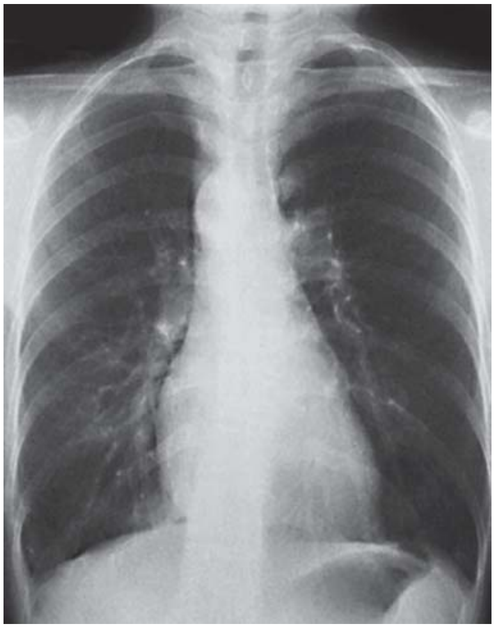


Fig. 24.14: Right sided aortic arch

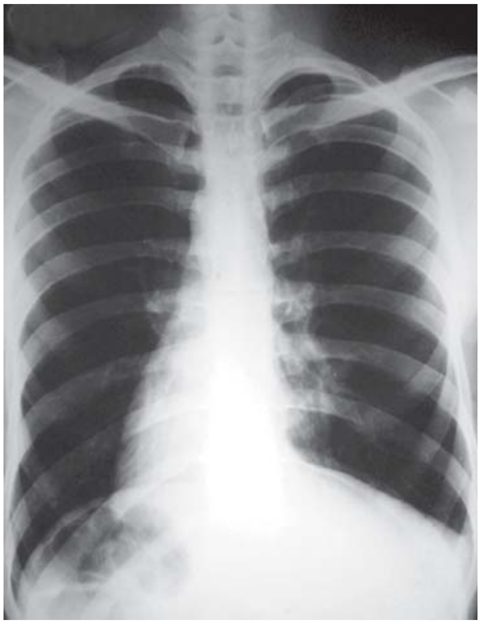


Fig. 24.16: CXR—Dextrocardia with situs inversus

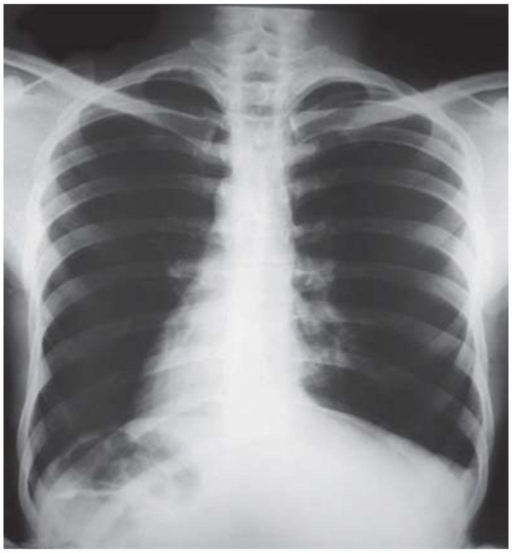


Fig. 24.15: Dextrocardia

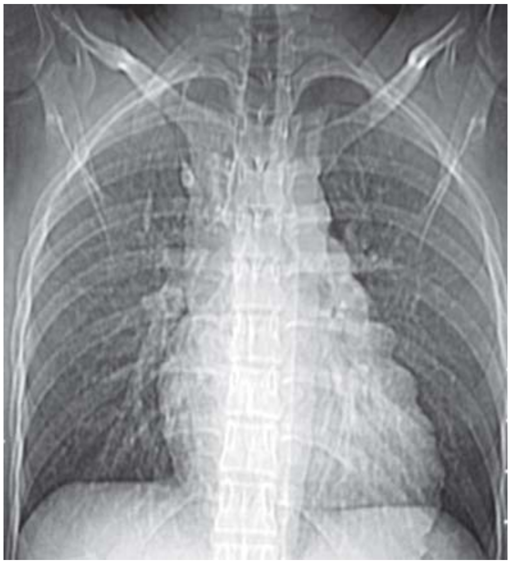


Fig. 24.17: Azygous fissure

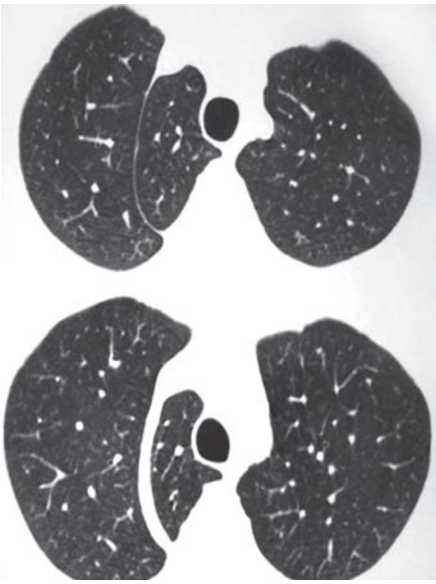


Fig. 24.18: Azygous fissure (CT-picture)

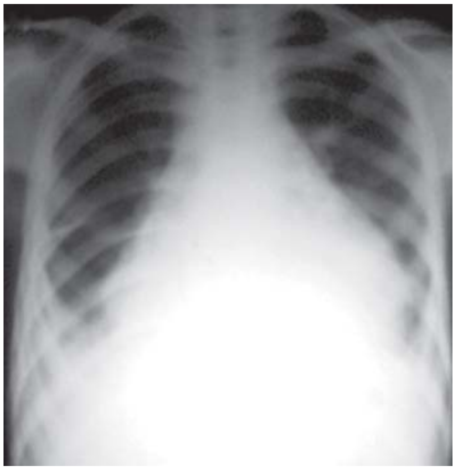


Fig. 24.19: CXR—Globular shaped heart shadow: Pericardial effusion

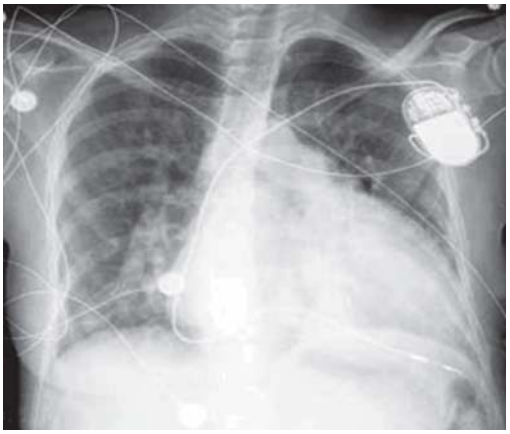


Fig. 24.20: Left ventriculomegaly

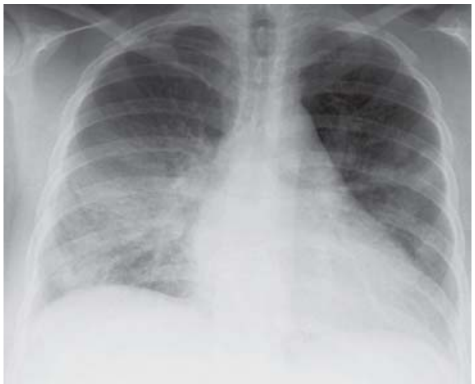


Fig. 24.21: Pulmonary edema

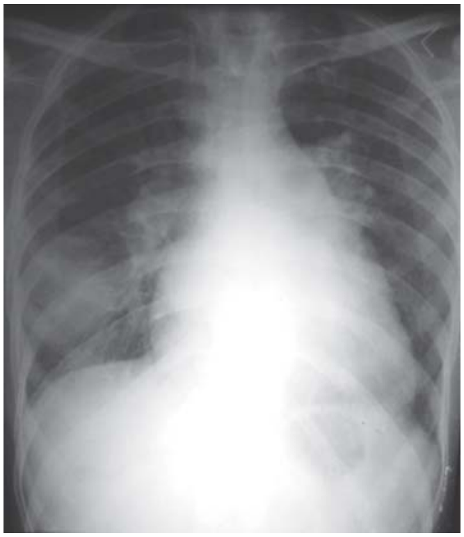


Fig. 24.22: Fluid in the major fissure in a case of congestive heart failure—pseudotumor

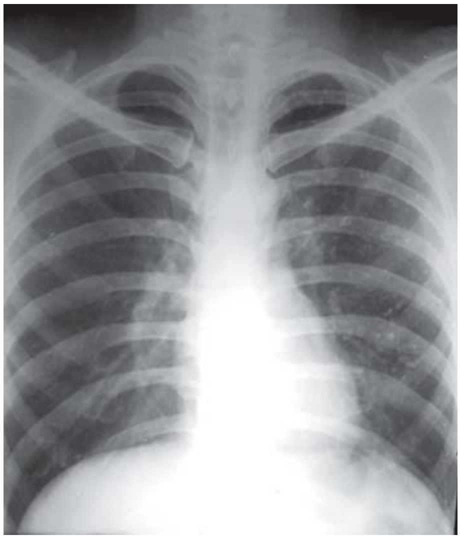


Fig. 24.23: Unilateral hyperluscent lung on the right side—congenital

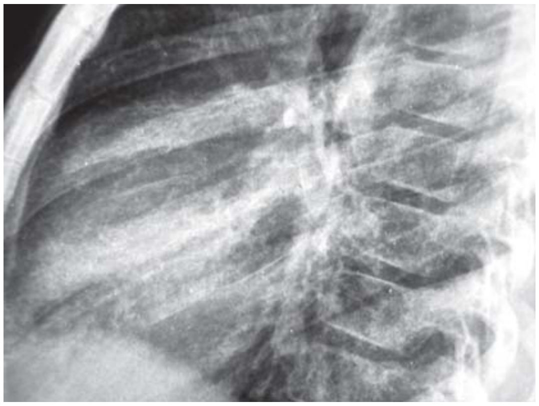


Fig. 24.24: Tooth in the bronchus—FOB is indicated

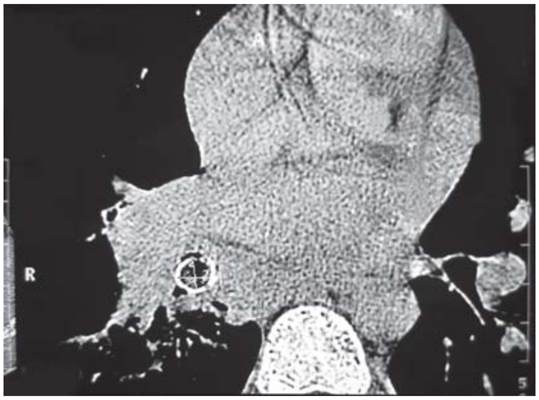


Fig. 24.27: Ear ring in the bronchus

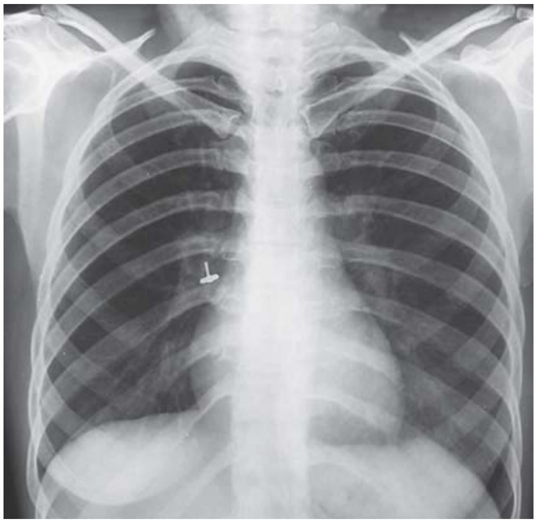


Fig. 24.25: Ear pendant in the bronchus

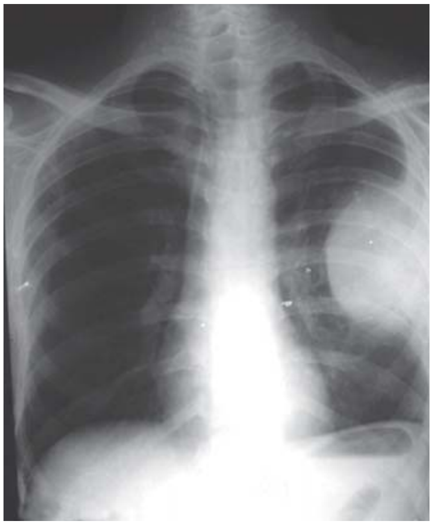


Fig. 24.28: Extrapulmonary sign—A case of pleural tumor

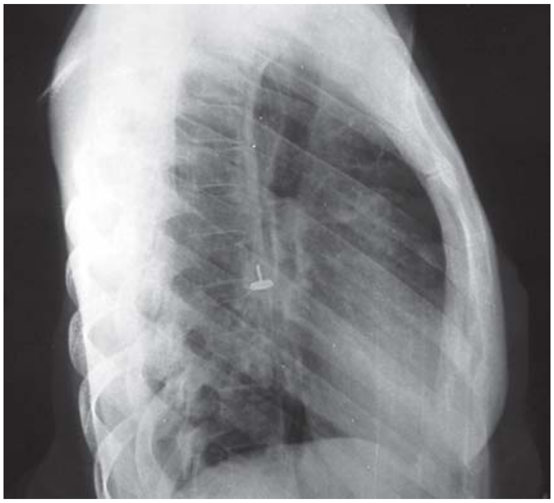


Fig. 24.26: Laternal view showing ear pendant in the bronchus

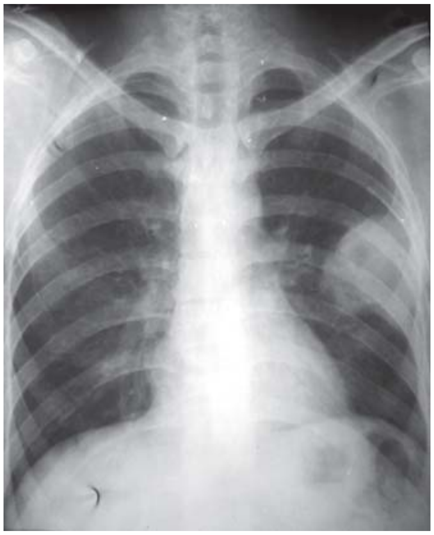


Fig. 24.29: The shadow is producing extrapleural sign. Note both the angles are obtuse

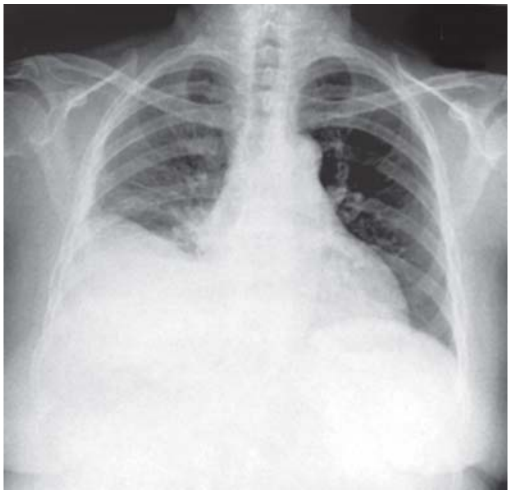


Fig. 24.30: Right subpulmonic effusion

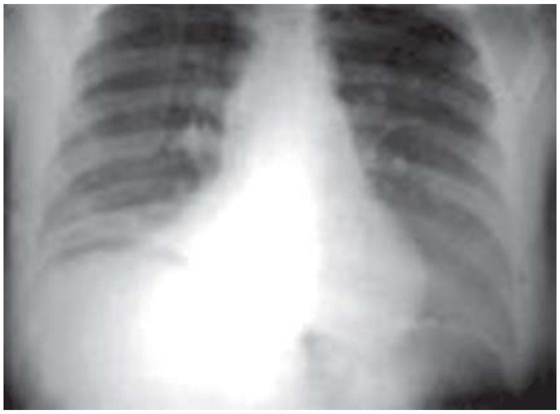


Fig. 24.31: Free air under right dome of diaphragm

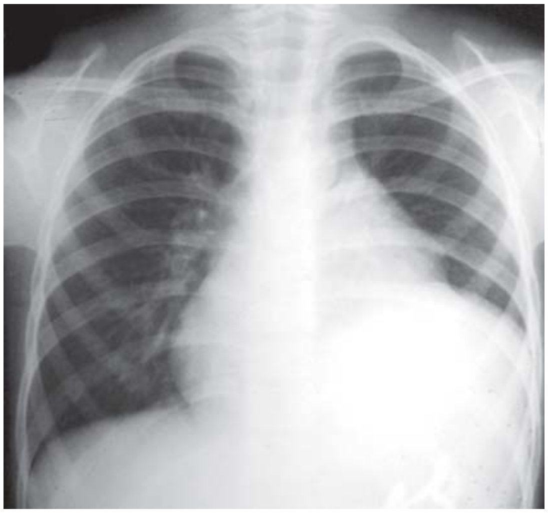


Fig. 24.32: CXR—Homogeneous opacity at left cardiophrenic angle (pleural effusion)

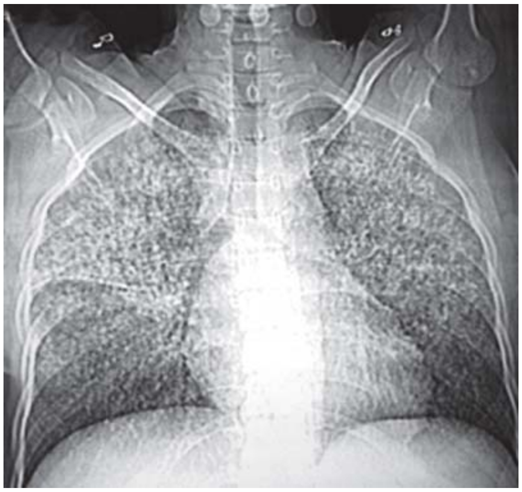


Fig. 24.33: CXR—Extensive miliary mottling

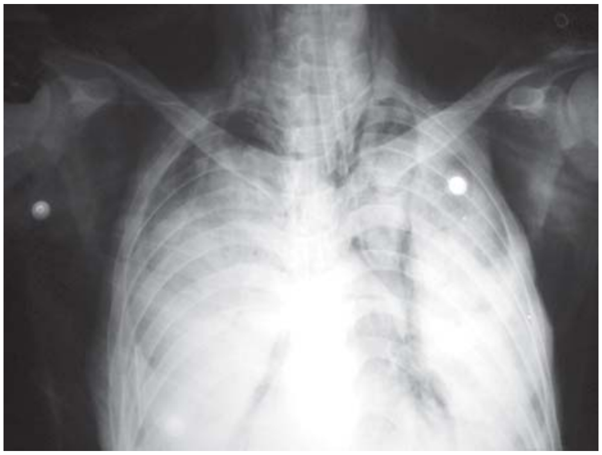


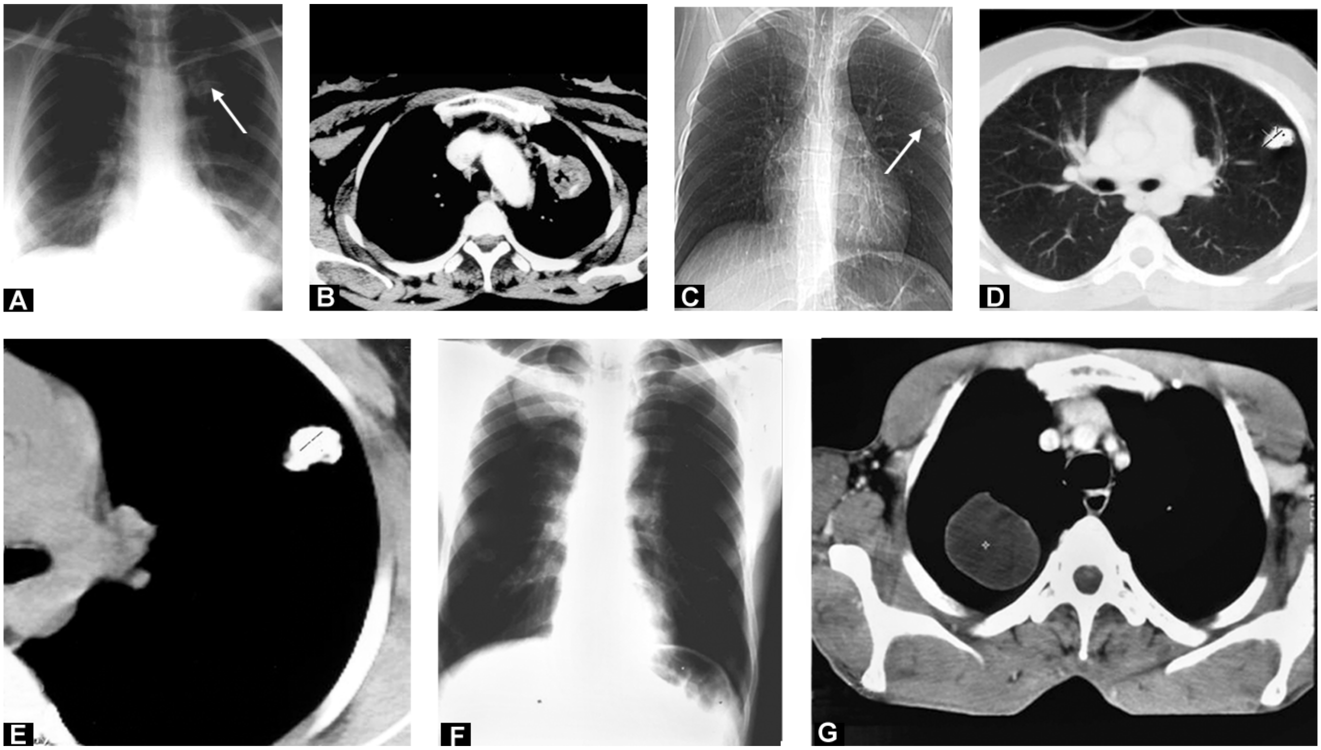
Fig. 24.34: Alveolar proteinosis

Limitations of Chest X-rays

Seven to twenty-one percent of normal chest X-rays reveal abnormalities on CT scan. Normal chest X-ray does not rule out mediastinal lymphadenopathy. Bronchiectasis, early interstitial lung disease, miliary shadows, nodules less than 5 mm may be missed on chest X-ray.

Abnormal Radiological Findings

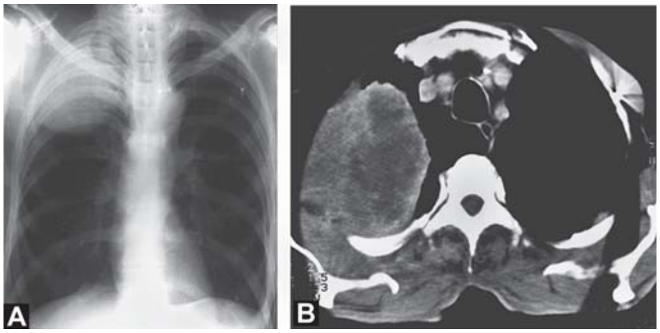
While it is not possible to describe all the radiological findings of all the pulmonary diseases, a generalized description of possible abnormalities in a chest skiagram will be discussed in brief. The findings may be divided into: (i) a solitary nodule; (ii) parenchymal shadows; (iii) hilar and mediastinal shadows and; (iv) abnormalities of the pleura.



Figs 24.35A to G: Solitary pulmonary nodule

Solitary Pulmonary Nodule (SPN) (Figs 24.35 and 24.36)

A solitary nodule[12] is defined as a shadow of either 4 cm or less in diameter with distinct borders and is surrounded by relatively normal lung parenchyma. When such a lesion is found in a chest skiagram, it is important to decide whether it is benign or malignant. Three points need special consideration: Age of the patient, doubling time, margins and calcifications if any. Solitary nodules in subjects below 40 years of age are relatively benign and in patients above the age of 40 years, carcinoma needs to be excluded particularly, if he is a smoker. All attempts should be made to obtain a previous skiagram, if one was taken, since a lesion lying for few years, is unlikely to be a malignant one. If the lesion in the present skiagram doubles in volume within seven days, it is more likely to be a benign one. However, secondaries from choriocarcinoma, testicular tumor and osteogenic sarcoma may grow very fast and for these a time limit of 11 days is suggested. On the other hand, lesions having a doubling time greater than 465 days are also benign. Anything outside these limits is more likely to be malignant. If the margins are lobular or nodular in appearance, the chances of malignancy are very high. A tail is suggestive of a granuloma or arteriovenous malformation. Small satellite lesions accompanying the nodule are common with tubercular lesions. Presence or absence of calcification in the nodule is another indicator of the benign or malignant nature of the lesion. While presence of calcification is taken as a sign of benign lesions, exceptions are there. Calcified nodules may be malignant in the following conditions. (a) a primary carcinoma engulfing a preexisting calcified granuloma; (b) solitary metastases from osteogenic sarcoma or chondrosarcoma; (c) primary



Figs 24.36A and B: Not solitary pulmonary nodule – not well-defined, invading the surrounding structure

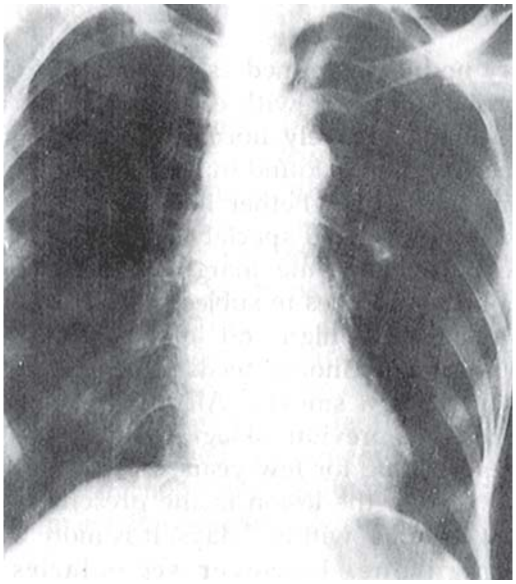


Fig. 24.37: Calcified solitary nodule on the left mid zone (tuberculoma)

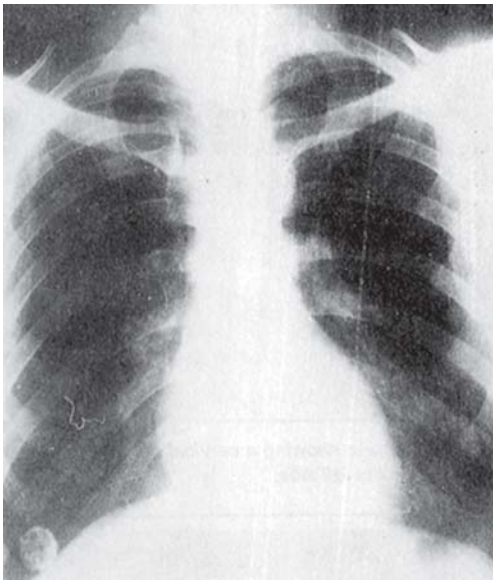


Fig. 24.38: Note popcorn calcifiction in a hamartoma in the right lower zone

peripheral squamous cell carcinoma or papillary adenocarcinoma (primary or metastatic); and (d) rare cases of carcinoid tumors or metastases from mucinous adenocarcinomas from colon. Benign lesions, which usually calcify, are: Tuberculoma, histoplasmoma or other fungal diseases (Fig. 24.37). The pattern of calcification is sometimes characteristic of certain lesions. A small central nidus is seen in granulomas or hamartomas; laminated appearance is almost pathognomonic of granulomas and indicates a benign nature of the disease; popcorn ball calcification is a characteristic feature of hamartomas (Fig. 24.38); and multiple punctate foci throughout the lesion may be seen either in a granuloma or hamartoma.

Other spherical lesions seen in a chest skiagram are due to: Carcinoids, cylindromas, leiomyomas, fibromas, neural tumors, tuberculomas, histoplasmomas, cryptococcomas, hydatid cyst, syphilitic gummas, lung abscess, progressive massive fibrosis, Caplan's syndrome, paraffin granulomas, aspiration pneumonias, rheumatoid nodules, Wegener's granulomatosis, bronchocentric granuloma, arteriovenous malformation, sequestration of lung, infarcts and interlobar effusion.

With the availability of different modern diagnostic techniques, assessment of solitary pulmonary nodule has become easier. But the problem is of high sensitivity of these methods. The main concern is the nature of the nodule—whether it is malignant or benign. Too sensitive methods will expose the patients for unnecessary exploration and many benign lesions will be resected unnecessarily. An SPN diagnostic approach that includes a transbronchial biopsy, then Percutaneous Needle Aspiration (PCNA), clinical observation, repeat CT scans, and repeat biopsies for continued suspicion of malignancy appears to reduce the unnecessary surgical excision of benign nodules from the current rate of 60% to 5% of SPN resections without affecting the survival of patients who have malignant SPNs. Both the ultrasound and radio-guided techniques are accurate to detect solitary pulmonary nodules, but the radio-guided method yields complications as compared with the ultrasound.[13] Ultrathin section with Multislice Computed Tomography (MSCT) and Multiplanar Reconstructions (MPR), Curved Multiplanar Reconstructions (CMPR) and Surface-Shaded Display (SSD) reconstruction can improve the demonstration of the patterns of tumor-bronchus relationships, which can reflect the pathological changes of the nodules to some extent and help differentiate malignant from benign tumors. According to one report CT demonstrated the relationship between the SPN and bronchi in 46 (86.8%) malignant and 18 (75.0%) benign nodules. Five types of tumor-bronchus relationships were identified with MSCT. Type I: The bronchus was obstructed abruptly by the SPN; type II: The bronchus penetrated into the SPN with tapered narrowing and interruption; type III: The bronchial lumen shown within the SPN was patent and intact; type IV: The bronchus ran around the periphery of the SPN with intact lumen; type V: The bronchus was displaced, compressed and narrowed by the SPN. Malignant nodules were most commonly of type I (58.5%), secondly of type IV (26.4%) and rarely of type V (1.9%). Benign nodules were most often of type V (36.0%), followed by type III (20.0%), type I (16.0%), and there were no type II. Types I, II and IV were more common in malignant nodules, whereas type V was seen more frequently in benign nodules ($p < 0.05$). There was no statistically significant difference between the two groups regarding type III.[14] Dynamic MR imaging and CT seem to be equally well suited for the differentiation between benign and malignant SPNs.[15]

Computer-Aided Diagnosis (CAD) has the potential to improve radiologists' diagnostic accuracy in distinguishing small benign nodules from malignant ones on High Resolution Computed Tomography (HRCT).[16] With a preoperative selection of the patients the rate of secondary thoracotomies due to bronchial carcinoma is low (4%). In patients with a previous history of malignant disease, 22% of the pulmonary lesions are benign. Video-Assisted Thoracoscopic Surgery (VATS) is a safe diagnostic method, with little discomfort for the patient.[17] Thoracoscopic resection of solitary pulmonary nodules is safely feasible. It results in better patient satisfaction, less nursing care and shorter in-hospital stay and the procedure can be performed without general anesthesia.[18] Ill-defined margins, spiculation, involvement of bronchi or vessels, and tumor enlargement visualized by CT are still important signs of malignancy even for nodules less than 10 mm in size. Tumor size, even for lung cancers measuring less than 10 mm, is not an indication for limited resection.[19] The use of MPR for CT-guided lung biopsy is useful for improving diagnostic accuracy with no significant increase in pneumothorax rate or total procedure time.[20] Recently, Dynamic MR imaging delineates significant kinetic and morphologic differences in vascularity and perfusion between malignant and benign solitary pulmonary nodules. Washout seems to be highly specific for malignancy. Malignant nodules show stronger enhancement with a higher maximum peak and a faster slope ($P < 001$). Significant washout (> 0.1% increase in signal intensity per second) is found only in malignant lesions (14 of 27 lesions). Sensitivity, specificity, and accuracy are 96%, 88% and 92 %, respectively, for maximum peak; 96%, 75% and 86% for slope; and 52%, 100%, and 75% for washout. When curve profiles and morphologic enhancement patterns are combined, sensitivity increases to 100%.[21]

Established methods (radiography for detection, spiral CT for characterization), after thorough evaluation, will soon be replaced by Magnetic Resonance Imaging (MRI). Recent experience with MRI points to its potential for the detection and characterization of pulmonary nodules while avoiding ionizing radiation. The development of indications for MRI of the lung (e.g. pediatric radiology) is not yet clear.[22] Pulmonologists are frequently asked to evaluate the CT-detected, small, noncalcified nodule invisible on standard chest radiography. Immediate biopsy is justified, if the likelihood of cancer is high, but if that likelihood is low or intermediate, a period of observation by CT is appropriate. VATS or thoracotomy are rarely necessary for a diagnosis of lung cancer in the CT-detected small pulmonary nodule.[23]

The challenge of diagnosis and management of solitary pulmonary nodules is among the most common yet most important areas of pulmonary medicine. Ideally, the goal of diagnosis and management is to promptly bring to surgery all patients with operable malignant nodules while avoiding unnecessary thoracotomy in patients with benign disease. Effective management of the solitary pulmonary nodule depends upon an understanding of decision analysis principles so that diverse technologies can be integrated into a systematic approach. In almost all patients, Computed Tomography (CT) is the best first step. Three key questions can then help to guide the workup of the SPN. These are what is the pretest probability of cancer, what is the risk of surgical complications, and does the appearance of the nodule on CT scan suggest a benign or malignant etiology. In patients with average surgical risk, Positron Emission Tomography (PET) scan is warranted when there is discordance between the pretest probability of cancer and the appearance of the nodule on CT scan. Thus, when either the patient has a low risk of cancer and the CT suggests a malignant origin, or when there is high risk of cancer and the CT appears benign, PET scan will be cost-effective. In most other situations, PET scanning is only marginally more effective than CT and fine needle aspiration strategies, but costs much more.[24]

Pulmonary hamartoma is the most common type of benign lung tumor. The vast majority of pulmonary hamartomas represent as solitary pulmonary nodules. Definite diagnosis and the treatment can be achieved by surgical resection with minimal morbidity. Tumor recurrence is very rare.[25]

Airspace Disease

Either liquid, or cells, or both replace the air within the acinus. Typically many contiguous acini are involved producing a homogenous opacity (Fig. 24.39). The size may vary from few centimeters to a whole lobe. Usual causes of such airspace opacities include: Alveolar edema, both cardiac and noncardiogenic, pneumonic

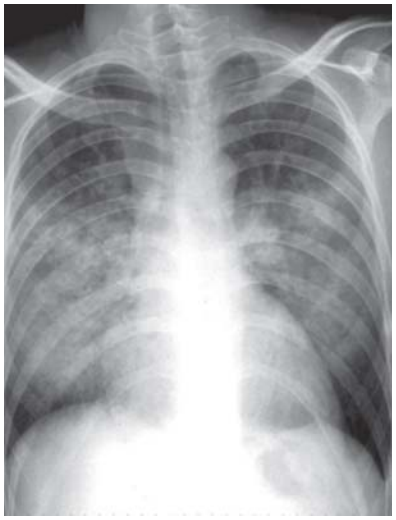
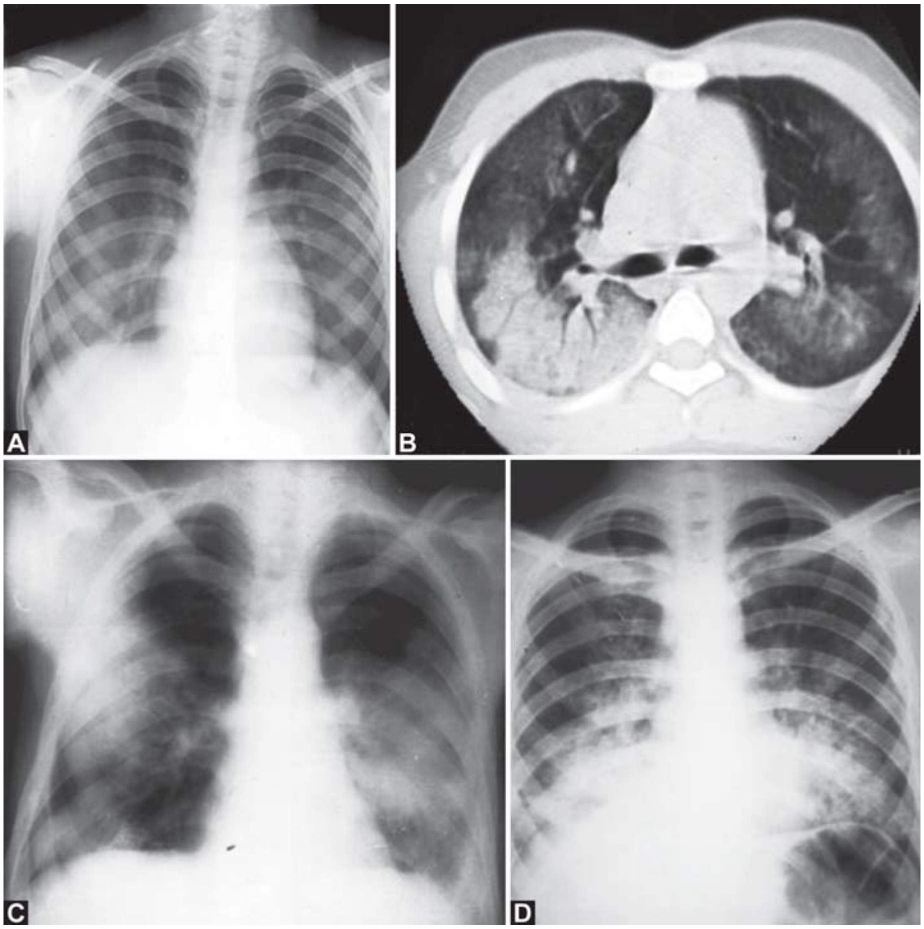


Fig. 24.39: Alveolar vs interstitial pathology

consolidations bleeding into the acinus; aspiration of blood or lipid; neoplastic infiltrations (bronchoalveolar cell carcinoma and lymphomas); alveolar proteinosis and early stages of fibrosing alveolitis. The classical findings of airspace disease include alveolar nodules or alveolar shadows, coalescence, poor margination, presence of airless bronchograms or bronchiolograms, air alveolograms, no or minimal atelectasis and the evolution is usually rapid. An alveolar shadow or the alveolar pattern of the shadow is nodular in shape measuring 4–10 mm in diameter with well-defined margins and there will be the presence of small multiple radiolucencies. Another characteristic feature of airspace consolidation is that it does not respect segmental or subsegmental boundaries as is usual with pneumococcal pneumonias or pulmonary edema. However, diseases produced by vascular route or through the tracheobronchial tree usually have a segmental distribution as in an-aspiration pneumonia. Air bronchogram commonly seen in a consolidation, is due to a patent bronchus containing the air column in the bronchi visible in the skiagram. The area of the lung should be completely airless for visualization of air bronchogram, as in collapse or consolidation (Figs 24.39 to 24.46).



Figs 24.40A to D: Consolidation

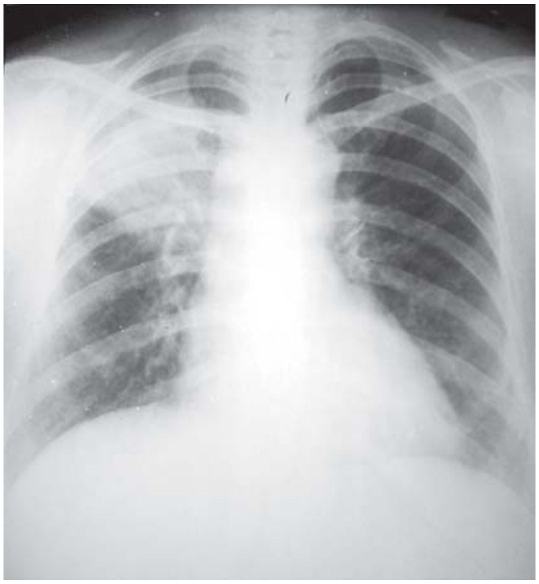


Fig. 24.41: Consolidation of right upper lobe. Note air bronchogram

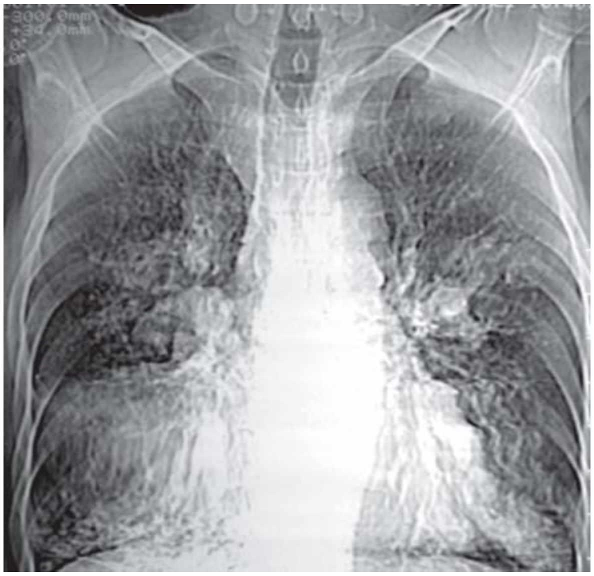


Fig. 24.42: CXR—Basal consolidation with air-bronchograms—BOOP

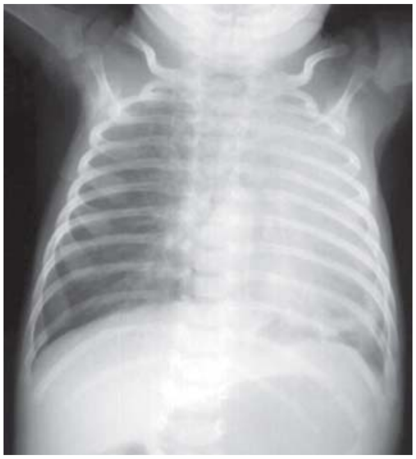


Fig. 24.43: Left upper lobe consolidation – Anteroposterior view

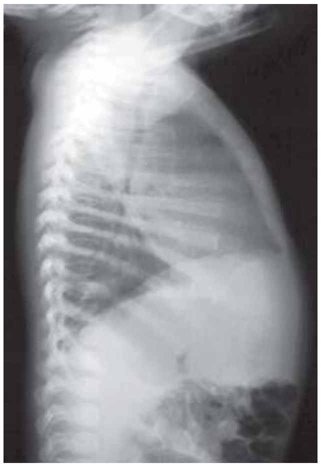


Fig. 24.44: Left upper lobe consolidation – Lateral view

Parenchymal Atelectasis

The basic difference between a consolidation and an atelectasis (collapse) is that while in the former the lung volume is maintained, in the latter, there is a volume loss (Figs 24.47 to 24.56). Common types of atelectasis described are: Resorption atelectasis and compression or passive atelectasis. A resorption atelectasis is mainly due to bronchial obstruction and consequent absorption of air from the alveoli distal to the obstruction rendering the alveoli airless. However, this type of atelectasis can occur without bronchial obstruction as in bronchiectasis. The only definite roentgenographic sign of this type of collapse is a loss of lung volume evidenced radiologically as the displacement of interlobar fissures. Other features are an increase in density locally, elevation of the ipsilateral hemidiaphragm, shift of the mediastinum to the side of collapse, compensatory overinflation, displacement of hilum, crowding of the ribs and absence

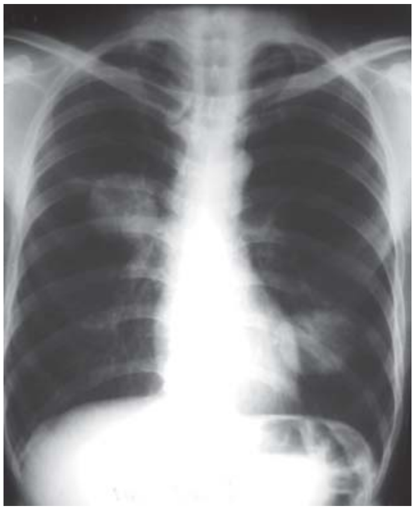


Fig. 24.45A: Round pneumonia in both the lungs

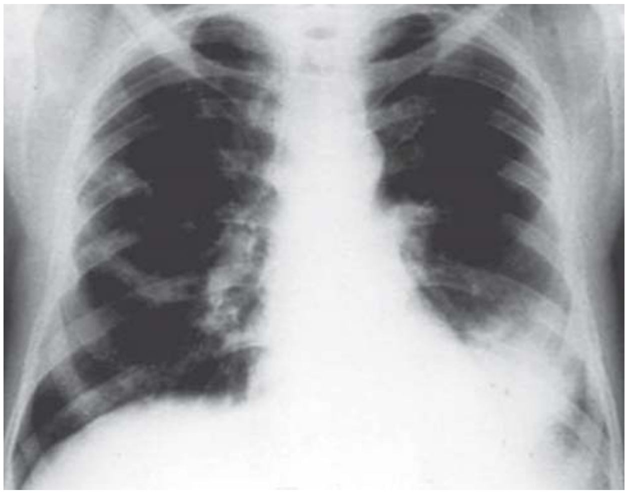
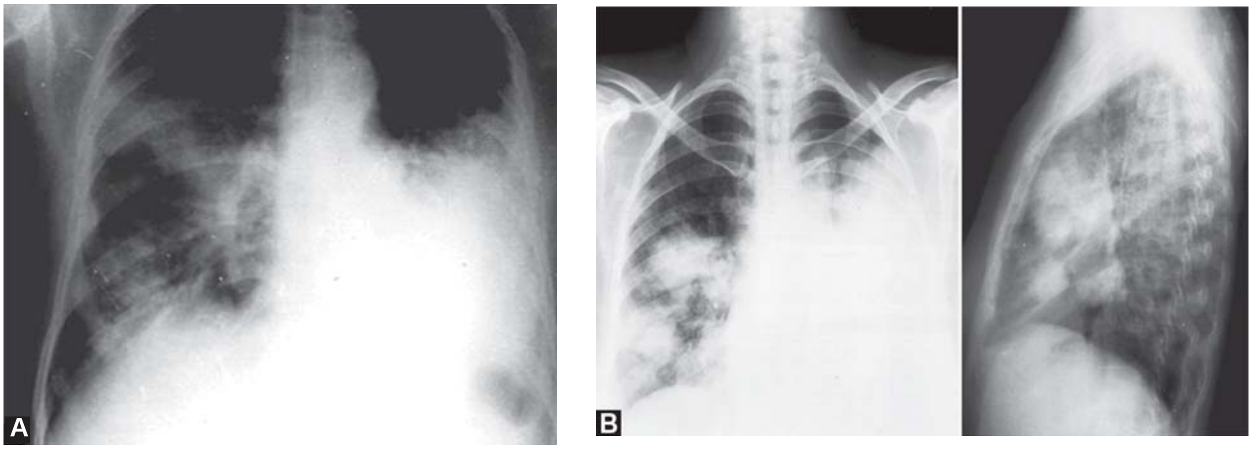
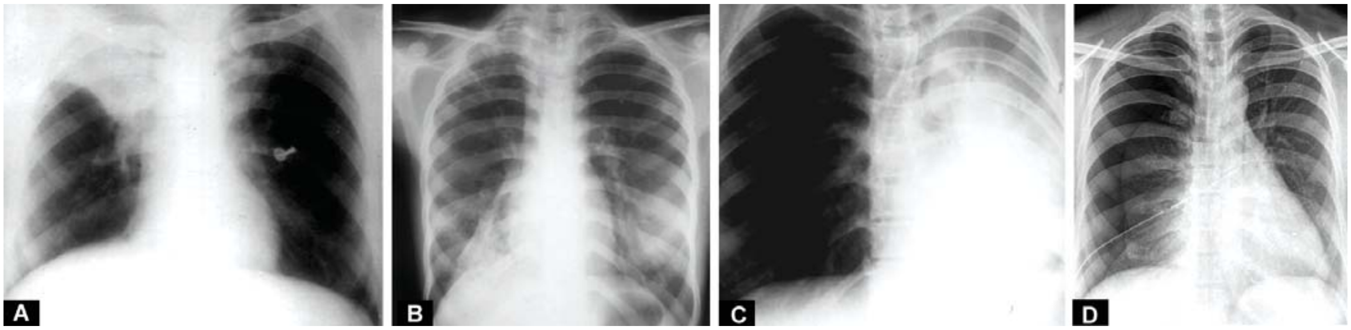


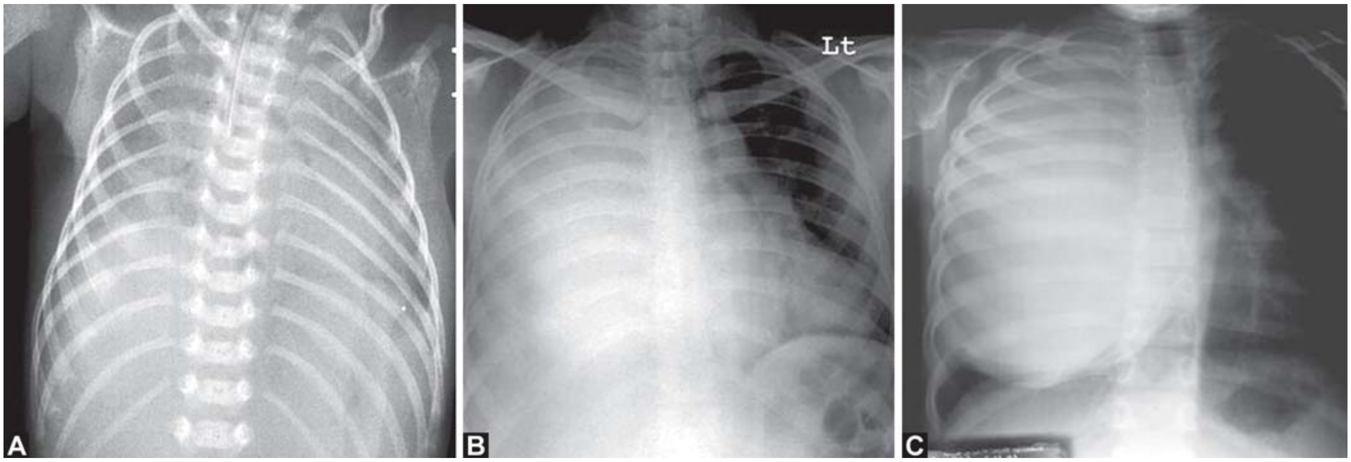
Fig. 24.45B: Consolidation in left lower zone



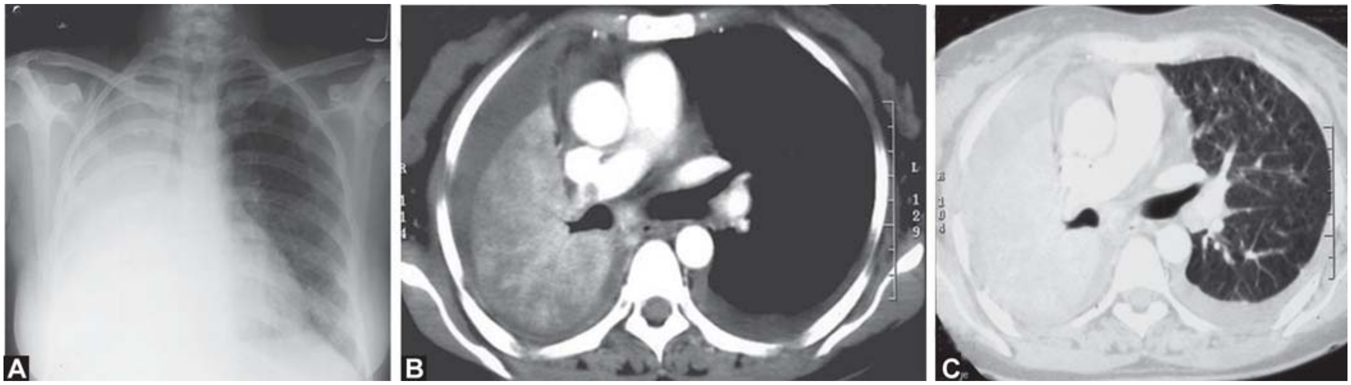
Figs 24.46A and B: Nonresolving consolidation



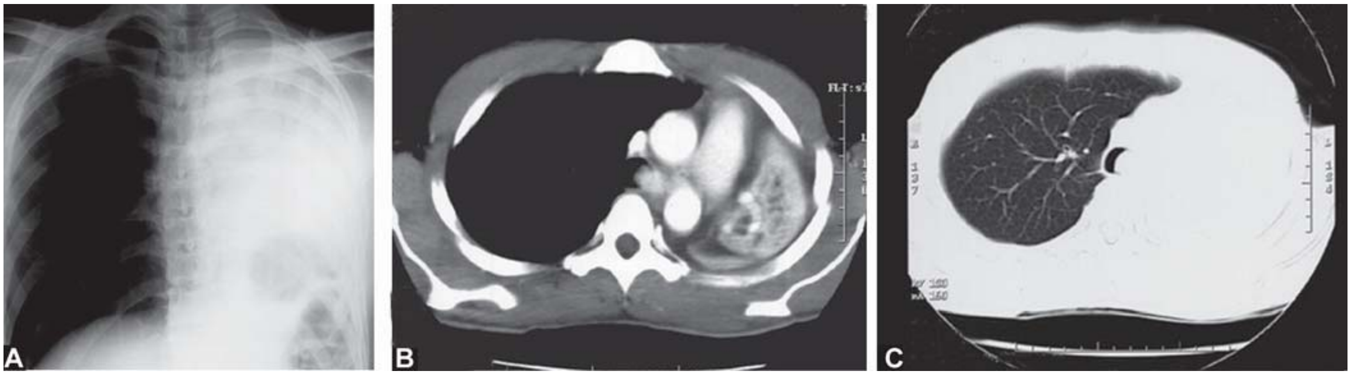
Figs 24.47Ato D: Pulmonary collapse



Figs 24.48A to C: Opaque hemithorax



Figs 24.49A to C: Opaque hemithorax: Due to collapse of right lung



Figs 24.50A to C: Opaque hemithorax: Due to collapse of left lung

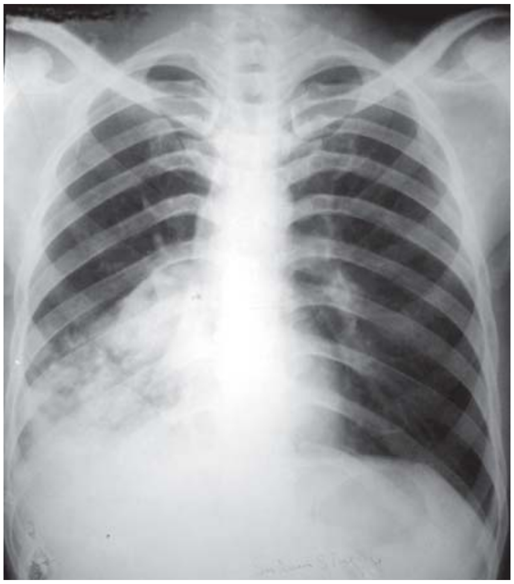


Fig. 24.51: Postobstructive collapse consolidation on the right lower lobe

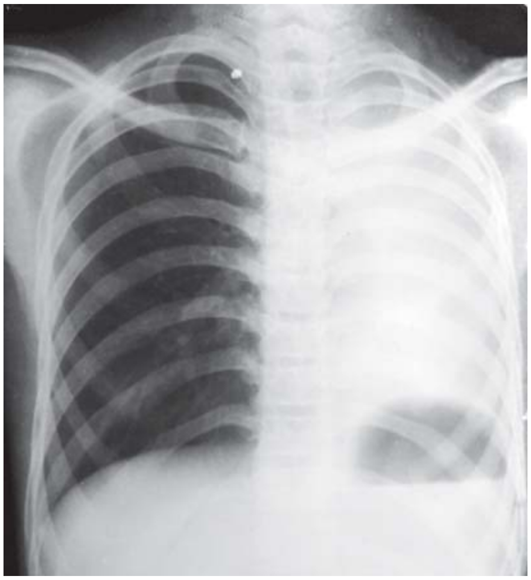


Fig. 24.52: Entire left lung collapse

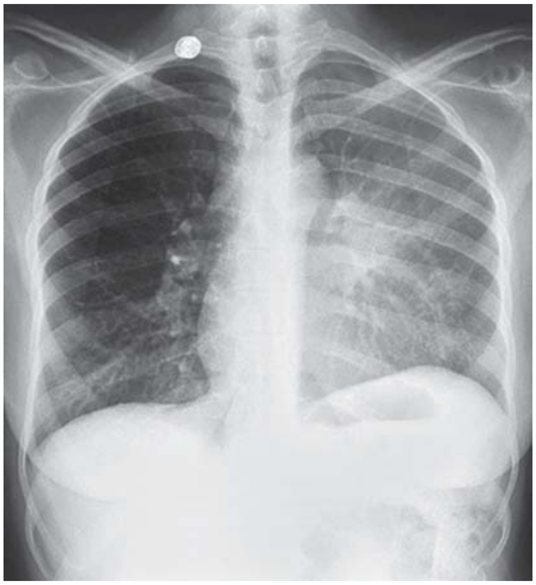


Fig. 24.53: Left upper lobe collapse – Anteroposterior view

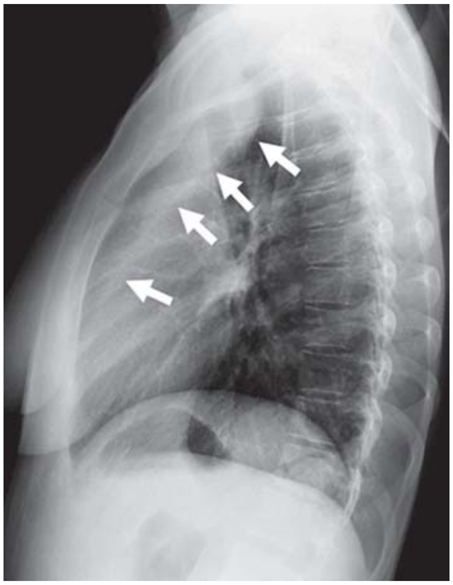


Fig. 24.54: Left upper lobe collapse – Lateral view

of air bronchogram. *Compression or relaxation* or *passive atelectasis* is seen with pneumothorax or pleural effusion. The lung is compressed medially. The compressed lung is greatly diminished in volume. Since the bronchi are usually patent unless there is an obstruction, air bronchogram is commonly present and should be looked for in all cases of pneumothorax and pleural effusion. Absence of this sign should raise the doubt of a proximal obstruction. *Rounded or helical atelectasis* is a recently described unusual radiological shadow. On conventional roentgenograph, the lesion is a fairly homogenous ill-defined pleural-based opacity, 6 to 7 cm in diameter, most commonly situated in the posterior portions of the lower lobes. The bronchovascular bundles in the vicinity of the mass are gathered together in a curvilinear fashion as they pass towards the mass simulating the tail of a comet

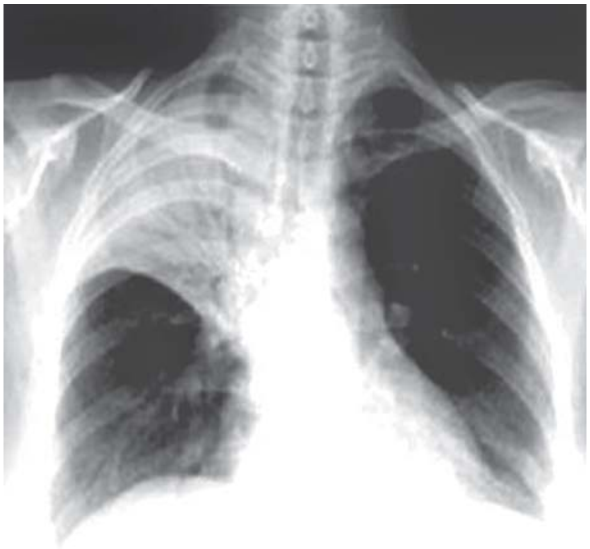


Fig. 24.55: Right upper lobe collapse

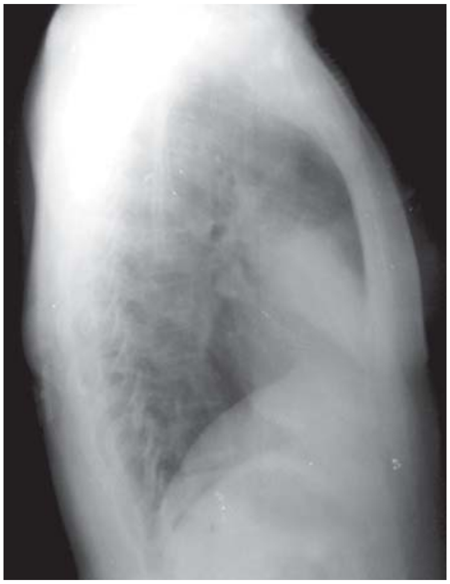


Fig. 24.56: Right middle lobe collapse. Note the shadow is bound by the two fissures which are also displaced

(Comet tail sign). The round opacity is due to a chronic inflammatory process in the parenchyma and most often confused with malignancy. The pathogenesis of this is due to pleural fibrosis, which contracts resulting in the compression of the nearby lung parenchyma.

Metastasis

Metastatic lesions to the lungs are common from many parts of the body because blood from all parts of the body comes to the lungs and because of the rich vascular supply in the lungs. Though typically, the metastatic lesions are rounded, multiple and more abundant in the lower lung fields, (Figs 24.57 to 24.59) many atypical forms can be seen. This can be in the form of lymphangitis carcinomatosis (linear streaky shadows) (Figs 24.60 and 24.61) cannonball lesions and cavitating lesions. Pulmonary metastases typically present as mostly multiple and bilateral, well-defined, noncalcified pulmonary nodules with predominantly basal and peripheral location. Ill-defined, cavitating, calcified and endobronchial metastases are uncommon. In the absence of pathognomonic findings precise differentiation from other even benign pulmonary nodules is almost impossible. Demonstration of contrast enhancement at CT or MRI or evidence of growth at serial examinations supports the diagnosis of pulmonary metastases. In uncertain cases percutaneous fine-needle aspiration or cutting needle biopsy will allow diagnosis with the acceptable risk of complications and patient discomfort. The only relatively common complication of pneumothorax can and should be controlled by the interventional radiologist by aspiration or drainage.[26]

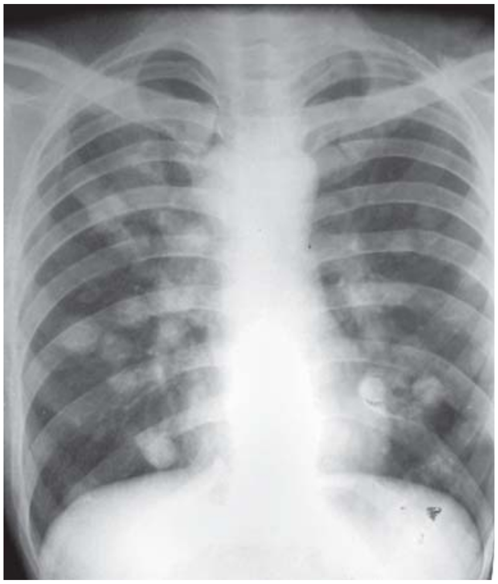


Fig. 24.57: Canonball metastasis

Fibrosis

Parenchymal fibrosis has the same findings as in a resorption collapse except that it is a more chronic process and the opacity is not uniform. Signs of chronicity in the

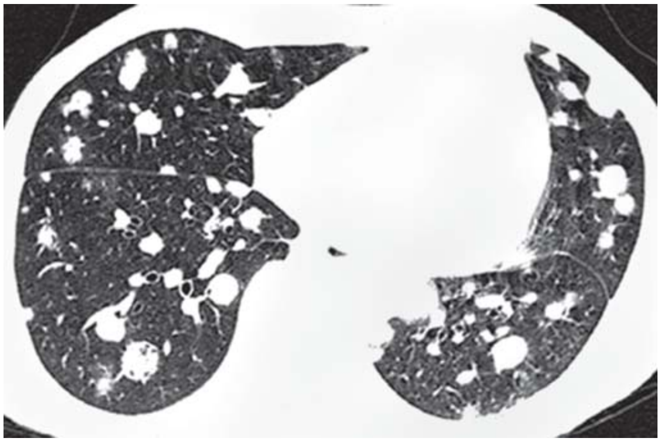


Fig. 24.58: CT—Metastatic lesions in lungs

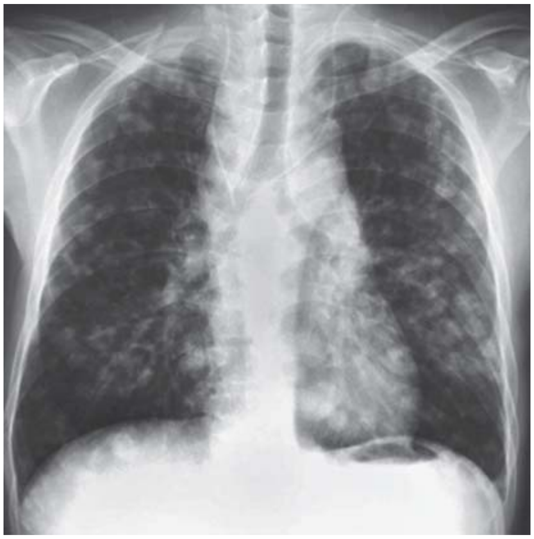


Fig. 24.59: Metastasis in lungs

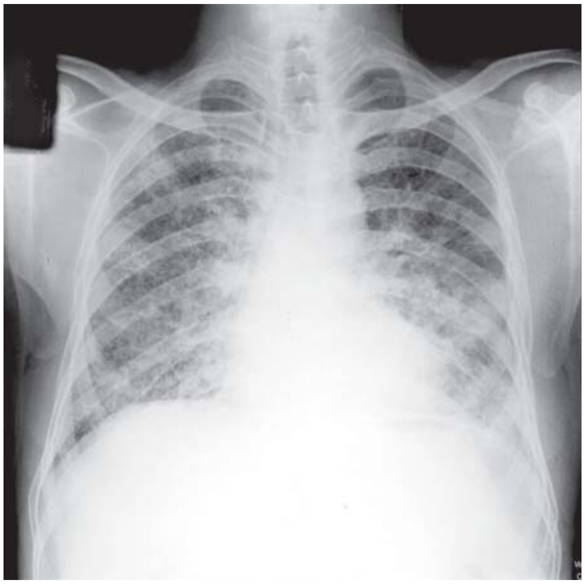


Fig. 24.60: Lymphangitis carcinomatosis

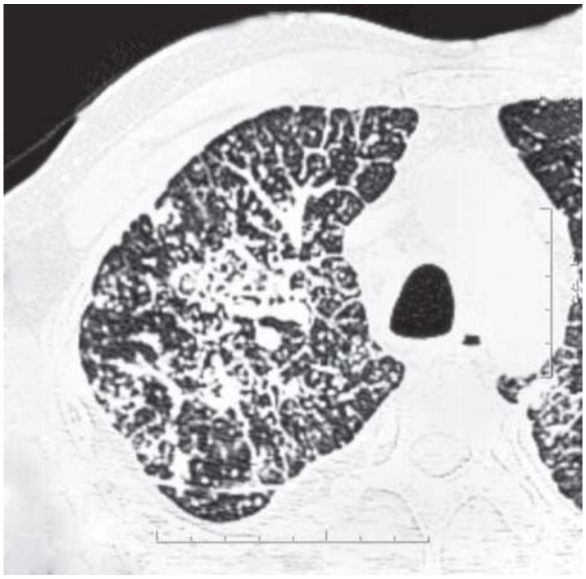


Fig. 24.61: CT picture of lymphangitis carcinomatosis

form of rib crowding and alterations of the thoracic shape may be there. Associated cavity may be seen, as the common cause of fibrosis is tuberculosis (Fig. 24.62).

Interstitial Disease

Four radiological patterns have been described, (a) Reticular pattern (Fig. 24.63): These are a network of curvilinear opacities surrounding spaces of air density and are due to the thickening of the interstitium due to an increase in the total amount of tissue. It may be fine, medium or coarse. Fine reticulation is a prominence of interstitial shadows. Coarse reticulation is characterized by large cystic spaces, 1 cm or more in diameter ringed by soft tissue shadows. Medium reticulation lies between these two extremities and is characterized by 3 to 10 mm cystic spaces. Honeycombing or honeycomb pattern denotes cystic spaces in the range of medium and coarse reticulation. (b) Nodular pattern: A nodular pattern is produced when spherical lesions accumulate within the interstitium. Interstitial nodules differ from airspace nodules in that these are homogenous, well circum-

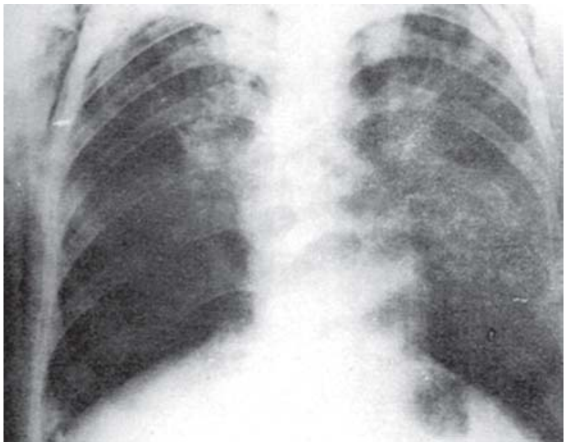


Fig. 24.62: Fibrosis with cavities in both upper zones because of pulmonary tuberculosis. Note the subcutaneous emphysema. Rounded hyperluscent areas overlying heart and mediastinum are due to air in the tissue plane

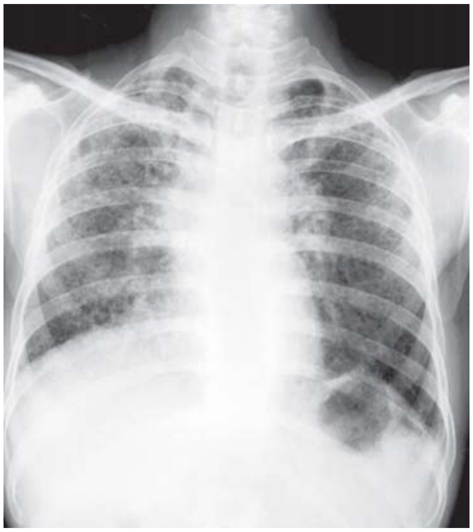


Fig. 24.64: Reticulonodular shadows

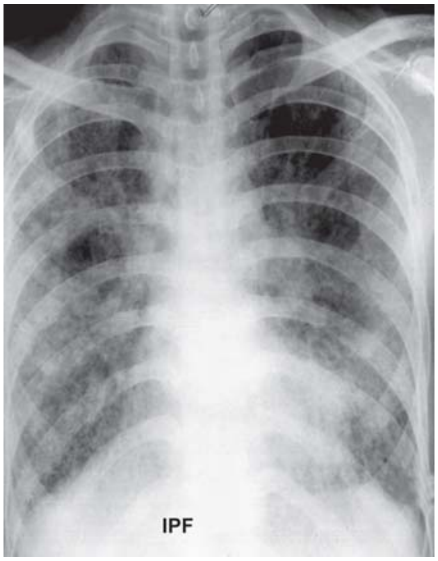


Fig. 24.63: Interstitial pathology

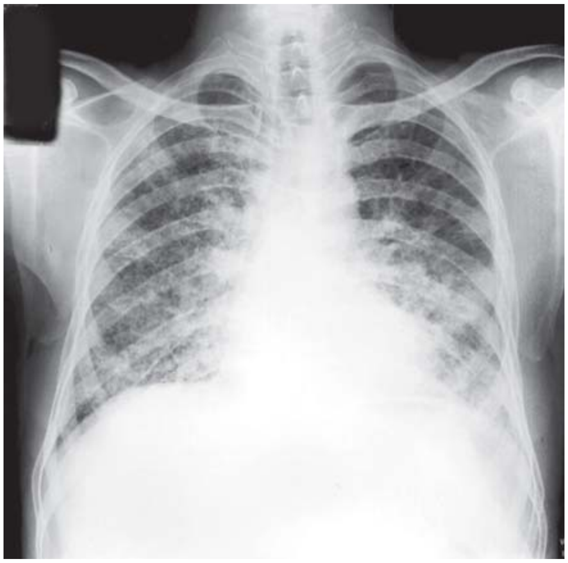
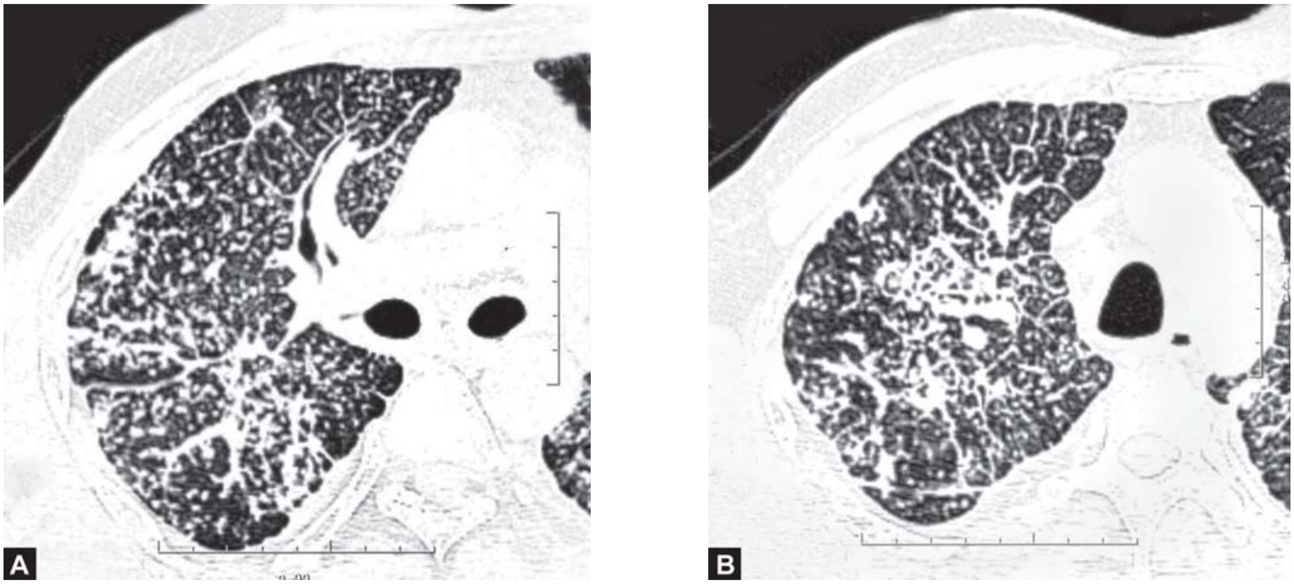


Fig. 24.65: Lymphangitis carcinomatosis

scribed and are of variable size. Such nodular diseases are common in miliary tuberculosis, early disseminated hematogenous carcinomatosis, silicosis and sarcoidosis. (c) Reticulonodular pattern (Fig. 24.64): When both the reticular and nodular patterns are seen in the X-ray, it is called as a reticulonodular pattern. This is commonly seen in sarcoidosis and interstitial pneumonitis. (d) Linear pattern: This pattern is due to thickening in or around the bronchoarterial bundle, perivenous interstitium or interlobular septa (Kerley A and B lines). Besides early pulmonary edema, lymphangitis carcinomatosis produces these types of shadows (Figs 24.65 and 24.66).

Miscellaneous Radiological Features

The smoothness of contour of a shadow in general suggests a benign nature of the lesion, whereas nodularity or lobulation indicates malignancy. "Satellite lesions" are small punctate opacities in close proximity to a larger



Figs 24.66A and B: CT picture of lymphangitis carcinomatosis

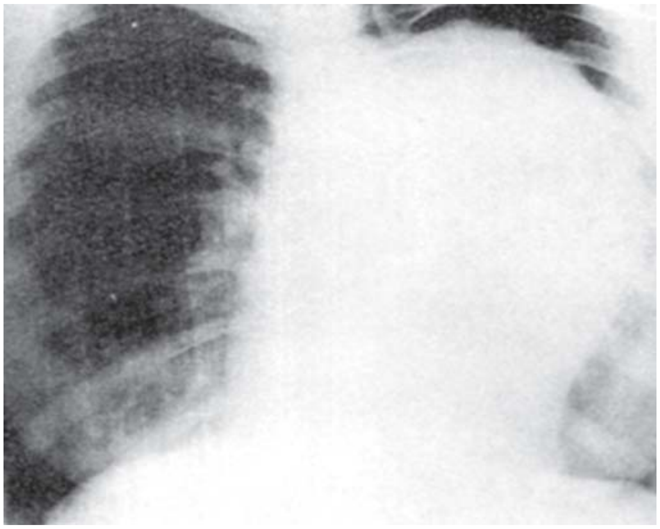


Fig. 24.67: Mediastinal mass. Note the medial border is merged with mediastinum

lesion, usually a solitary pulmonary nodule, and are thought to suggest an inflammatory nature of the lesion and are most common in tuberculosis.

The contour and margin of an opacity are important to decide whether it is a mediastinal, intrapulmonary or extrapulmonary mass. If the medial border is contiguous with the mediastinum and the mediastinal margin cannot be distinguished, it is usually a mediastinal mass (Fig. 24.67).

A mass that originates within the pleural space or extrapleurally, displaces the pleura and the underlying lung inwards such that the angle formed by the margins of the mass and the chest wall is obtuse. By contrast, an intrapulmonary mass tends to relate to contiguous pleura with an acute angle. This is called the "extrapleural sign" (Figs 24.68A and B). Occasionally there are exceptions to this rule.

Position of the interlobar fissures provides important clues to the underlying pathology (Figs 24.69 to 24.71). As mentioned earlier, displacement of the fissure towards a zone of opacity indicates volume loss and usual with atelectasis. Displacement to the opposite direction and bulging of fissure indicates an increase in the volume of the lobe and is a characteristic feature of *Klebsiella pneumonia*. Rarely Staphylococcal pneumonia, *Yersinia pneumonia*, acute lung abscess and space occupying lesions produce this bulging of the fissure. Transgression of the fissure is very uncommon in many lung diseases as the fissure behaves as a barrier; however, such transgression is not uncommon in fungal infections and in actinomycosis.

Cavity

A cavity is a gas containing space with a wall thickness of greater than 1 mm (Figs 24.72 to 24.75). An abscess is a

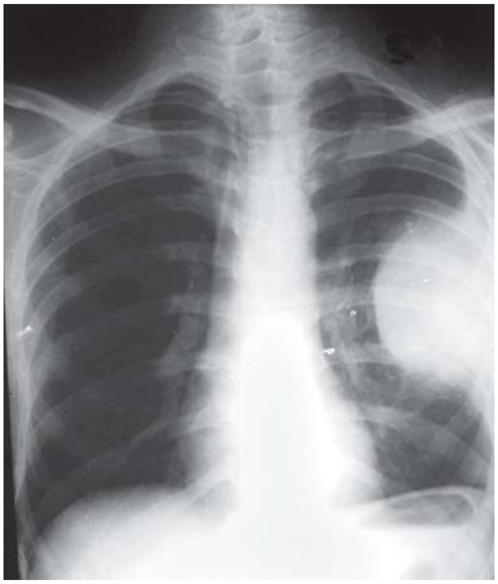


Fig. 24.68A: Extrapulmonary sign—A case of pleural tumor

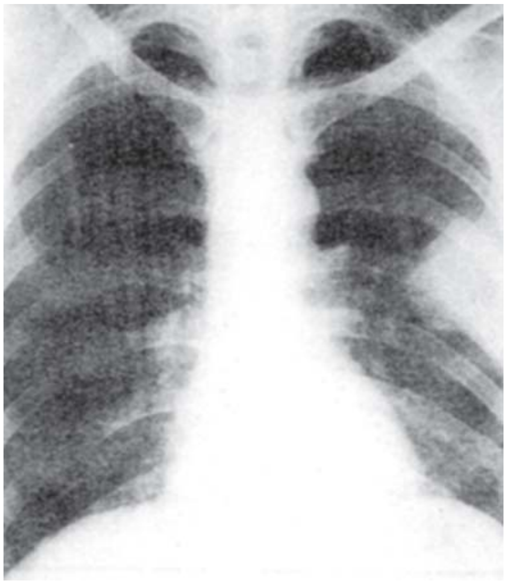


Fig. 24.68B: Extrapleural sign. Note the obtuse angle the shadow produces

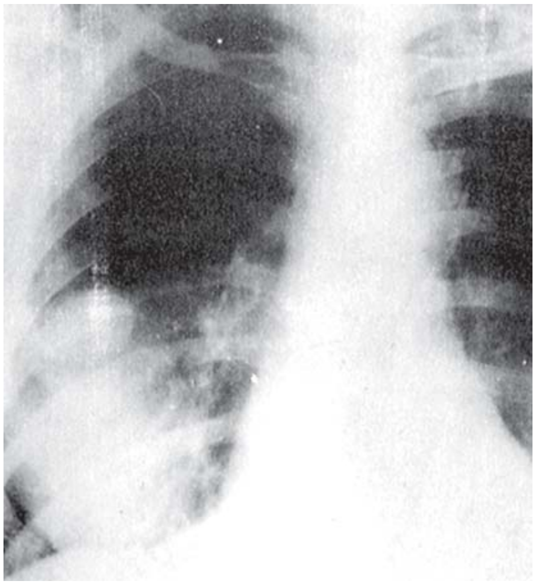


Fig. 24.69: Two homogenous opacities in the right mid and lower zones. The shadows are confused with secondaries or cysts. Lateral chest skiagram (*see* Fig. 24.70) reveals the true diagnosis

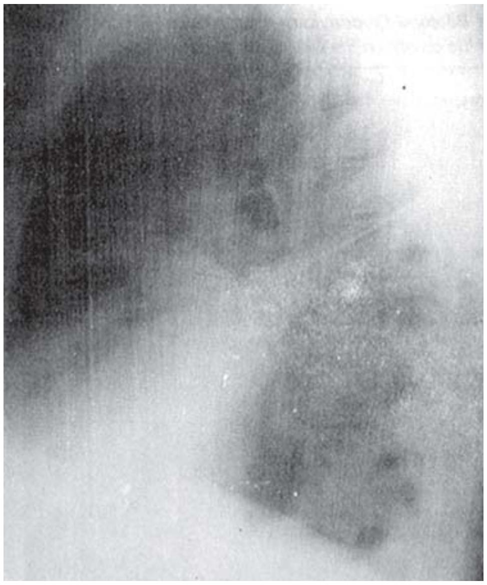


Fig. 24.70: Pleural effusion (encysted) in the oblique (major) and horizontal (minor) fissures

cavity containing fluid. It may even be solid when there is no necrosis or communication with the bronchial tree. In any cavity, the wall, regularity of its inner lining, contents, and the number should be noted. The cavity wall is usually thick in acute lung abscess, primary and secondary carcinomas, and Wegener's granulomatosis. The wall is thin in infected bullae, posttraumatic cysts and INH cavities (Fig. 24.76). It is observed that all lesions in which the thickest part of the cavitary wall is 1 mm, are benign; when 4 mm or less, 92% are benign; between

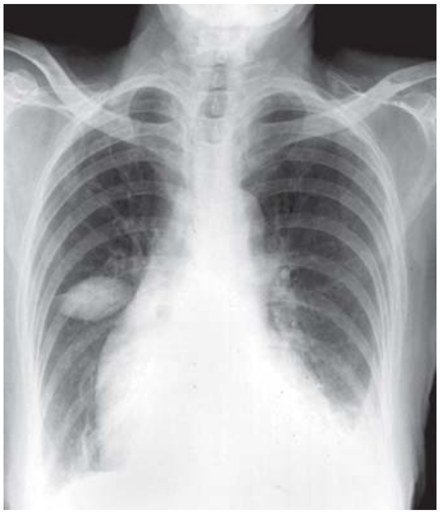


Fig. 24.71: Pleural effusion – Loculation in the fissure

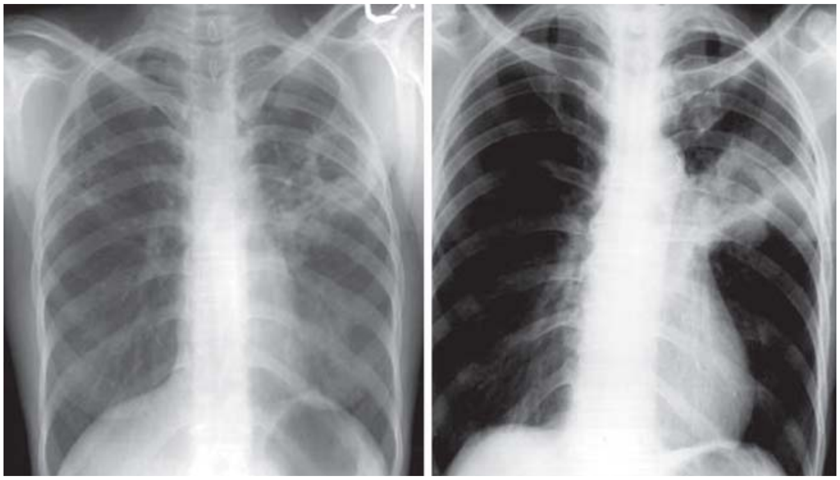


Fig. 24.72: Cavities in left upper zone

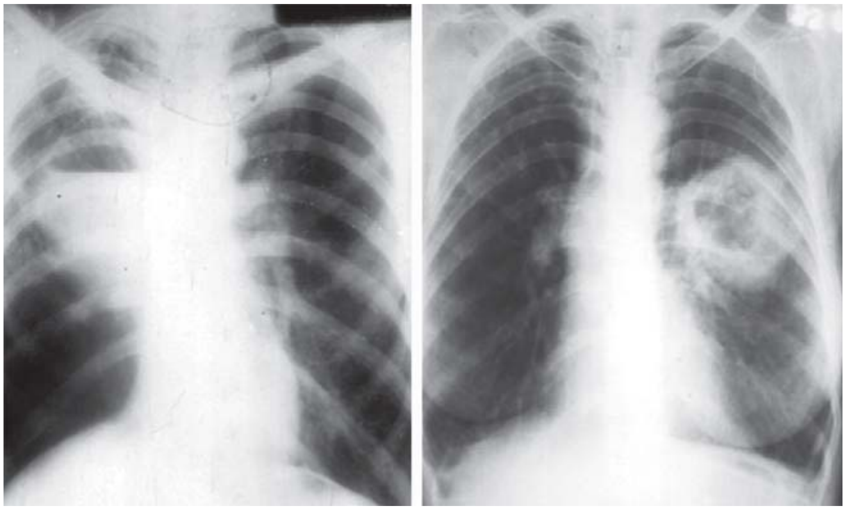


Fig. 24.73: Note cavities

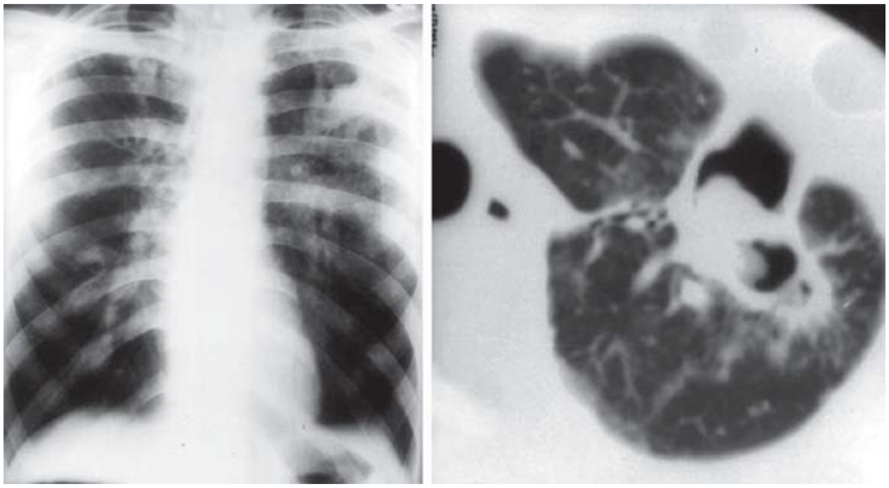


Fig. 24.74: Pulmonary cavitation

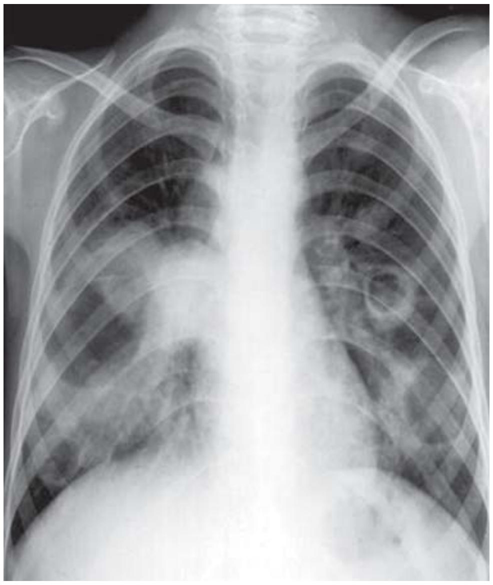


Fig. 24.75: Multiple cavitation

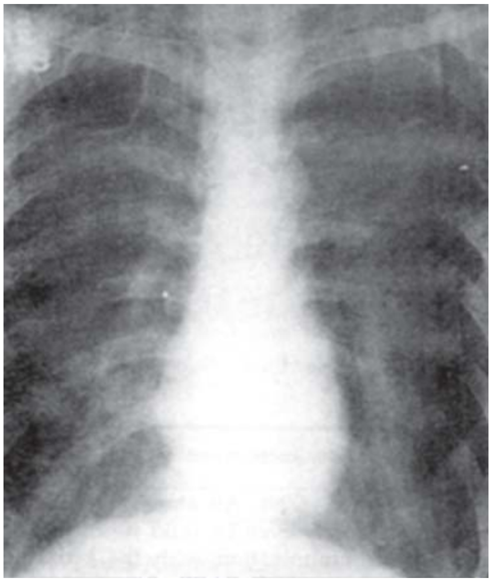


Fig. 24.76: Thin walled INH cavities in the upper zones

5–15 mm the chances of benign and malignant are equal; and when greater than 15 mm, 92% chance is that the lesion is malignant. It is important to measure at the thickest part of the wall. The inner lining is irregular and nodular in malignant cavities (Fig. 24.77), shaggy in acute lung abscess and smooth in most other cavitary diseases. The content of the cavity is mostly liquid (pus) in infective conditions. A fungus ball or blood clots in a cavity may give rise to a crescent around the mass and they change their position (Fig. 24.78). The collapsed membrane of a ruptured hydatid cyst float on top of the fluid within the cyst giving rise to the "water lily sign" (Fig. 24.79). Pulmonary gangrene may also be present as a floating mass inside a cavity, seen sometimes in *Klebsiella pneumonia*. A solitary cavity is usually seen in acute lung abscess (Fig. 24.80), primary cavitary carcinoma and posttraumatic cavities. Multiple cavities are, seen in cavitating secondaries, Wegener's granulomatosis and acute pyemic abscesses secondary to bacterial endocarditis and other septicemia.

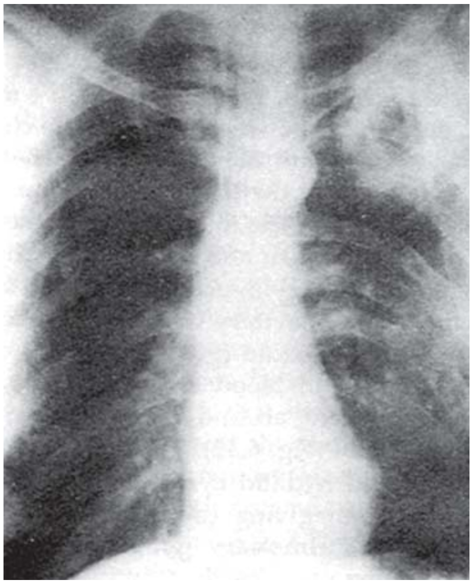


Fig. 24.77: Cavitating bronchogenic carcinoma (squamous cell type). Note the thick wall of the cavity

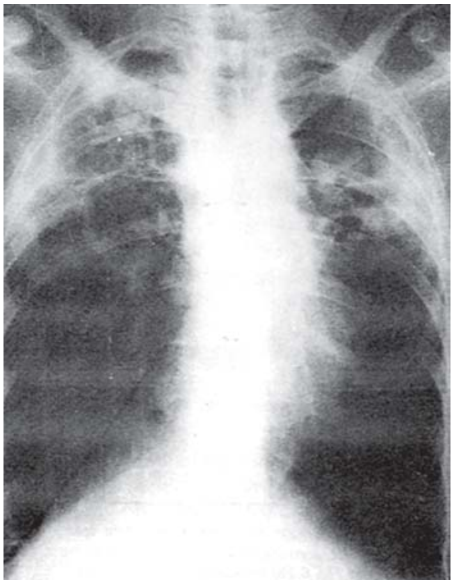


Fig. 24.78: Bilateral fibrocavitary tuberculosis. A homogenous opacity is seen in the cavity on the left upper zone (mycetoma)

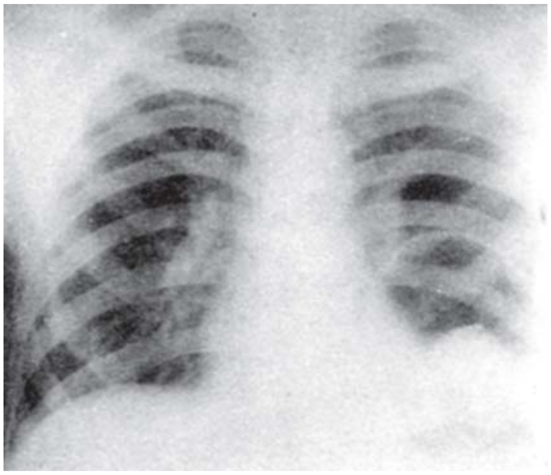


Fig. 24.79: Hydatid cyst in the left lower lobe. Note the "water-lily" sign

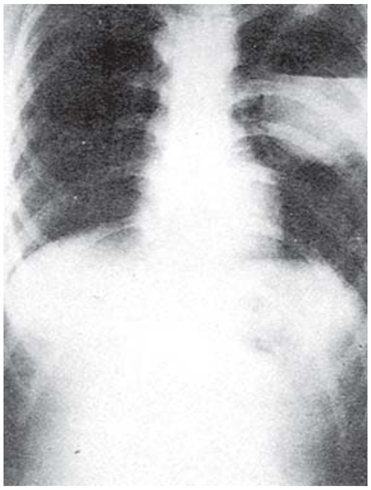


Fig. 24.80: Lung abscess in the left upper lobe

Bullae or Cyst

These are air containing spaces more than 1 cm in diameter and less than 1 mm wall thickness (Fig. 24.81). Bulla is associated with emphysema (Fig. 24.82). Acute staphylococcal infections in children produce multiple cystic lesions called pneumatoceles due to a check valve type of obstruction of bronchioles and necrosis of the lung parenchyma. Other diseases producing bullae or cysts are: Bullous emphysema, cystic bronchiectasis, bronchopulmonary dysplasia and Wilson-Mikity syndrome, cystic adenoid malformation of the lung, staphylococcal and Gram-negative pneumonia, necrobiotic nodule of rheumatoid arthritis and traumatic lung cysts.

Calcification

It is an important radiological sign and should always be looked for. Most commonly they are of dystrophic type (calcification in dead or damaged tissue) and less

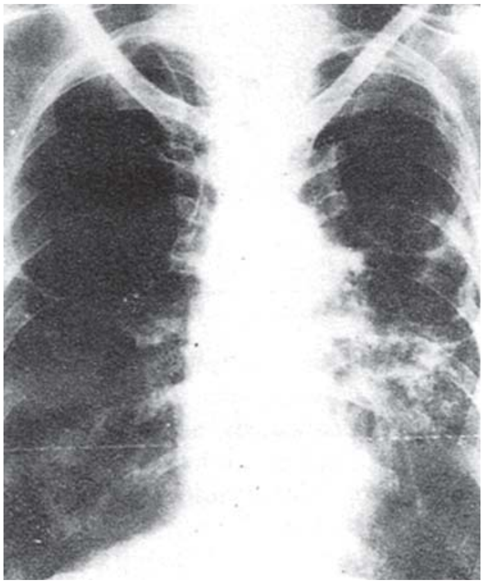


Fig. 24.81: Thin walled cysts in both upper zones

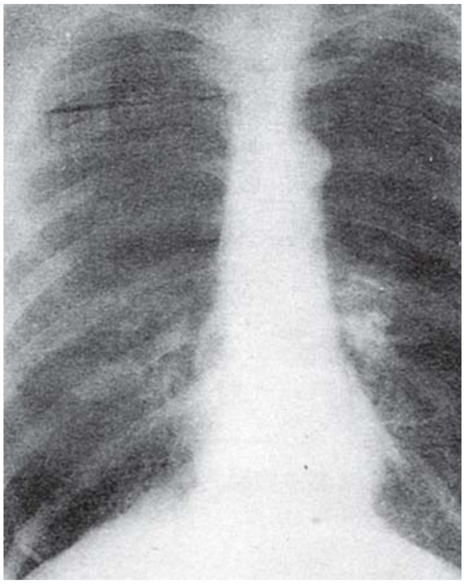


Fig. 24.82: Bullae seen on both upper lobes in a case of emphysema

commonly they are metastatic in nature (calcification of living tissue) as in hypercalcemia. Calcification may be either (a) pulmonary (b) pleural (c) lymph nodal or (d) mediastinal.

Pulmonary: Single calcifications are more common than multiple diffuse areas of calcification. Usual causes of a densely calcified focus are healed granulomatous lesions (Fig. 24.83) like tuberculosis, histoplasmosis, coccidioidomycosis and blastomycosis. Calcification in solitary pulmonary nodules has been discussed earlier. Diffuse patchy calcification (Fig. 24.84) is seen in healed disseminated tuberculosis, alveolar microlithiasis (typically tiny punctate calcispherites), silicosis (multiple nodular calcification or ossification), mitral stenosis (larger sized; greater than 8 mm in size, may even ossify), disseminated histoplasmosis and varicella pneumonia. Intensive

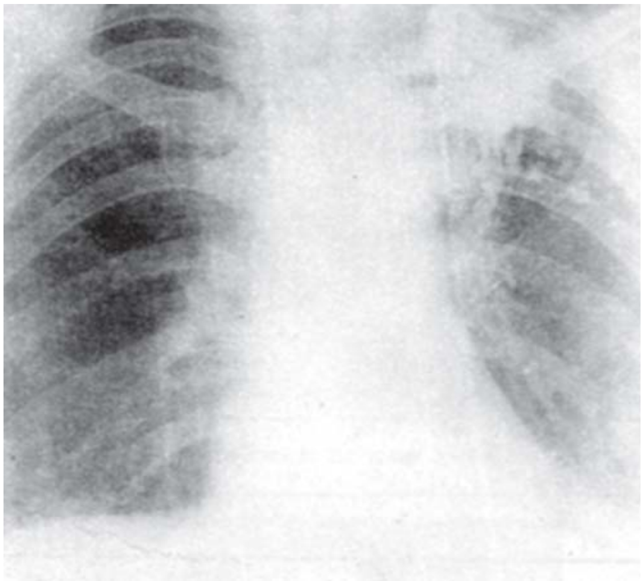


Fig. 24.83: Dense calcification in left upper zone after healed tuberculosis

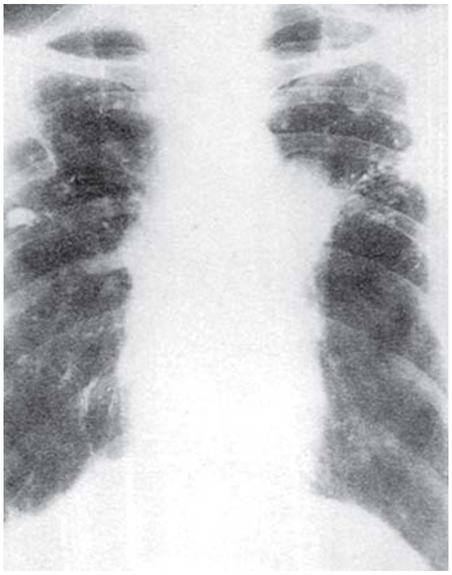


Fig. 24.84: Discrete parenchymal calcification following pulmonary tuberculosis

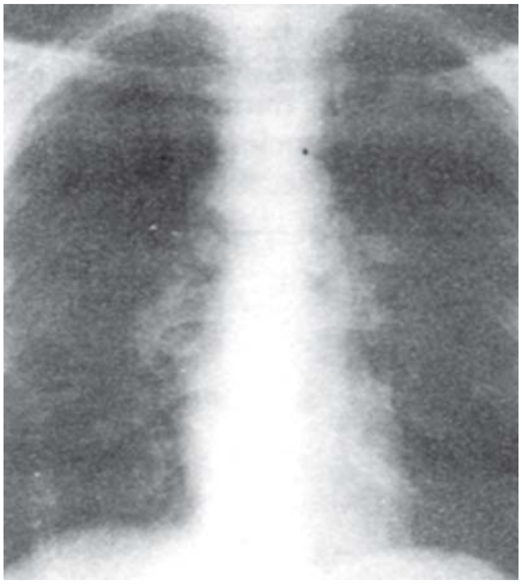


Fig. 24.85: Lymph node calcification in both hilar areas

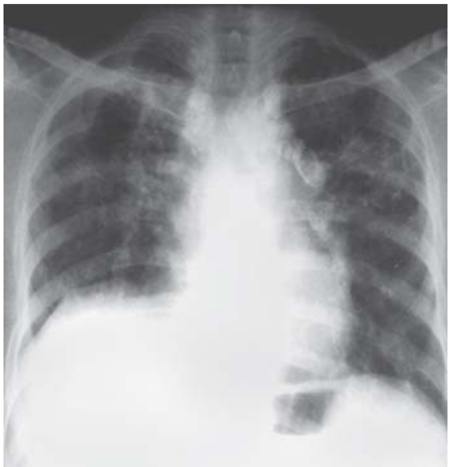


Fig. 24.86: “Eggshell” calcification in a case of silicosis

ossification of the pulmonary tissue is rare and may occur in fibrosing alveolitis, following Busulfan therapy and it may be idiopathic. Metastatic calcification can occur in long-standing hypercalcemia due to secondary hyperparathyroidism as in chronic renal failure and specifically in those who are maintained on hemodialysis. Other causes can be diffuse myelomatosis and in conditions of elevated serum calcium and phosphorus. Metastatic type of calcification has a predilection for the apical and subapical zones.

Lymph node calcification: The calcification in the lymph nodes is irregularly distributed throughout the node and the usual causes include healed tuberculosis, and histoplasmosis (Fig. 24.85). Eggshell type of calcification is uncommon and typically is a ring of calcium at the periphery of the lymph node (Fig. 24.86). Silicosis and coal workers pneumoconiosis are the usual causes. Rarely, sarcoidosis, irradiation of the lymph nodes particularly due to Hodgkin’s disease, blastomycosis, histoplasmosis, progressive systemic sclerosis and amyloidosis can produce this type of calcification.

Pleural calcification (Figs 24.87 to 24.89)*:* The common causes of this type of calcification are: Hemothorax, pyothorax, tubercular empyema and all other causes associated with a thickened pleura and fibrothorax (Fig. 24.90). They may form a broad, continuous sheet or multiple discrete plaques. The calcification usually extends from about the level of the midthorax posteriorly around the lateral lung margin going inferiorly and roughly runs parallel to the major fissures. Calcification

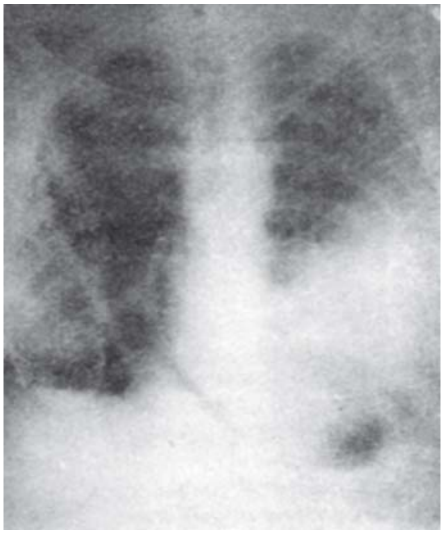


Fig. 24.87: Sheet-like calcification in the right pleura. An encysted empyema is seen on the left side

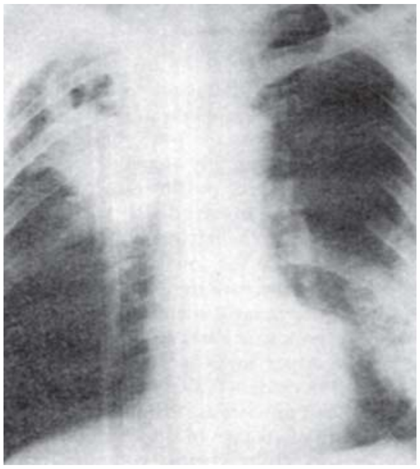


Fig. 24.88: Pleural calcification (left) with a cavitating carcinoma on the right side

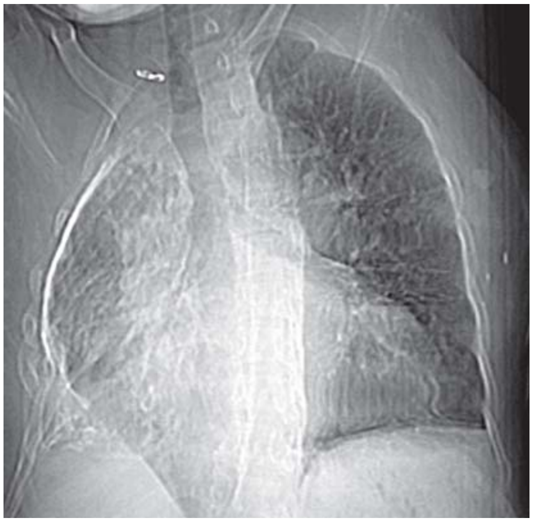


Fig. 24.89: CXR—Dense right pleural calcification

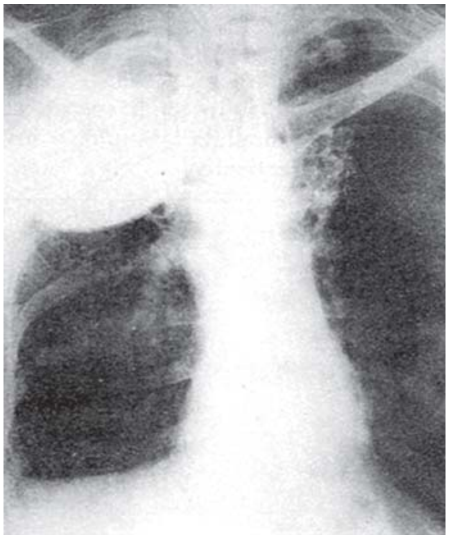


Fig. 24.90: Calcification in an encysted empyema. Note hilar calcification on left side

may be on the inner surface of the thickened visceral or parietal pleura. Other causes of pleural calcification include silicatoses (asbestosis and talcosis). Calcification in asbestosis is characteristically present as bilateral plaques involving the parietal pleura with extensive thickening. It is rarely associated with pulmonary fibrosis or carcinoma, the two other complications of asbestos exposure. The exposure to asbestos for such calcification may be very short and mechanical irritation is the probable underlying mechanism of pleural calcification of asbestosis.

Other rare sites of calcification may be the cartilages of trachea, bronchi and is common in elderly women. Tracheobronchopathica osteochondroplastica is a rare condition where nodules or spicules of cartilages and bones are formed in the submucosa of trachea and bronchi and is associated with chronic airflow limitation. The pulmonary arteries can rarely be calcified.

Anatomic Distribution

Certain lesions have characteristic anatomic distribution. Aspiration pneumonia is gravity dependent and in the supine position, the posterior segments of the upper lobes are commonly affected than the anterior segments. In the erect posture, lower lobes are the common sites to be involved. The right lung is most often involved than the left one. Pulmonary infarction is more common in the lower lobes than the upper lobes because of the pattern of blood flow being more to the former. Similarly metastatic lesions are more common in the lower lobes (Fig. 24.91) and a solitary mass in the upper lobes is rarely metastatic. However, in a bedridden patient the upper lobe is the common site of metastasis. Primary and cavitary carcinomas are more often seen in upper lobes. Postprimary tuberculosis in adults is more common in the apical and posterior segments of the upper lobes and superior segments of the lower lobes possibly because of a high ventilation-perfusion ratio and high PO_2 in the

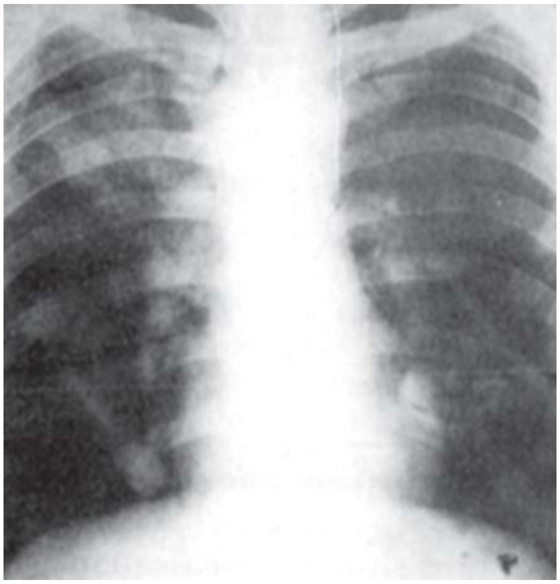
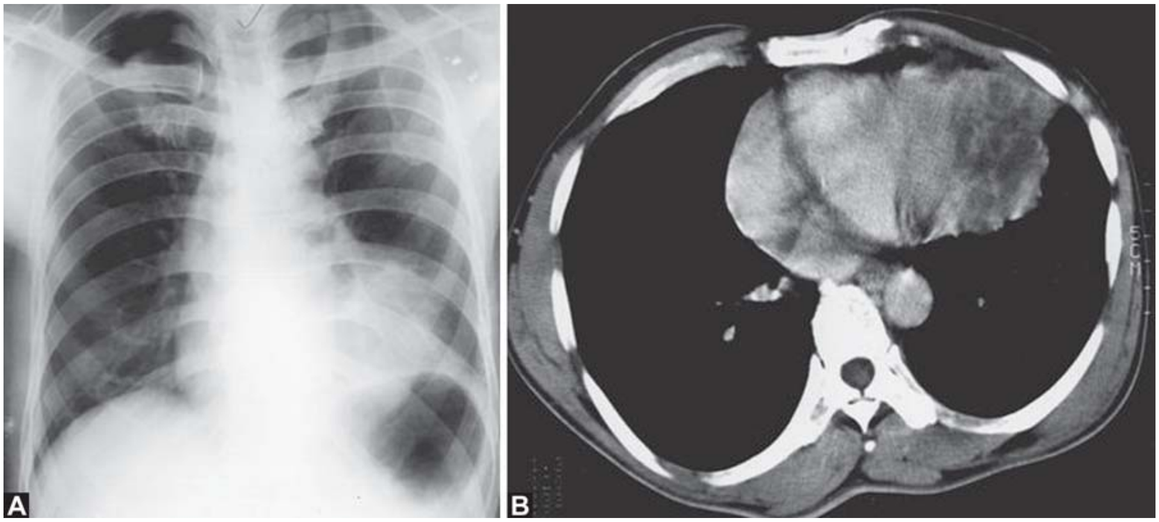


Fig. 24.91: Cannonball secondaries in the lungs from a testicular seminoma

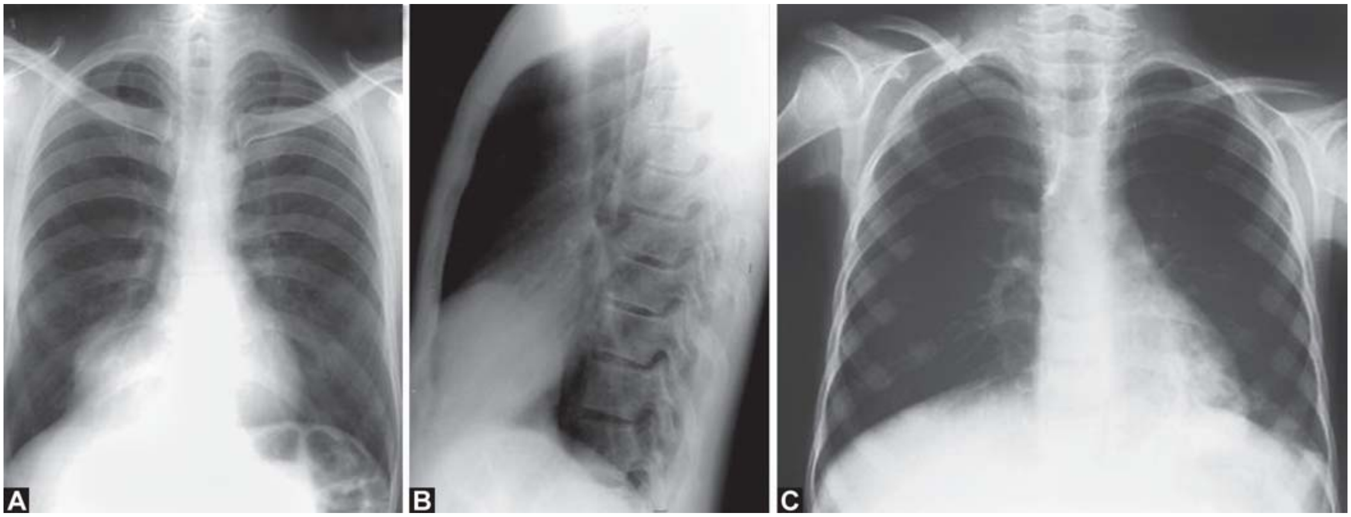


Figs 24.92A and B: Note obliteration of left cardiac border and part of diaphragm

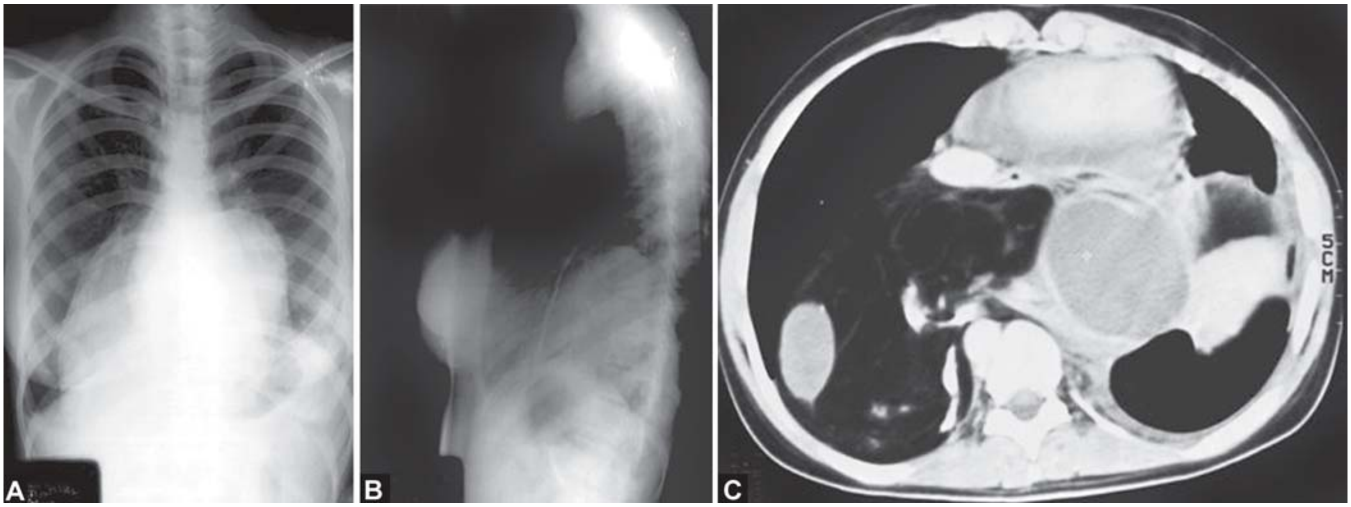
upper lobes. Tuberculosis is rare in lateral lung zones. However, it must be remembered that this may not be true always. Primary tuberculosis commonly involves the anterior segments of the right upper lobe and middle lobe. Radiological changes in interstitial fibrosis are more evident in the lower lobes. Silicosis, sarcoidosis and eosinophilic granuloma involve the upper lobes more frequently.

Silhouette Sign

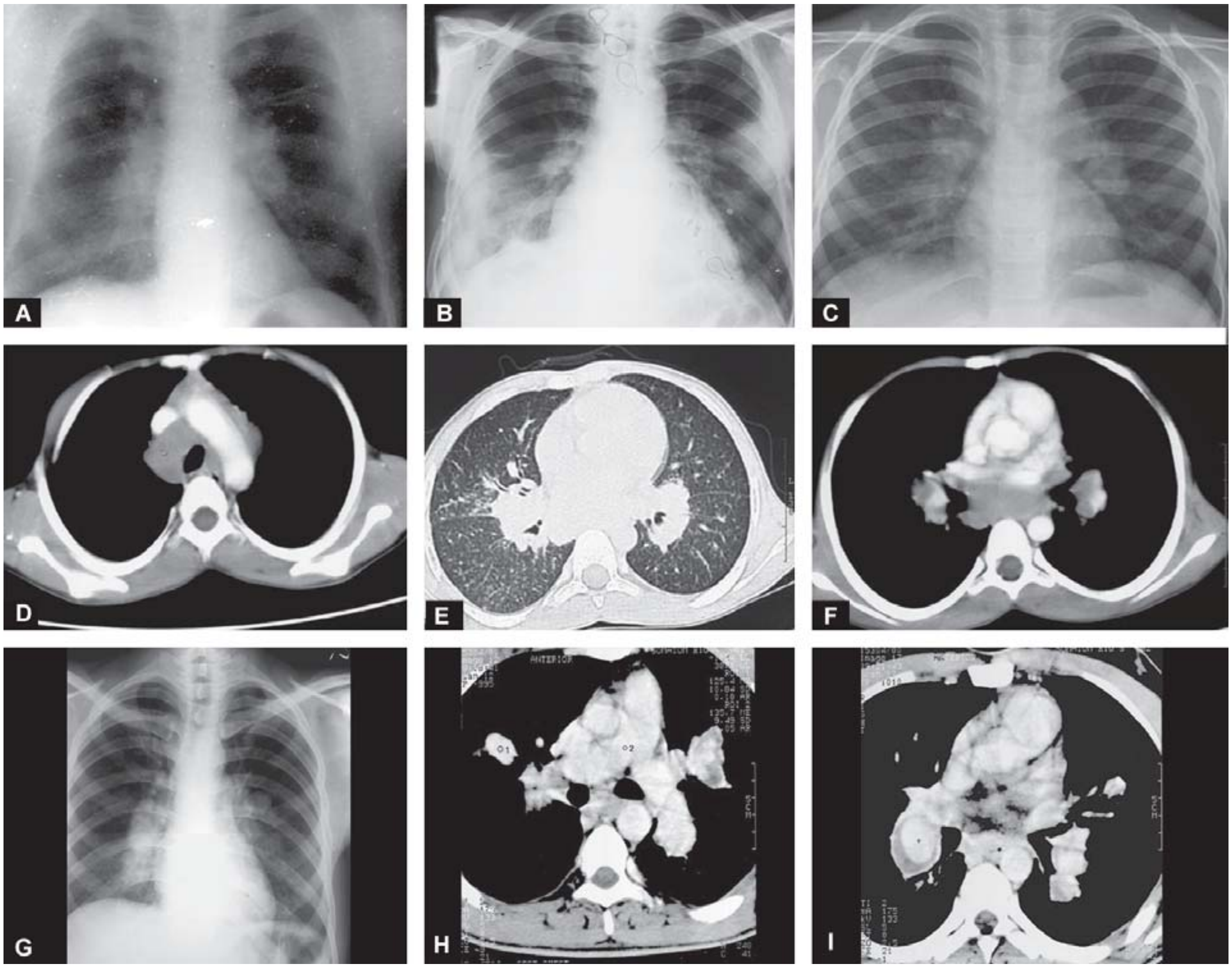
This is another important radiological sign (Figs 24.92 to 24.94) helpful to localize the lesion in the lungs. Although anatomical localization of most pulmonary lesions is possible in most cases from a PA and lateral views, it may not be possible when there are multiple segments of both lungs involved and when only an AP view is available for study. In these circumstances Silhouette sign is very helpful. Normally, the mediastinum and the diaphragm are radiologically visible because of the contrast with the contiguous air containing lungs. However, when opacity is situated in any position of the lung adjacent to the mediastinal or diaphragmatic border, that border is obliterated and can no longer be distinguished roentgenographically. Accordingly, an opacity within the lungs that does not obliterate the mediastinal or diaphragmatic contour cannot be situated within the lung contiguous to these structures. The sign is helpful in distinguishing right middle lobe and lingular segments on the left from the lower lobes, which will obliterate the



Figs 24.93A to C: Silhouette sign



Figs 24.94A to C: No Silhouette sign



Figs 24.95A to I: Hilar enlargement

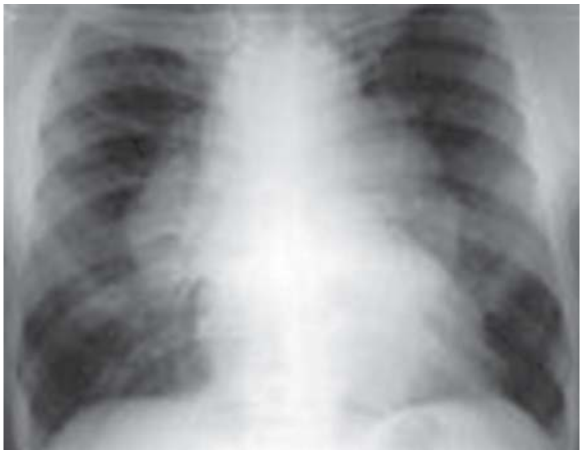


Fig. 24.96: Bilateral hilar lymphadenopathy

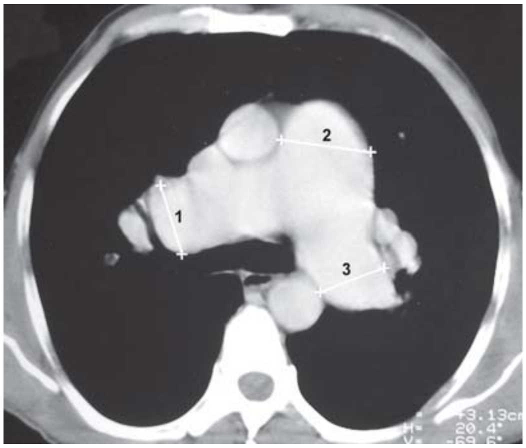


Fig. 24.97: Pulmonary hypertension

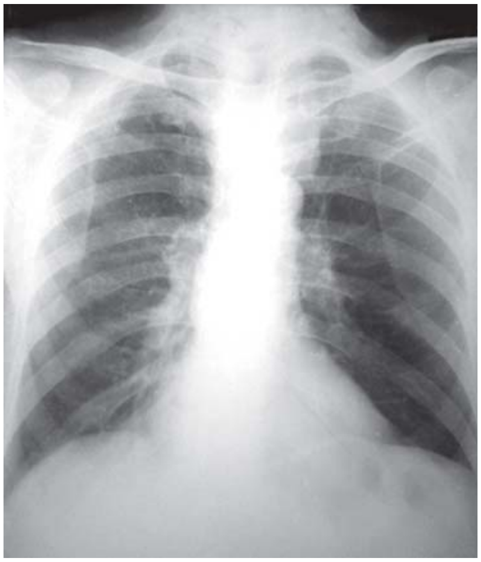


Fig. 24.98: Right paratracheal lymph node

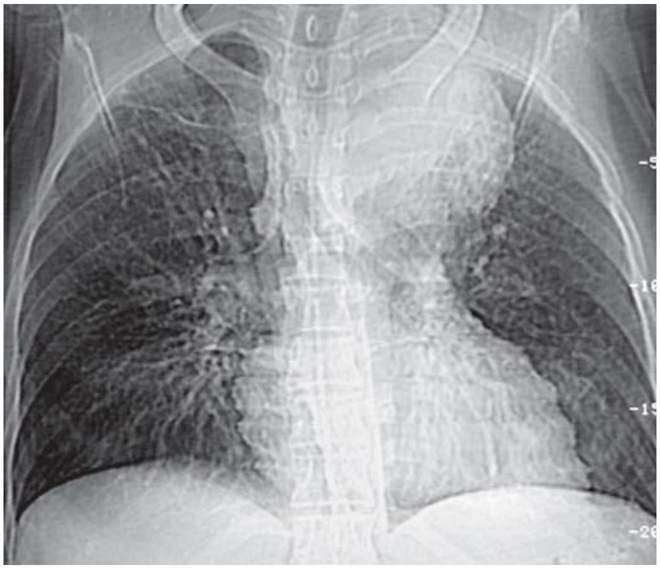


Fig. 24.99: CXR—Left paratracheal mass: Castleman disease

right and left cardiac borders respectively. Similarly obliteration of the aortic knuckle indicates involvement of the posterior segment of the left upper lobe; obliteration of the ascending aorta and superior vena cava indicates involvement of the anterior segment of the right upper lobe and the posterior paraspinal gutter is obliterated by opacities in the left posterior gutter.

Mediastinal and Hilar Shadows

All suspected mediastinal and hilar shadows must be confirmed by lateral X-rays. Common causes of hilar enlargements are; bronchogenic carcinoma, lymph node enlargement and dilatation of pulmonary arteries. Lymph node enlargement is typically lobulated and may extend up to the paratracheal glands. Bronchogenic carcinoma, tuberculosis, lymphoma and sarcoidosis may cause hilar lymphadenopathy. Whereas, sarcoidosis causes bilateral symmetrical lymph node enlargement, in lymphoma there will be bilateral and asymmetrical enlargement of the nodes. Tuberculosis and metastatic carcinoma will produce unilateral lymph node enlargement. Rarely, silicosis, glandular fever, fungal infections, generalized drug reactions and berylliosis can produce hilar lymph node enlargement. Enlarged pulmonary arteries are due to cor pulmonale secondary to chronic obstructive pulmonary disease, mitral valve disease, and left to right shunts, multiple pulmonary thromboembolism, aneurysms and

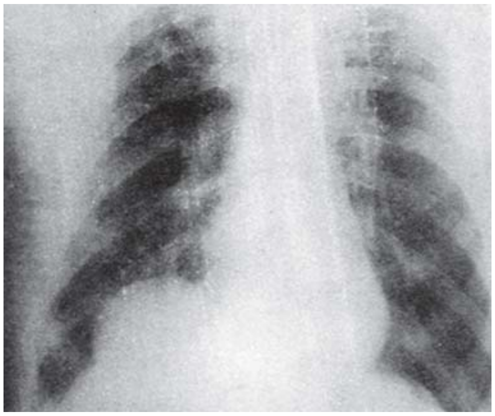


Fig. 24.100: Pericardial cyst right common site in the cardiophrenic angle

poststenotic dilatation in pulmonary stenosis. It may be idiopathic also. Some of the X-ray pictures of hilar enlargement are shown in Figures 24.95 to 24.99.

Mediastinal enlargement will be dealt with in more detail in the chapter on mediastinum. Briefly, the anterior mediastinal shadows are due to dermoid cyst, thymoma, intrathoracic goiter, hernia through the foramen of Morgagni, bronchogenic carcinoma and lymphoma; middle mediastinal lesions include hilar nodes, bronchogenic cyst, cystic hygroma, pericardial cyst (Fig. 24.100) and lipomas; and lesions in the posterior mediastinum are mostly neurogenic tumors. Other lesions in the posterior mediastinum are hiatus and Bochdalek's hernia, esophageal dilatation due to achalasia and aneurysm of the aorta.

Pleural lesions will be discussed in the chapter on pleural diseases.

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25

Pulmonary Imaging: Systematic Approach to Interpretation of Computed Tomography of the Chest

Rubal Patel, Rakesh Shah, Sabiha Raoof, Suhail Raoof

INTRODUCTION

Computed Tomography (CT) was discovered independently by Sir Godfrey Hounsfield and Dr Alan Cormack in the 1970s and has undergone substantial advancement corresponding to the progression of modern computer technology. CT has become a fundamental part of clinical decision making. Technologic developments in CT have significantly influenced the diagnostic approach to many clinical diseases and expanded the indications for thoracic imaging. This chapter focuses on a comprehensive review of the diagnostic and interpretative findings seen on CT imaging. It is broken down into three general parts: (1) the technical aspects of CT imaging with a summary of the special features and clinical indications of each technique; (2) normal components of the pulmonary parenchyma, airways and pulmonary vasculature with a description of specific radiographic signs pertaining to each component; and (3) diseases involving the tracheobronchial tree, pulmonary parenchyma, mediastinum and a mention of a few miscellaneous conditions.

TECHNICAL ASPECTS

In general, CT provides comparatively more information than plain radiography. It provides good contrast between tissues allowing for detection of even subtle differences between tissues. Plain radiographs detect differences in the contrast of about 5%, whereas CT can detect differences of less than 0.5%. Images on CT are free of superimposition of structures, thereby eliminating the effects of overlapping anatomy. Images can be obtained rapidly with a wide field of view and an ability to provide cross-sectional images of the thorax. CT can localize diseases seen on conventional radiography, assist in the guidance of interventional procedures, can contribute new information or detect unsuspected abnormalities.

Disadvantages of CT include the exposure to more radiation than plain chest radiography; requirement of patient transport to the CT scanner, which may be difficult in critically ill patient; and the risk of intravenous contrast administration. The wide range of indications for CT and unlimited variation of pathologic presentations make it essential to alter each CT examination to the clinical diagnosis in question. There are several technical parameters, such as slice thickness, scan times, pitch, reconstruction intervals and window settings that can be selected. In general, three modes of CT imaging are currently in practice: Conventional CT, high-resolution CT and volumetric or spiral/helical CT.

Conventional CT

It provides multiple contiguous cross-sectional images (greater than 2 mm thick) through the thorax while the patient is stationary with table position incremented between acquisitions. Narrower collimation of 5 mm may be utilized when scanning through the hilar regions, and 1 to 2 mm to demonstrate small pulmonary nodules and for high resolution CT of the lung parenchyma. Conventional CT is broadly accepted and available for the work-up of many pulmonary conditions. Disadvantages of conventional CT include the motion artifact and loss of details from volume averaging.

Multislice CT

It has largely replaced single slice scanners and allows for extended anatomic coverage and shorter examination times.[1] Several hundred image slices are generated in less than a minute. Depending on the type of multislice CT scanner, images can be scanned up to 64 times faster than single slice CT scanners. Consequently, they can cover more patient length per unit time, a predetermined scanning volume, or the same volume in the same time with thinner slices. The entire chest can be scanned in less than 10 seconds. There is improved temporal and spatial resolution with thinner sections and greater contrast enhancement. Diagnosis of vascular abnormalities, such as subsegmental pulmonary emboli, characterization of small pulmonary nodules and the recognition of airway disease are significantly improved. The distribution and morphology of diffuse lung disease is better illustrated with 1 mm collimation and can be viewed in the coronal and sagital planes.

Reconstruction images are created by workstations that have a range of computer software programs and processing tools, which determine the quality or characteristics of the image. The reconstruction of CT data sets obtained on multislice scanners may result in several (1,000–5,000) images per examination. This makes it difficult to extract all the information present by using standard two-dimensional techniques. Therefore, post processing volume imaging and 3-D image display are crucial to volume visualization. Various software and workstation designs are available to improve volume visualization. Techniques, such as volume rendering and maximum intensity projection, which are computer-implemented algorithms, are used to transform serially acquired axial CT image data into 3-D images.

High-Resolution CT (HRCT)

It shows very thin (less than 2 mm) cross-sectional images at 10 or 20 mm intervals (noncontiguous) with high spatial resolution, allowing for detailed analysis of lung structure. This provides more detail than conventional CT scanning. The basic lung unit that is visible on HRCT is the secondary pulmonary lobule, around which many pathologic processes can also be visualized.[2] HRCT is particularly helpful in the detection of metastatic lesions, solitary pulmonary nodules, bronchiectasis and characterization of interstitial lung diseases, where detailed assessment is necessary.[3] It can provide an accurate assessment of the configuration, distribution, and even the degree of disease activity and potential reversibility of diffuse lung disease and has shown to have a correlation between radiographic and histopathologic appearances. The pattern of scanning may be specified to the suspected diagnosis. For instance, scanning should be performed at 1 cm intervals for diffuse lung disease, but should be limited to the involved area in focal lung processes and solitary pulmonary nodules.

Helical (Spiral or Volumetric) CT

Helical CT scanning is one major technical development in CT scanning. It provides multiplanar images of the entire chest during a single breath-hold (8 to 10 seconds), while the patient is moved continuously through the CT gantry with continuous rotation of the X-ray tube and detector assembly. The main advantages include speed, less radiation exposure, and an ability to retrospectively construct 3-dimensional images. Respiratory motion is eliminated and volumetric data can be manipulated to obtain overlapping axial sections without additional radiation to the patient.[4] However, the requirement for breath-holding may not be feasible for patients with symptomatic pulmonary disease. It is useful in the evaluation of mediastinal abnormalities.

CT Angiography

CT angiography is obtained during a 15 to 30 second helical scan. The influx time of the contrast medium and the degree of vascular and parenchymal enhancement are dependent upon the concentration of contrast material, the rate of injection, and the cardiac output. It is exceedingly effective in the diagnosis of pulmonary embolism. Several studies have confirmed comparable results of CT angiography to conventional pulmonary angiography.

The special features, advantages and disadvantages and clinical indications of these techniques are summarized in Table 25.1.

NORMAL COMPONENTS OF THE PULMONARY PARENCHYMA

A strong knowledge of lung anatomy is necessary to understand the CT features of lung diseases. It allows for better understanding of the pattern of the disease, as well as its specific distribution in the lung. The lung is composed of anatomical elements of similar architecture at gradually smaller sizes. These include lungs, lobes, segments, subsegments, secondary lobules and acini. Each division is organized around central supporting structures, such as airways and arteries and peripheral

TABLE 25.1: Clinical indications, special features, advantages and disadvantages of various techniques of CT chest imaging

CT Technique	*Indications*	*Special Features*	*Advantages/Disadvantages*
Conventional	Work-up of many pulmonary conditions: • Localization and characterization of mediastinal mass • Staging of Lung Cancer • Detection of pulmonary metastases approach for biopsy	• Provides multiple contiguous cross-sectional images • Allows for scanning throughout the thorax	• Susceptible to motion artifact • Loss of detail from volume averaging
Multislice	Diagnosis of vascular abnormalities: • Subsegmental pulmonary emboli • Characterization of small pulmonary nodules • Evaluation of airway disease	• Improved resolution • Improved contrast enhancement • Ability to create retrospective reconstructions • Thinner sections	• Faster imaging • Less motion artifacts • Greater anatomic coverage
HRCT	Evaluation and detailed characterization of: • Solitary pulmonary nodule • Interstitial lung disease • Bronchiectasis • Metastatic lesions	• Thinner cross-sectional images • Provides more detail than conventional CT scanning	• Accurately assessment of the pattern and distribution of diffuse lung disease • Characterization of disease activity • Guidance for lung biopsy • Does not provide contiguous images – skips areas between the thin sections
Helical	Evaluation of various thoracic injuries: • Aortic dissection • Pneumothorax • Pulmonary contusions and lacerations • Tracheobronchial injury • Skeletal injuries such as rib, sternal, vertebral fractures • Diaphragmatic injuries	• Increased scanning speed • Improved vascular enhancement • Thinner collimation • Acquires volumetric data of the thorax, allowing for manipulation of image data • Able to generate high quality multiplanar 2-D and 3-D reconstructions	• Capable of scanning large volumes of tissue during a single breath hold • Minimizes motion artifact • Generates high quality images with the ability to show branching or oblique airway or vascular anatomy • Assists in surgical planning
CT Angiogram	Detection and evaluation of vascular abnormalities: • Aortic disease • Pulmonary embolism	• Requires rapid intravenous injection of contrast material • Ability to use volume rendering to improve diagnostic accuracy • Technical details may be manipulated to obtain optimal vascular studies	• Proper injection timing is essential to ensure imaging at the time of peak intravascular enhancement • The volume of contrast used should be adequate to maintain maximal vascular opacification throughout the spiral acquisition • With optimal technique, CT angiography can provide accurate images, eliminating the need for conventional angiography

supporting structures, such as pleura and connective tissue septa[5] (Fig. 25.1).

The support system of the lung consists of a network of connective tissues, which forms the interstitium. It maintains a strong structural support for the airways, blood vessels and alveoli, but is also thin enough to allow for gas exchange. The interstitium can be divided into three components that communicate freely: The peripheral, axial and parenchymal connective tissue[6] (Fig. 25.2). The peripheral connective tissue extends from the lung pleura to the lung septa. The septa are incomplete partitions within the lung that divide the lung segments, subsegments and secondary pulmonary lobules and acini. The axial connective tissue stems from

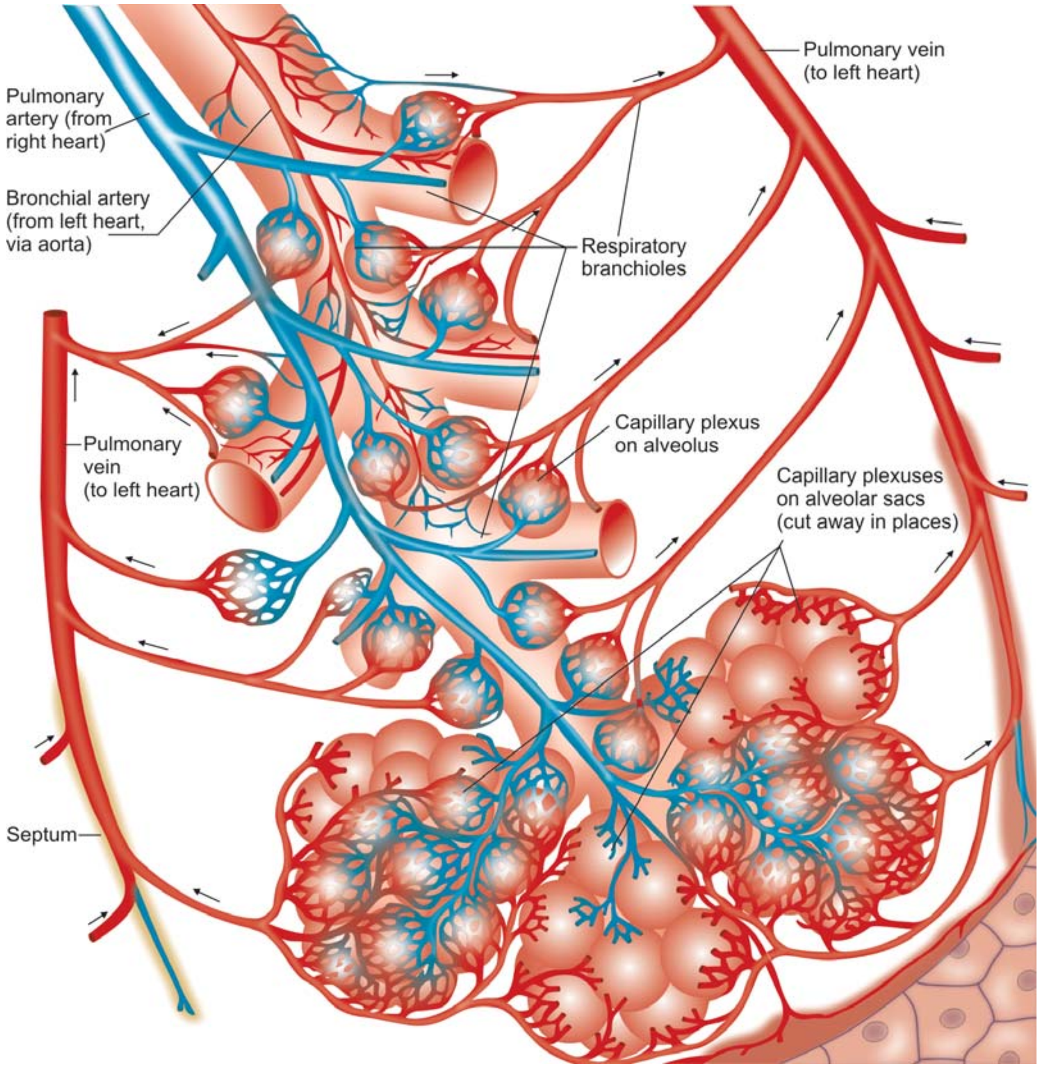

Pulmonary artery (from right heart)
Bronchial artery (from left heart, via aorta)
Pulmonary vein (to left heart)
Respiratory branchioles
Pulmonary vein (to left heart)
Capillary plexus on alveolus
Capillary plexuses on alveolar sacs (cut away in places)
Septum

Fig. 25.1: Anatomic components of the lung. The centrilobular structures consist of the terminal bronchiole and pulmonary artery. The peripheral structures are composed of the pulmonary veins and the lymphatic system. This structural organization is present from the largest to the smallest lung unit (Netter illustration from www.netterimages.com. © Elsevier Inc. All rights reserved)

the hilum and surrounds the bronchovascular structures, extending peripherally. The parenchymal connective tissue is located in between the alveoli and capillaries, where gas exchange takes place. It extends to the axial and peripheral connective tissues.[6]

The normal segmentation of pulmonary lobes includes three (upper, middle and lower) in the right lung and two (upper and lower) in the left lung. They are separated by interlobar fissures. Lobes are identified on CT by the visualization of interlobar fissures or an avasular plane on which they lie, or by identifying bronchial branches that lead to the corresponding lobes.[7] Pulmonary segments and subsegments are not as easily discerned as lobes. At the subsegmental level, of the three units of lung structure present, i.e. the primary pulmonary lobule, acinus and secondary pulmonary lobule, the secondary lobule is the smallest unit of lung structure that is seen on HRCT bordered by interlobular septa[8] (Figs 25.3 and 25.4).

The secondary lobules are the building blocks around which CT patterns are constructed. These structures are extremely important in the interpretation of lung changes seen on CT. The interpretation of HRCT is exceptionally useful for the diagnosis of various diffuse and focal lung diseases, which are centered around the secondary pulmonary lobule. Therefore, a good knowledge of the anatomy of the secondary lobule is essential to determine

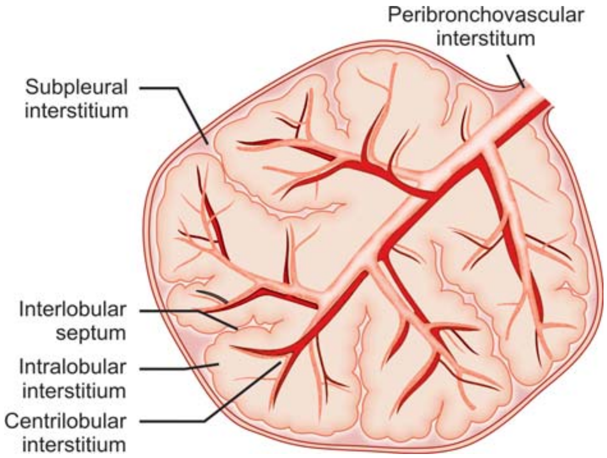

Peribronchovascular interstitium
Subpleural interstitium
Interlobular septum
Intralobular interstitium
Centrilobular interstitium

Fig. 25.2: Divisions of the pulmonary interstitium. The interstitium can be divided into three components that communicates freely: the peripheral, axial and parenchymal connective tissue. The peripheral support system consists of the subpleural and interlobular septa. The axial support system consists of the peribronchial and centrilobular interstitium

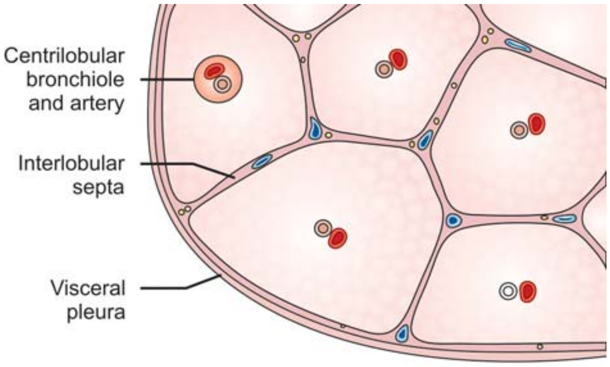

Centrilobular bronchiole and artery
Interlobular septa
Visceral pleura

Fig. 25.3: The secondary pulmonary lobule. The central structures include the intralobular pulmonary artery and terminal bronchiole. The septal structures include the pulmonary venules, lymphatics and fibrous septa

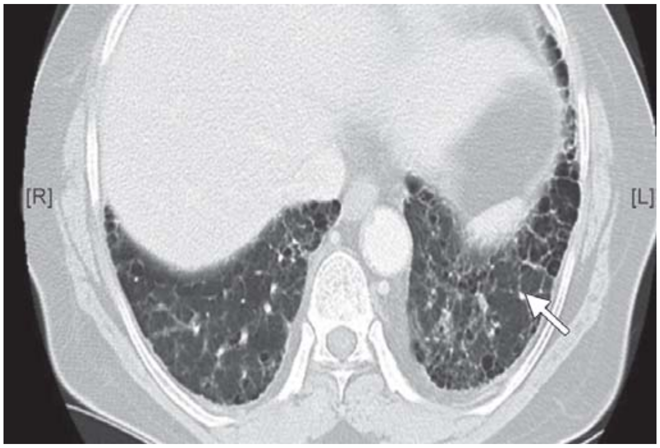


Fig. 25.4: HRCT chest performed at the lung base, showing interlobular septal thickening (arrow), reticular opacities and some honeycombing changes

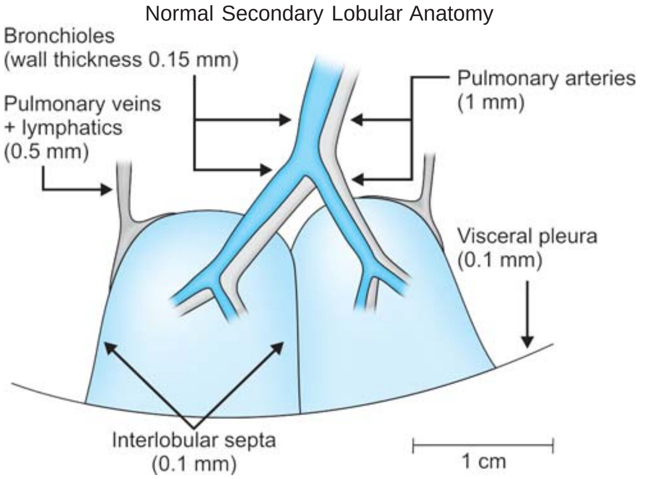

Normal Secondary Lobular Anatomy
Bronchioles (wall thickness 0.15 mm)
Pulmonary veins + lymphatics (0.5 mm)
Pulmonary arteries (1 mm)
Visceral pleura (0.1 mm)
Interlobular septa (0.1 mm)
1 cm

Fig. 25.5: The secondary pulmonary lobule. Each secondary lobule is made up of a small bronchiole and pulmonary artery and bordered by interlobular septa, where a pulmonary vein and lymphatic branches reside[10] (Raoof S, Amchentsev A, Vlahos I, et al. Pictorial essay: mulitinodular disease: a high-resolution CT scan diagnostic algorithm. Chest. 2006; 129(3):805-15)

the distribution pattern of the disease. Differential diagnosis of lung disease can be limited by the evaluation of whether the disease is located in or around the airways, the blood vessels, the lymphatics or the lung interstitium.[9]

The Secondary Pulmonary Lobule

The secondary pulmonary lobules are polyhedral in shape and differ in size from 1.0 to 2.5 cm and are formed by a collection of acini.[2,6,9] The reported number of acini that form a secondary pulmonary lobule vary considerably, a range of 3–12 have been described. An acinus is the largest lung unit where all airways participate in gas exchange. Each secondary lobule is made up of a small bronchiole and pulmonary artery, and bordered by interlobular septa, where a pulmonary vein and lymphatic branches reside[9,10] (Fig. 25.5).

Interlobular Septa

The secondary lobules are surrounded by interlobular septa made by connective tissue. The lymphatic system draining the visceral pleura, courses within the interlobular septa along with the septal veins leading to the lymphatics and nodes within the hila. The interlobular septa measure 0.1 mm in the subpleural location, are much thinner and less defined in the center.[2] The thickness of the peripheral interlobular septa are at the lower limit of HRCT resolution, may or may not always be seen, especially in CT scans of normal patients.

Centrilobular Region

The central part of the secondary lobule contains the peribronchovascular interstitium that surrounds the terminal pulmonary artery and the terminal bronchial branches.[9] It is difficult to discern the bronchial or arterial structures and the HRCT appearance of these structures is dependent on their size. A linear, branching or dot-like opacity usually seen within the center of the lobule represents the intralobular artery branch and its distributions.[2] The centrilobular arteries are not seen to extend to the pleural surface. The airway wall thickness determines the visibility on HRCT. The wall thickness of a normal terminal bronchiole measures 0.1 mm, which is below the resolution of HRCT.[11] Therefore on HRCT imaging, intralobular bronchioles are not usually identified and are not normally seen within 1 cm of the pleural surface.

Specific Signs

The diagnostic approach for HRCT relies upon a good understanding of lung anatomy in general, particularly the secondary pulmonary lobule; the pattern and the distribution of disease; and on associated findings, such as pleural plaques, calcifications, thickening, effusions, lymph node enlargement and the clinical history.

The principal parenchymal patterns seen on HRCT include reticular and nodular structures, increased opacity (ground-glass and air space filling or consolidation), and decreased opacity, including cystic lesions, mosaic attenuation and air trapping.[5] Accompanying findings include linear opacities, parenchymal bands and architectural distortion (Fig. 25.6)

Reticular Patterns

Reticular opacities occur with thickening of the pulmonary interstitium by fluid, fibrosis, or other infiltrative processes (Fig. 25.7). The reticular pattern can be coarse, intermediate or fine. The coarse reticular pattern (1 cm) is due to the thickening of interlobular septa, intermediate reticular changes are seen with honeycombing, and fine reticular changes are seen with intralobular septal thickening. The reticular pattern may be smooth, nodular or irregular.

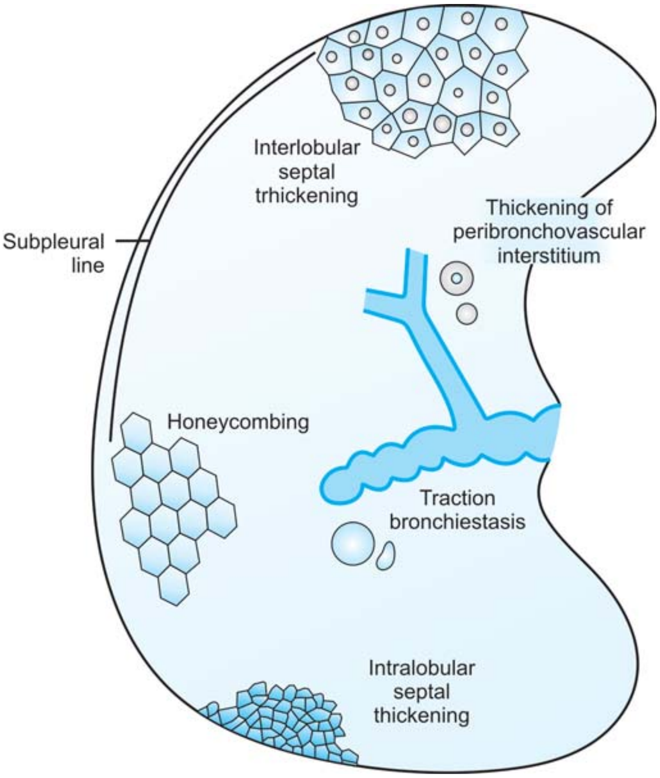


Fig. 25.6: Pictorial representation of reticular opacities: Thickening of the peribronchovascular interstitium, interlobular septal thickening, honeycombing and traction bronchiectasis

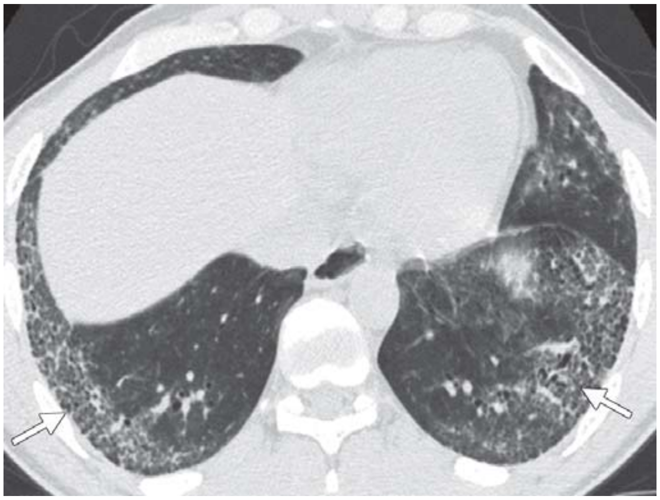


Fig. 25.7: HRCT through the lung bases showing subpleural reticulation in a patient with idiopathic pulmonary fibrosis. Also visible are small cysts (arrows) from honeycombing

The interface sign: It is the most common and earliest HRCT abnormality found in interstitial disease with an irregular and thickened appearance of the normally smooth septa bordering the parenchyma with vessels, bronchi and visceral pleura.[5] It is however a nonspecific sign of interstitial diseases. Other findings include interlobular septal thickening, peribronchial thickening, intralobular linear opacities and cysts.

Interlobular septal thickening: It is a characteristic finding of interstitial lung disease. They appear as 1–2 cm lines that are perpendicular to the pleura and extend out to the pleural space. Centrally they form polygonal structures outlining the secondary lobules (Figs 25.4 and 25.6).

Peribronchial or perivascular interstitial thickening: It results from thickening of the connective tissue surrounding the bronchi or pulmonary vessels. The thickening may be smooth or irregular. Dilatation of the bronchi may result in cases where surrounding fibrosis results in traction, known as traction bronchiectasis (Figs 25.6 and 25.8).

Intralobular linear opacities: It occurs with the thickening of the interstium within the secondary pulmonary lobule. This forms a fine reticular pattern with small irregular lines separated by only a few millimeters. This pattern is most commonly caused by fibrosis, the distribution (upper vs lower lobes) and associated findings vary with different diseases.

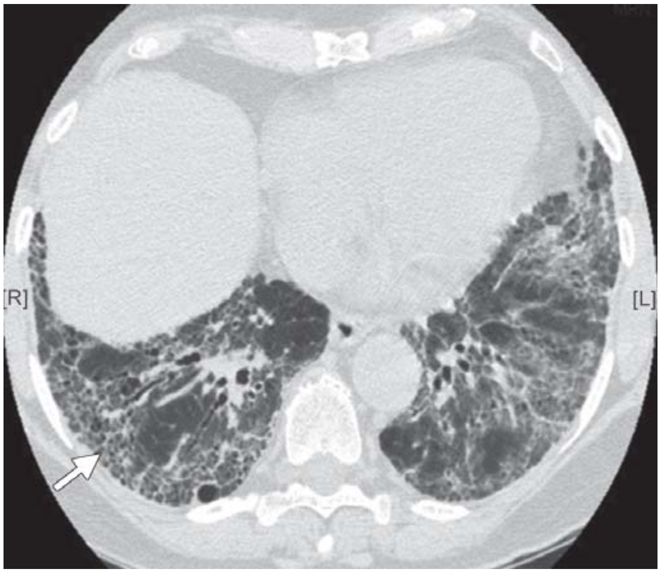


Fig. 25.8: HRCT through the lower lung zones showing honeycombing (arrow) with dilated non-tapering bronchi especially on the right side (traction bronchiectasis) and architectural distortion

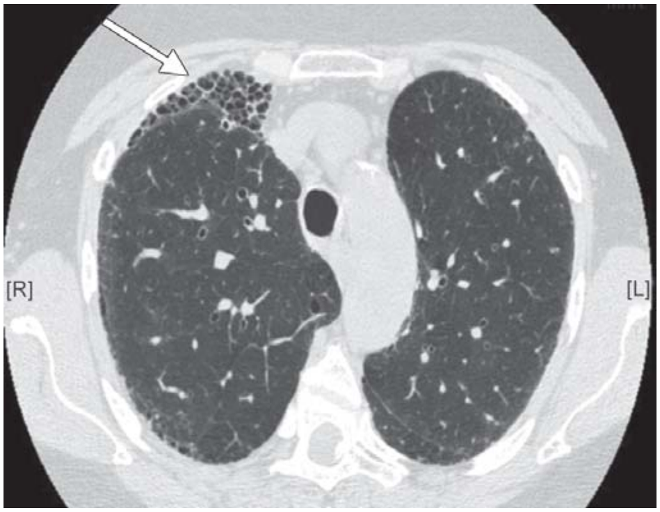


Fig. 25.9: HRCT through the upper lung zones demonstrating numerous cysts (arrow) involving the subpleural regions resulting in honeycombing. Note dilated bronchi adjacent to branches of the pulmonary artery

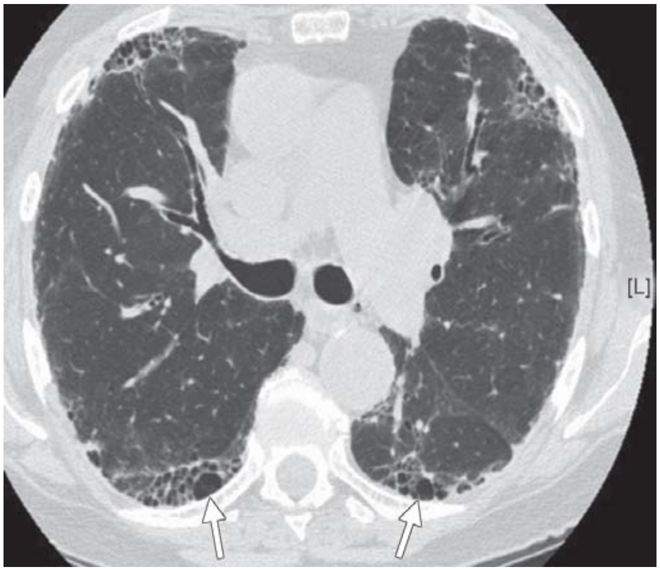


Fig. 25.10: HRCT demonstrating cystic changes in the subpleural regions (arrows) resulting in a honeycombing pattern in a patient with idiopathic pulmonary fibrosis. Note dilated bronchi (right upper lobe dilated bronchi) and paucity of ground glass opacity

Cysts: These are rounded air-containing spaces surrounded by well-defined walls. When they are 4–5 mm in size and present in the subpleural region, they represent honeycombing in end-stage fibrosis and are associated with traction bronchiectasis and architectural distortion (Figs 25.9 and 25.10).

Nodules

Nodules of less than 1 cm may be seen in several acute and chronic infiltrative lung diseases. Nodular patterns include airspace lesions with ill-defined or ground-glass borders, and interstitial nodules with sharp, hazy or stellate margination.[7] The distribution of nodules is useful in narrowing the differential diagnosis.[10] Nodules may predominantly follow a perilymphatic, centrilobular or random distribution. The perilymphatic nodules are found along the bronchovascular interstitium, interlobular septa and subpleural areas. Centrilobular nodules are usually poorly defined and are seen in the center of each secondary lobule. Random nodules are due to hematogenous spread, usually well-defined and randomly situated in the lung.

Increased Opacities

Ground glass opacification: A ground glass opacity refers to the presence of either a *focal or diffuse hazy* increased attenuation of the lung, which does not obscure the vascular or bronchial structures and is not associated with air bronchograms[12] (Figs 25.11 and 25.12). It is caused by partial filling of the airspace. Although ground glass attenuation is a nonspecific sign, it represents an active process, which may potentially be treated or reversed.[13]

Consolidations or airspace filling defects: Parenchymal consolidation or airspace filling causes opacification with the obscuration of vascular structures accompanied by air bronchograms. These two features differentiate it from ground-glass changes (Figs 25.13 and 25.14). These changes result from replacement of alveolar gas by pus, edema, blood or cells.[13]

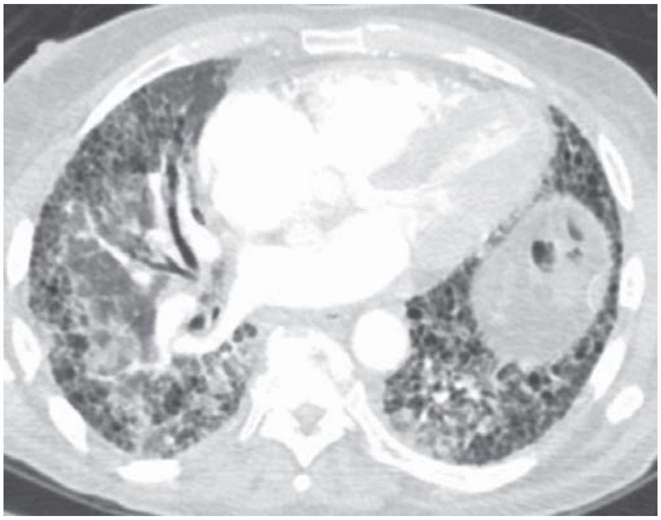


Fig. 25.11: HRCT through the basilar lung showing areas of extensive ground glass attenuation, honeycombing and peribronchial thickening

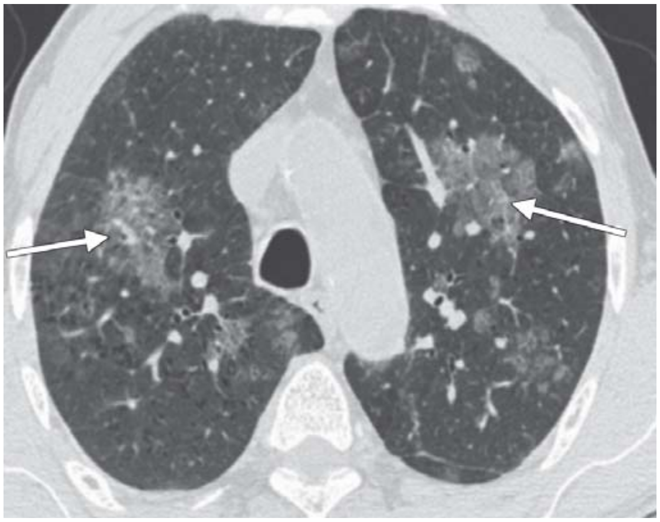


Fig. 25.12: High resolution CT scan of the upper lung zone demonstrating patchy ground glass attenuation (arrows) in a patient with desquamative interstitial pneumonia

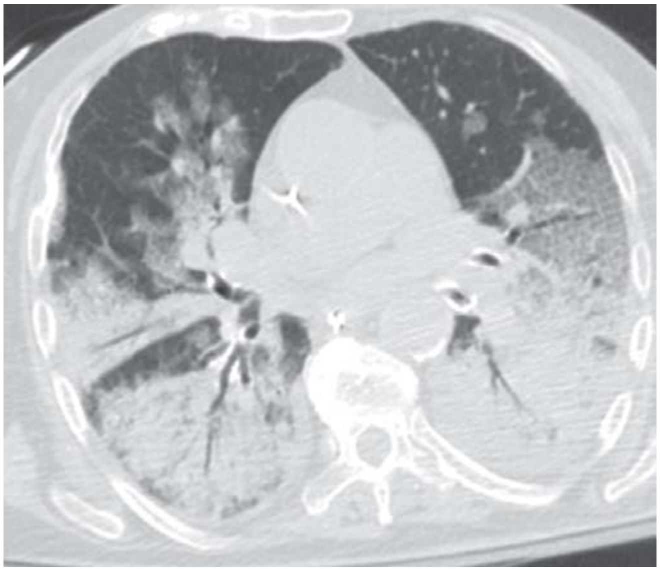


Fig. 25.13: CT chest through mid-lung showing bilateral dense opacity with air bronchograms. This is typical of air space disease

Decreased attenuation: Decreased lung attenuation can occur from lung damage, e.g. emphysema or diminished blood flow, e.g. pulmonary vascular or airway abnormalities.

In emphysema, areas of abnormally low attenuation develop that may have no identifiable walls[14] (Figs 25.15

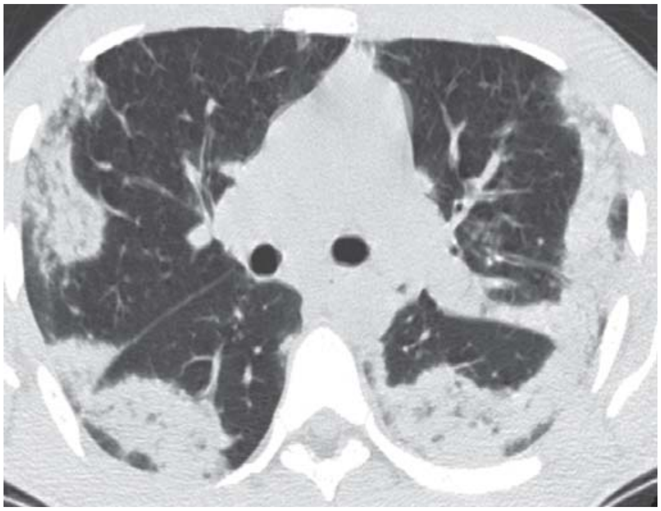


Fig. 25.14: HRCT chest at the level of the main stem bronchi illustrating dense bilateral opacities in a peripheral distribution. The patient had chronic eosinophilic pneumonia

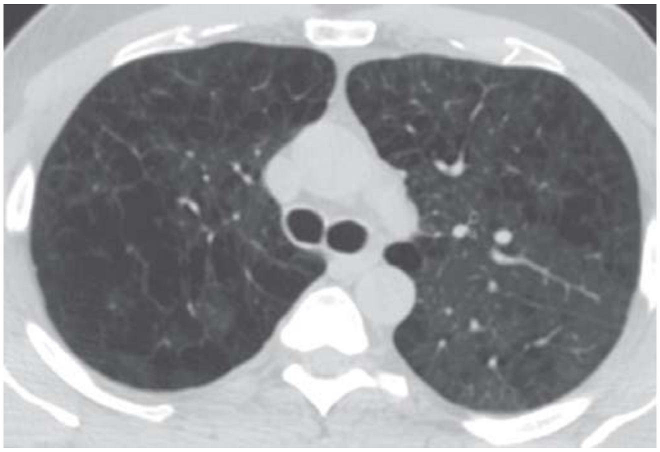


Fig. 25.15: CT chest through the upper lobes showing focal areas of decreased attenuation. No definable walls are visible in these focal areas of hyperlucency. This patient was a smoker with centrilobular emphysema

and 25.16). There are three main forms of emphysema: centrilobular, panlobular and distal acinar emphysema.

Low attenuated areas may also result from decreased perfusion arising from blood flow redistribution in vascular obstruction or airway abnormalities. Redistribution of blood flow away from the areas of vascular obstruction or airway obstruction leads to increased attenuation in the areas of normal lung parenchyma. This pattern of variable regional areas of decreased and increased attenuation due to regional differences in perfusion is termed mosaic attenuation[12] (Fig. 25.17). The two processes, i.e. vasculature versus airway abnormalities may be differentiated by performing expiratory CT.[15] Airway disease will show no change in the lucent areas where there is air trapping, whereas in primary vascular disease, the attenuation in both the hyperlucent and hypolucent areas will increase equally on end expiration. The differentiation of mosaic attenuation (due to blood flow redistribution) from true ground-glass attenuation can be accomplished by evaluating the vessel size in the

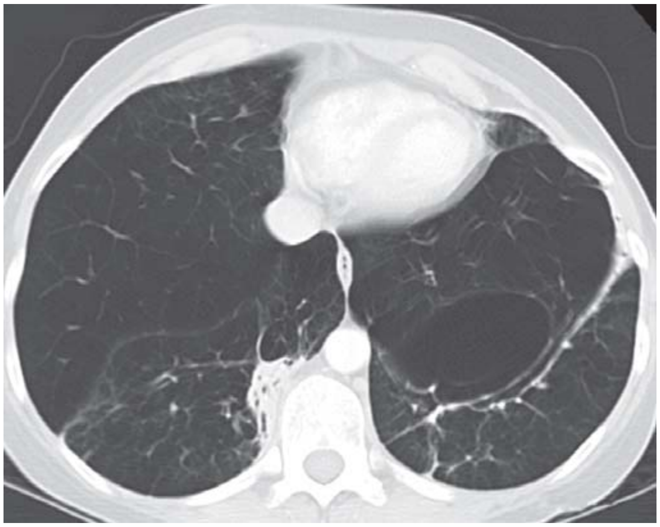


Fig. 25.16: CT chest through the lower lobes showing extensive panlobular emphysema in a patient with alpha 1 antitrypsin deficiency

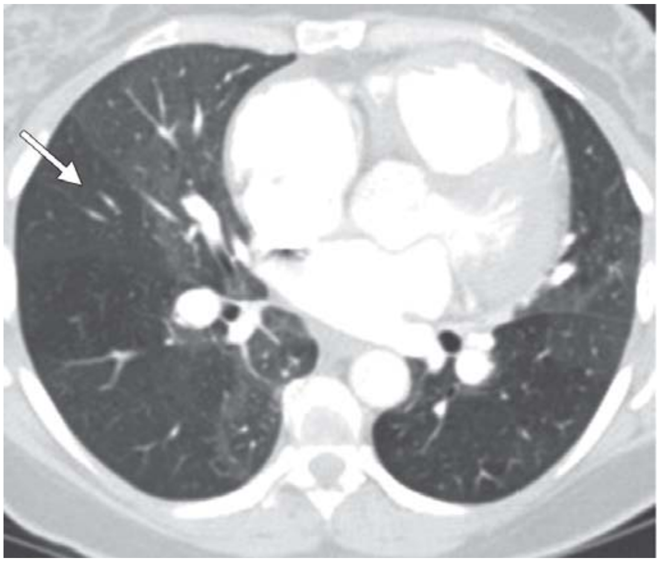


Fig. 25.17: CT chest through the lower lobes demonstrating a pattern of variable regional areas of decreased and increased attenuation, also known as mosaic attenuation. This patient had chronic thromboembolism. Note the decreased vascularity in the hypolucent areas of the lung (arrow)

TABLE 25.2: Differential diagnosis of mosaic attenuation

Abnormality	*Causes*	*Caliber of Vessels*	*Effect of Exhalation*
Small airways disease	• Asthma • Bronchiolitis obliterans • Cystic fibrosis	Decreased size and number of vessels in hypo-attenuated areas due to regional air trapping and hypoxic vasoconstriction	Unequal attenuation in the hyperlucent and hypolucent areas No change in hypolucent areas (air-trapping)
Small vessel disease	• Chronic pulmonary embolism	Decreased size and number of vessels in hypo-attenuated areas due to obliteration of small vessels	Attenuation in both the hyperlucent and hypolucent areas will increase equally (no air-trapping)
Infiltrative disease	• Pneumocystis jiroveci pneumonia • Eosinophillic pneumonia • Hypersensitivity pneumonia	Equal size and number of vessels in areas of increased and decreased attenuation	Attenuation in both the hyperlucent and hypolucent areas will increase equally (no air-trapping)

increased and decreased areas. In infiltrative lung disease, the vessel size and number will be equal in the areas of increased and decreased attenuation. In airways or vascular disease, vessel size and number will be decreased in the regions of hypo attenuation.[15] These findings are summarized in Table 25.2.

NORMAL LUNG COMPONENTS OF THE AIRWAYS

The airways divide by asymmetric dichotomous branching with approximately 23 generations of branches from the trachea to the alveoli that become thin walled as they branch. The accuracy of CT to evaluate the central airways is well established.[16]

Trachea

The trachea is a cartilaginous structure extending from the inferior border of the cricoid to the carina. It may be divided into extrathoracic and intrathoracic segments along the manubrium and is approximately 10–12 cm in length.[17] There are 16 to 22 cartilaginous horseshoe-shaped rings that form the trachea anteriorly. The posterior portion of the trachea consists of a thin fibromuscular membrane, without cartilage. The blood supply to the trachea comes superiorly from the branches of the inferior thyroid artery and right intercostal artery and inferiorly from the bronchial arteries and third intercostal artery (Fig. 25.18). The cross-sectional appearance of the trachea may be oval, rounded or horseshoe shaped (Fig. 25.19). The average tracheal diameter in men is 19.5 mm and in women 17.5 mm.[18] The shape of the trachea may vary with expiration, resulting in a cresenteric shape during forceful expiration, due to posterior tracheal bowing.[19]

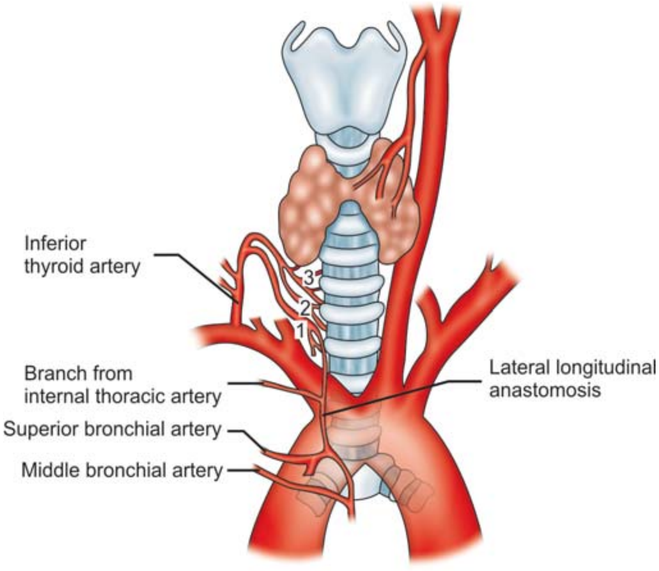

Inferior thyroid artery
3
2
1
Branch from internal thoracic artery
Superior bronchial artery
Middle bronchial artery
Lateral longitudinal anastomosis

Fig. 25.18: Arterial blood supply to the larynx and upper trachea. (F. Charles Brunicardi MD, FACS, ed. 2010. Schwartz's Principles of Surgery. New York. McGraw-Hill Health Professions Division)

The trachea splits into main bronchi, which divide into lobar bronchi. The lobar bronchi divide into segmental bronchi, which ultimately branch into subsegmental bronchi. After several more divisions at this level, the terminal bronchi emerge to give rise to the bronchioles.

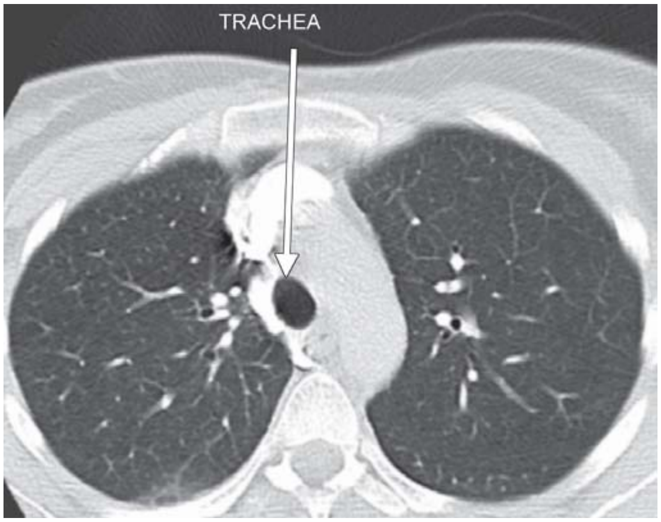


Fig. 25.19: CT chest through the upper lobes demonstrating normal oval tracheal lumen during inspiration

Bronchi

The bronchi are also composed of cartilaginous and fibromuscular structures, but the distribution is less regular than the trachea. They become more difficult to see in the periphery of the lung. Bronchi contain cartilage and glands within their walls, unlike bronchioles. Bronchioles can be divided into membranous bronchioles, which solely conduct air, and respiratory bronchioles, which have alveoli in their wall and are involved in gas exchange. Bronchioles along with corresponding pulmonary artery branches lie within the center of the secondary pulmonary lobule.

Evaluation of the airways should be done using spiral CT technique with thin collimation. The ability of CT to image a particular bronchus depends on its size and orientation relative to the scan plane. The main bronchi and bronchus intermedius are easily detected due to their large size. The origin of the proximal lobar and segmental bronchi can also be identified in most cases. Figure 25.8 illustrates the nomenclature of the bronchial tree (Table 25.3). Figures 25.20 to 25.26 illustrate the division of the bronchial anatomy as seen on spiral CT. The bronchi and large arteries usually run together, with their diameters being of approximate equal size. In general, airways of less than 2 mm in diameter or close to 1–2 mm to the pleural surface are below the resolution of HRCT images.[2] The presence of visible bronchial structures in the lung periphery signifies pathologic thickening or ectasia.

Specific Signs

Saber-Sheath Trachea

A "saber-sheath trachea" is a condition with marked reduction in the transverse diameter of the intrathoracic trachea greater than the half of the sagittal diameter (Fig. 25.27). It results from conditions such as chronic obstructive pulmonary disease.[20]

Tracheobronchomegaly

Tracheobronchomegaly results when the tracheal diameter increases and can be due to congenital or acquired disease[21] (Fig. 25.28). It is also known as Mounier-Kuhn syndrome and is commonly associated with tracheal diverticulosis, bronchiectasis and recurrent infections.

TABLE 25.3: Nomenclature of the bronchial tree

Right lung		Left lung		
Lobes	Segments	Lobes		Segments
Upper	Apical posterior anterior	Upper	Upper division	Apical-posterior anterior
			Lower (lingular) division	Superior inferior
Middle	Lateral medial			
Lower	Superior medial basal anterior basal lateral basal posterior basal	Lower		Superior anterior-medial basal lateral basal posterior basal

Jackson CL, Huber JF. Correlated applied anatomy of the bronchial tree and lungs with a system of nomenclature. Chest. 1943; 9:319-26

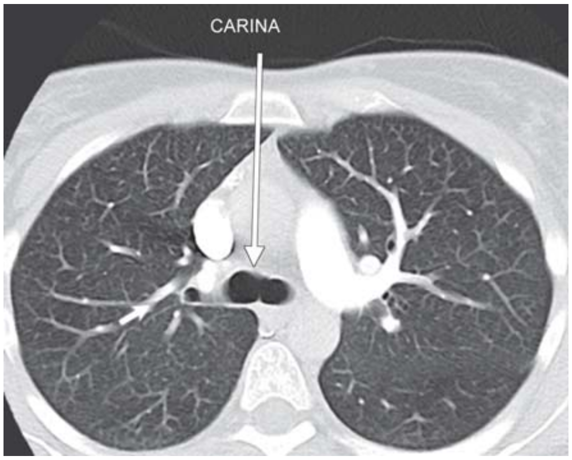


Fig. 25.20: CT chest showing tracheal division into the right and left main stem bronchi. Note the cross-sectional cut of the right upper lobe (thick arrow). Of note, a patchy area of hazy opacity is seen in the left upper lobe laterally

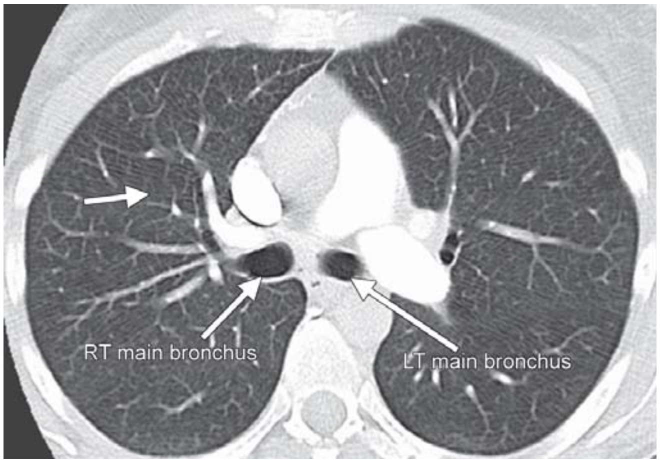

RT main bronchus
LT main bronchus

Fig. 25.21: CT chest showing the right and left main stem bronchi. Note the illustration of the right upper lobe (thick arrow), which almost always lies in the plane of scan

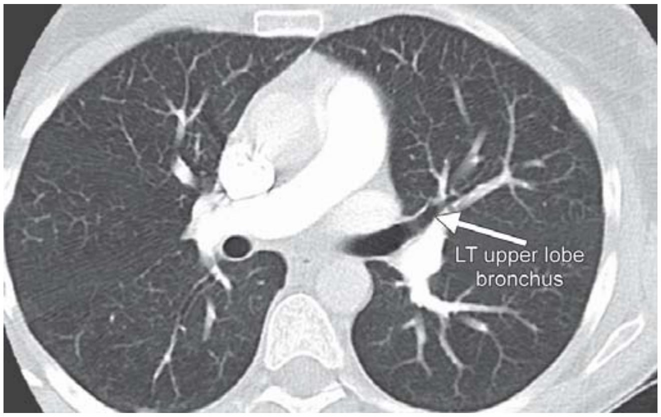

LT upper lobe
bronchus

Fig. 25.22: CT chest at the level of the left main stem bronchus showing the left upper lobe and bronchus

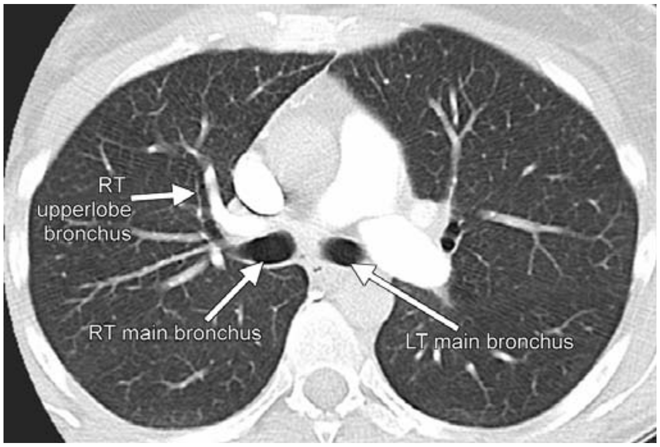

RT
upperlobe
bronchus
RT main bronchus
LT main bronchus

Fig. 25.23: CT chest showing left and right main stem bronchi with the take off of the right upper lobe bronchus

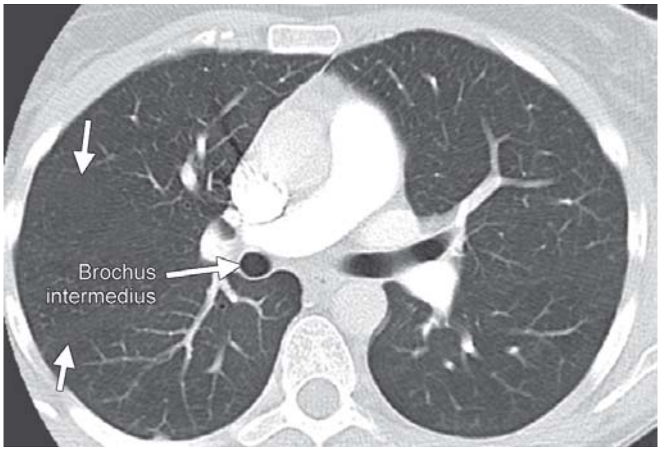

Brochus
intermedius

Fig. 25.24: CT chest illustrating a cross-sectional image of the bronchus intermedius and the left upper lobe bronchus. Note the presence of the minor fissure in the left lung, which is visible as an area with relative paucity of bronchovascular markings (thick arrows)

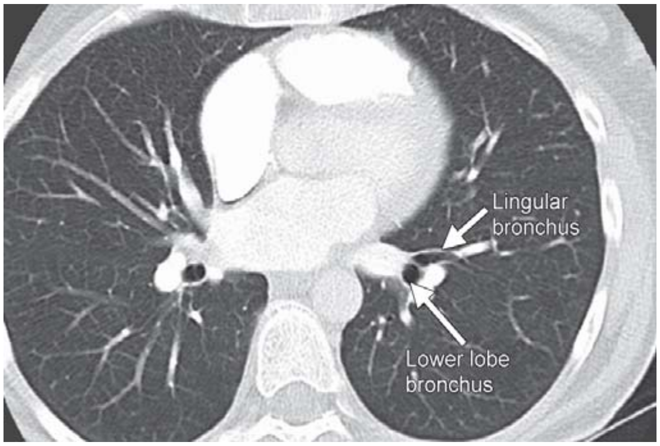

Lingular
bronchus
Lower lobe
bronchus

Fig. 25.25: CT chest showing the origin of the lingular and left lower lobe bronchus

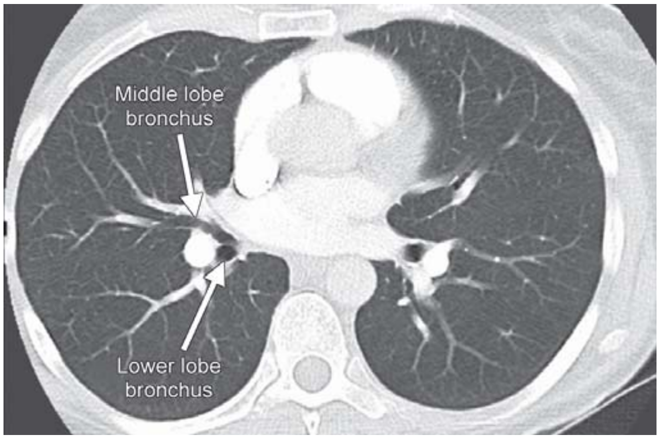


Fig. 25.26: CT chest illustrating right middle lobe and right lower lobe bronchi

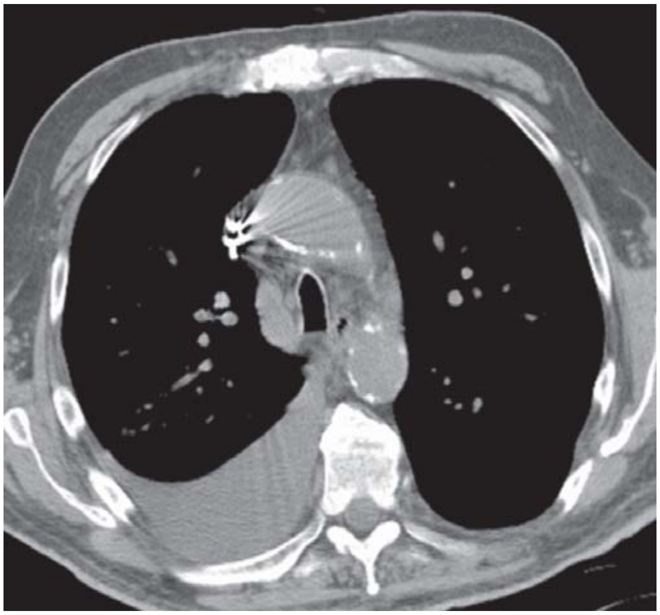


Fig. 25.27: CT chest showing marked reduction in the coronal diameter of the trachea as compared to the sagittal diameter indicating the characteristics appearance of a saber sheath trachea. Of note, there is a moderate sized pleural effusion on the right

Tracheal Diverticulosis

Tracheal diverticulosis results from the outpouching of the posterolateral tracheal wall secondary to weakness in the trachealis muscle. It may be congenital or acquired, and associated with recurrent infections and hemoptysis.[22]

Tracheobronchopathia Osteochondroplastica (TBO)

TBO is a rare benign condition of unknown etiology characterized by multiple submucosal osteocartilagous nodules involving the trachea and bronchi (Fig. 25.29). There is tracheal scalloping and nodularity with the irregular narrowing of the trachea. It spares the posterior tracheal membrane.[23]

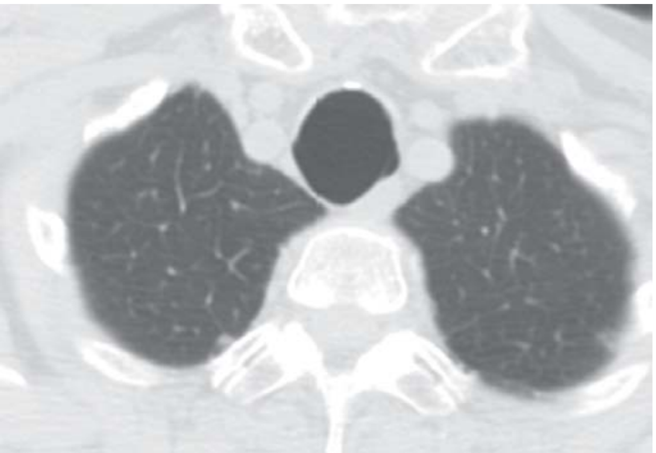


Fig. 25.28: CT chest showing an increased trachea diameter, resulting in tracheomegaly or Mounier-Kuhn syndrome. The normal tracheal diameter is 19.5 mm in a male and 17.5 mm in a female

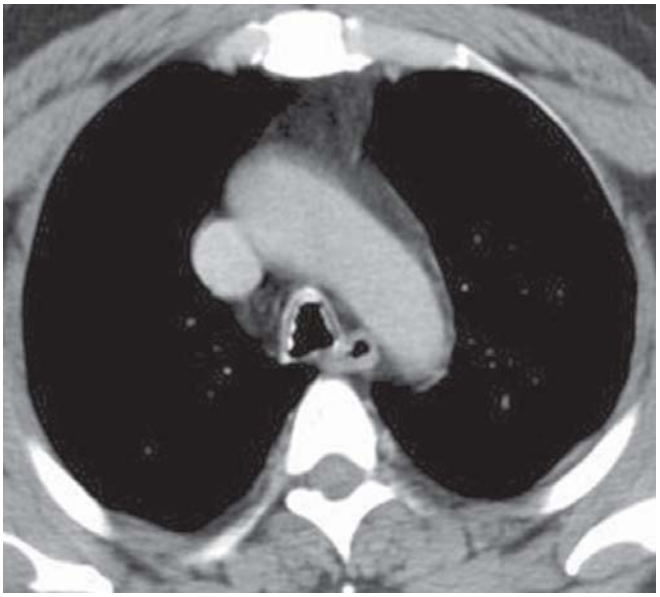


Fig. 25.29: CT chest section through the mid-trachea showing nodularity of the trachea with calcifications and sparing of the posterior tracheal wall, a characteristic finding in tracheobronchopathia osteochondroplastica

Tracheobronchomalacia (TBM)

TBM is a common and underrecognized cause of dyspnea and cough. It is a condition that results in excessive airway collapse of the tracheal and bronchial. By definition, in

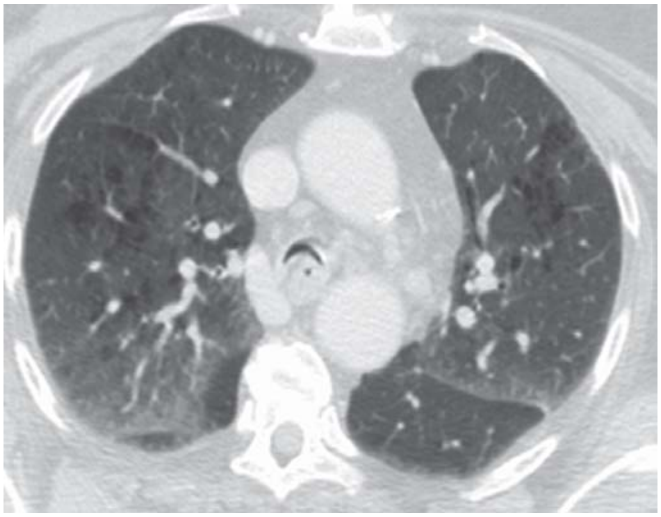


Fig. 25.30: CT chest in exhalation, showing excessive airway collapse with posterior bowing resulting in tracheomalacia

patients with TBM, the cross-sectional area of the trachea shows a reduction of at least 50% during quiet breathing, forming a crescent shaped airway (Fig. 25.30). It can result from several etiologies, including but not limited to external trauma, postintubation, chronic obstructive pulmonary diseases and chronic inflammatory diseases such as relapsing polychondritis. It is best diagnosed by paired inspiratory and expiratory dynamic CT imaging.[24]

NORMAL LUNG COMPONENT OF THE PULMONARY VASCULATURE

A comprehensive knowledge of the cross-sectional anatomy of the pulmonary arteries and veins is imperative in the diagnosis of vascular abnormalities and precise interpretation of CT images. The arteries accompany the airways and their pattern of division is similar to the branching of airways.

Pulmonary Arterial Anatomy

The main pulmonary artery begins from the base of the right ventricle, extends superiorly dividing into the right and left pulmonary arteries. These central pulmonary arteries are intrapericardial. Pulmonary arteries are elastic and thin-walled vessels. The main pulmonary artery on CT is the most anterior vascular structure arising from the heart. It is slightly smaller than the ascending aorta in normal subjects, measuring on average 28 mm in diameter.[25] This measurement is best taken at its bifurcation, lateral to the aorta in the short axis of the pulmonary artery. CT measurements of the pulmonary artery have been shown to correlate with pulmonary artery pressure.[25]

The main pulmonary artery divides lateral to the ascending aorta into the right and left pulmonary arteries. The right pulmonary artery arises nearly at a right angle and passes posteriorly to the ascending aorta and anteriorly to the right main bronchus as it crosses the mediastinum. It is seen along its length on CT since it lies in the scan plane. The left pulmonary artery appears as a direct communication of the main pulmonary artery. It passes slightly to the left of its origin and arches over the left main bronchus as it enters the hilum. The right and left pulmonary arteries are usually of equal size.

Similar to bronchial division, the pulmonary arteries divide by dichotomous branching. There are approximately 17 divisions from the bifurcation of the main pulmonary artery to arteries of a diameter of 10–15 mm.[26]

The right main pulmonary artery usually divides into an ascending trunk; trunchus anterior, primarily supplying the right upper lobe; and a descending trunk and interlobar branch, supplying mainly the right middle and lower lobes. The left pulmonary artery usually continues as the descending or interlobar left pulmonary artery, giving rise to segmental branches of the left upper and lower lobes (Fig. 25.31). The branching of the lobar, segmental and subsegmental pulmonary artery branches show considerable variation and are sometimes identified

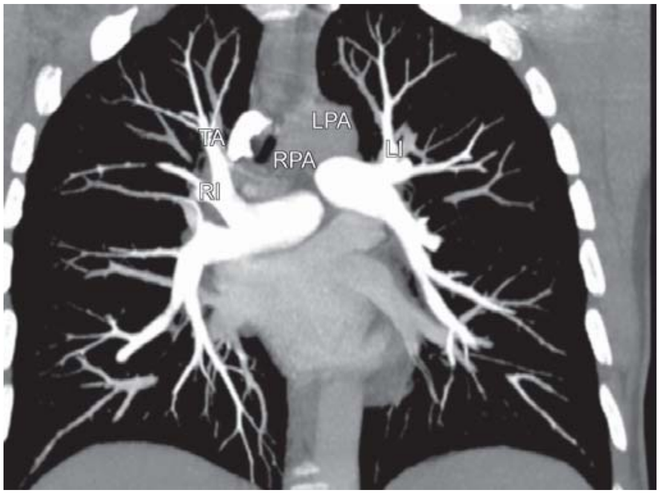


Fig. 25.31: Coronal image of CT chest showing normal hilar pulmonary artery branching. The right main pulmonary artery (RPA) divides into an ascending trunk, trunchus anterior (TA), primarily supplying the right upper lobe, and a descending trunk, interlobar branch (RI), supplying mainly the right middle and lower lobes. The left pulmonary artery (LPA) continues as the descending or interlobar left pulmonary artery (LI), giving rise to segmental branches of the left upper and lower lobes

by associated bronchi. Occlusion of segmental pulmonary arteries can easily be identified on CT, whereas subsegmental pulmonary arteries occlusion may not always be visualized.

Pulmonary Veins

The pulmonary veins arise from alveolar capillaries, where pulmonary venules form. Pulmonary veins run through the interlobular septa and then through the more central connective tissue sheaths to the left atrium.[27] The branching patterns of veins are more variable, but generally two superior and two inferior pulmonary veins are found on each side.

Bronchial Arteries

The bronchial arteries belong to a different arterial system that originates from the systemic circulation. They accompany the bronchi to the level of the terminal bronchi, where they ramify into pulmonary plexus and are drained by the pulmonary venous system.

Abnormalities

Pulmonary Artery Agenesis

Congenital abnormalities resulting in embryonic disappearance of the proximal segments of the right and the left sixth arch may result in the agenesis of either the right or left pulmonary artery respectively. It may occur as a separate condition or along with cardiac abnormalities. Features seen on CT include a small hemithorax, ipsilateral displacement of the mediastinum and absence of the analogous pulmonary artery.[28]

Anomalous Pulmonary Artery

An anomalous retrotracheal left pulmonary artery is seen on CT to arise from the right pulmonary artery, looping behind the trachea and right main stem bronchus before reaching the left hilum. This can result in symptomatic compression of the right main stem.[29]

Anomalous Pulmonary Vein

Anomalous pulmonary vein abnormalities results in the drainage of blood completely or partial into the right atrium.[30] The scimitar syndrome there is aberrant drainage of the right pulmonary artery into the inferior vena cava.

Pulmonary Embolism

Knowledge of the hilar vascular anatomy is crucial for the precise recognition of an acute pulmonary embolism. The identification of the pulmonary arteries is done using the bronchial anatomy as reference since the arteries tend to lie adjacent to the airways. The most consistent CT finding of a pulmonary embolism is an intraluminal filling defect (Fig. 25.32). Depending on the plane of the CT and orientation of the artery, these defects may appear as spherical, eccentric or serpiginous filling defects.[31] In large arteries they may also appear as free-floating masses. An acute pulmonary embolus forms an acute angle with the contrast-filled lumen. In chronic pulmonary embolism, the thrombi are smooth or irregular eccentric mural defects, representing organization of the thrombus.[32]

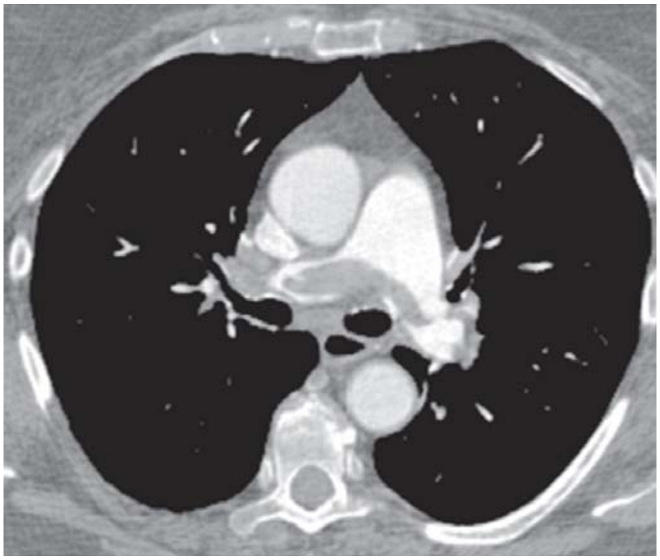


Fig. 25.32: CT angiogram showing a large filling defect at the division of the right and left main pulmonary arteries. This is also known as a saddle embolism. Note the acute angle formed by the embolus and the contrast filled lumen

Pulmonary Artery Aneurysm

Pulmonary artery aneurysms have been associated with a spectrum of conditions such as infections, congenital heart conditions, atrial and ventricular septal defects and vasculitis.[33] The primary cause of pulmonary artery aneurysm is cystic medial necrosis. A false aneurysm may also develop as a result of a pulmonary artery catheter. CT findings are often nonspecific and erroneously identified as masses, nodules or adenopathy.

Pulmonary Varix

Pulmonary varices may be easily identified on CT as an enlarged mass with aneurysmal dilatation of the pulmonary vein[34] (Fig. 25.33).

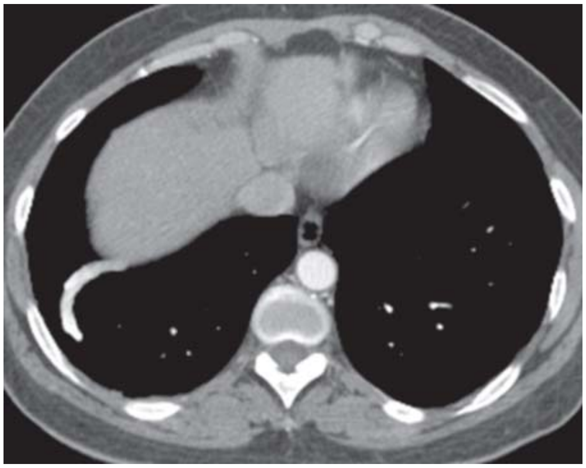


Fig. 25.33: CT chest with contrast showing a dilatation of the pulmonary vein from a pulmonary varix

TRACHEOBRONCHIAL DISEASES

Bronchiectasis

The definition of bronchiectasis is localized, irreversible dilatation of the bronchial tree.[12] Several conditions have been associated with bronchiectasis (Table 25.4). It commonly arises from acute, chronic or recurrent infections. Symptoms usually develop with severe disease and include a history of recurrent pulmonary infections, persistent productive cough or hemoptysis. The radiographic manifestations of bronchiectasis have been well studied. They include the loss of the clarity of vascular markings in specific lung segments, bronchial wall thickening; and in advanced bronchiectasis, distinct cystic masses, frequently demonstrating air-fluid levels.[35,36]

Bronchiectasis is classically described as *cylindrical, varicose, or cystic* based on appearance. Various other terms have also been used (Fig. 25.34). "Tram-tracks" are dilated airways coursing the scan plane. "Signet rings" describe cross-sectional dilated airways with adjacent pulmonary blood artery branches. "Beading airways" are saccular airways seen along their length. There are direct and indirect methods of diagnosing bronchiectasis on CT. Direct methods include bronchial dilatation, lack of normal bronchial tapering, and presence of airways in the periphery of the lungs. Indirect signs consist of bronchial wall thickening and irregularity and the presence of mucoid impaction within the airways.[36]

TABLE 25.4: Conditions associated with bronchiectasis

Disorders	*Description*
Focal distribution	
Bronchial obstruction	Foreign body Tumor Broncholithiasis Compression by peribronchial lymph nodes
Previous pneumonia	
Diffuse distribution	
CF	
Reduced host immunity	Congenital and acquired hypogammaglobulinemia (especially IgG and/or IgG subclasses) HIV infection
Primary ciliary dyskinesia	
Allergic bronchopulmonary mycoses	
Chronic MAC infection	
Aspiration or toxic inhalation	
Rheumatoid arthritis	
Inflammation bowel disease	
Other congenital disorders	α_1-antitrypsin deficiency Tracheobronchomegaly (Mounier-Kuhn syndrome) Cartilage deficiency (Williams-Campbell syndrome) Young syndrome Pulmonary sequestration Marfan syndrome
Yellow nail syndrome	

(Rosen M. Chronic cough due to bronchiectasis ACCP evidence-based clinical practice guidelines. Chest. 2006; 129:122S-31S)

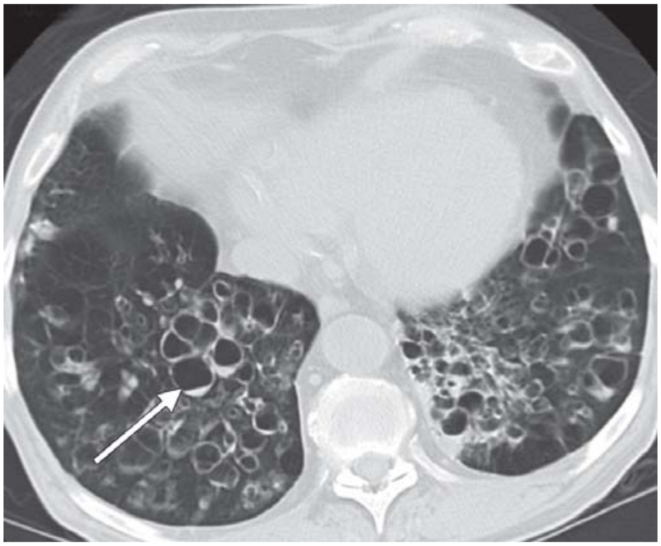


Fig. 25.34: CT chest through the lower lobes showing saccular bronchiectasis. Some of the bronchi have fluid (arrow) in them. This patient developed bronchiectasis from repeated childhood infections

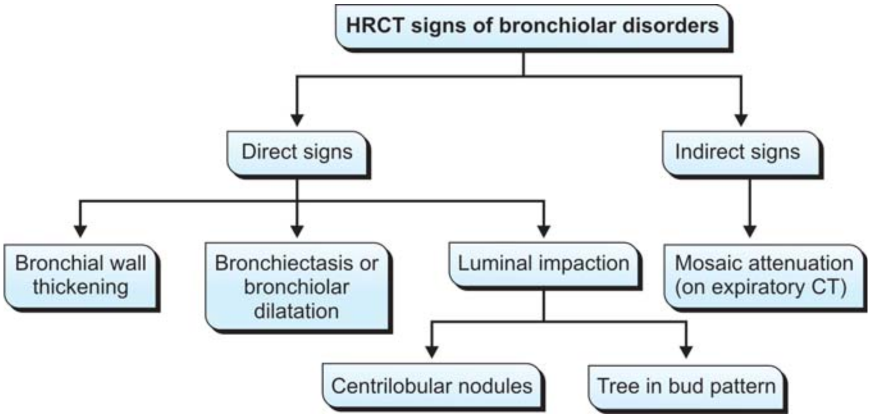
Bronchiolar Diseases

The introduction of HRCT on assessing small airway disease has significantly impacted the diagnosis and classification of bronchiolar disease.[37] Normal intralobular structures are beyond the resolution of CT, however direct and indirect signs of bronchiolar disease may be apparent (Flow chart 25.1). Direct signs include bronchiolar secretions, distinguished as branching Y-shaped linear densities; peribronchiolar inflammation, characterized by poorly defined centrilobular nodules; or bronchiolar wall thickening represented by focal small centrilobular lucencies. Indirect signs manifest as either the areas of mosaic attenuation on inspiration or as the areas of decreased attenuation on expiration.[38] Bronchiolar disease may be categorized on CT into four groups based on other associated signs.

Tree-in-Bud and Bronchiolar Disease

The characteristic finding in this category of bronchiolar disease is the finding of dilated, mucus-filled bronchioles, which result in a pattern of centrilobular nodular, as well as branching or Y-shaped densities, which imitate the appearance of a tree in bud.[39] This pattern is typically seen in the infectious bronchiolitis of several etiologies such as bacterial, viral and fungal causes. Common infections resulting in the tree-in-bud representation include mycobacterium tuberculosis infections, atypical mycobacterial infections, bacterial infections related to immunosupressive conditions such as HIV and cystic fibrosis.[38] It was initially described in patients with panbronchiolitis,[40] common in Asia. These patients have clinical symptoms of productive cough and dyspnea, with an obstructive impairment on pulmonary physiologic testing and characteristic ill-defined nodules and tree-in bud appearance on CT. Other proximal airway infection may also depict the tree-in-bud sign in association with other findings. Examples include cystic fibrosis, tuberculosis, postinfectious bronchiectasis and allergic bronchopulmonary mycoses.[41] Table 25.5 summarizes disorders associated with tree-in-bud opacities with individual characteristic features.

Flow chart 25.1: HRCT signs of bronchiolar disorders



HRCT signs of bronchiolar disorders
Direct signs
Indirect signs
Bronchial wall thickening
Bronchiectasis or bronchiolar dilatation
Luminal impaction
Mosaic attenuation (on expiratory CT)
Centrilobular nodules
Tree in bud pattern

(Devakonda A, Raoof S, Sung A, et al. Bronchiolar disorders. A clinical-radiological diagnostic algorithm. Chest. 2010; 137:938-51.)

TABLE 25.5: Characteristic features of bronchiolar diseases with tree-in-but opacities

	Characteristic clinical features	*Causes and/or associated conditions*	*HRCT features*	*Histophathologic features*
Infection	Wheezing with concomitant signs of respiratory tract infection	Viral, bacterial, parasitic, mycobacterial, fungal	Tree-in-bud pattern, centrilobular nodules, dense consolidation	Acute and chronic inflammation of small bronchioles with epithelial necrosis and sloughing
Immunologic disorders (allergic bronchopulmonary aspergillosis)	Cough, fever, wheezing; recurrent episodes of bronchial obstruction	Asthma	Tree-in-bud pattern, central bronchiectasis, mucoid impaction, upper lobe predominance	Mucoid impaction of bronchi, eosinophilic infiltration, bronchocentric granulomatosis
Congenital disorders (CF, dyskinetic cilia syndrome)	Recurrent purulent cough, airway hyperactivity	Genetic predisposition, multisystem disease	Tree-in-bud pattern, bronchial wall thickening, bronchiectasis, bronchiolectasis	Cellular infiltration
Neoplasms	Symptoms and signs of upper respirtory tract obstruction (hoarseness, stridor)	Juvenile laryngotracheo-bronchial papillomatosis	Tree-in-bud pattern, multiple solid or cystic nodules	Varies from multiple clusters of squamous cells within alveoli to large cavitary lesions
Diffuse aspiration bronchiolitis	Nonspecific	Elderly, bed bound	Tree-in-bud pattern, centrilobular nodules	Foreign body giant cell reaction
Idiopathic diffuse panbronchiolitis	Mainly in Japanese adults; subacute onset of cough, dyspnea	Associated sinusitis, HLABw54 antigen	Tree-in-bud pattern, thickened ecstatic bronchi, centrilobular nodules	Infiltration of lymphocytes, plasma cells and foamy macrophages at the level of respiratory bronchiole

CF = cystic fibrosis; HRCT = high-resolution CT.

(Devakonda A, Raoof S, Sung A, Travis WD, Naidich D. Bronchiolar disorders. A clinical-radiological diagnostic algorithm Chest 2010; 137; 938-51.)

Poorly Defined Centrilobular Nodules and Bronchiolar Disease

Compared to infectious bronchiolitis, the distinguishing finding of this group of bronchiolar disease is the presence of ill-defined centrilobular nodules in the absence of a tree-in-bud picture. A variety of diseases with peribronchiolar inflammation without the tree-in-bud pattern have been described. This includes subacute hypersensitivity pneumonitis, lymphocytic interstitial pneumonitis, follicular bronchiolitis, Respiratory Bronchiolitis-Interstitial Lung Disease (RBILD) and mineral dust-induced bronchiolitis.[37]

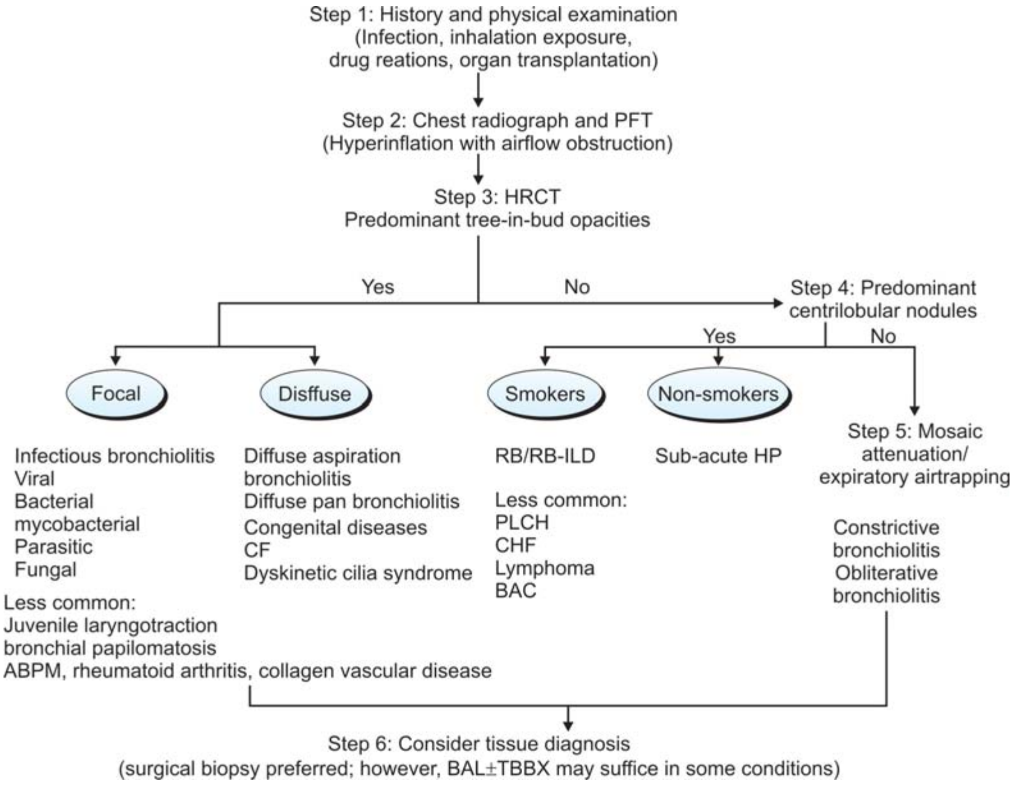
Focal Ground Glass Attenuation or Consolidation and Bronchiolar Disease

This presentation of focal ground glass attenuation is most characteristic of Cryptogenic Organizing Pneumonia (COP) or Bronchiolitis Obliterans with Organizing Pneumonia (BOOP).[42] Patients usually complain of symptoms of nonproductive cough for several months, low-grade fever and increasing dyspnea. The most common radiologic finding on HRCT in COP is patchy bilateral consolidation commonly with peribronchial and subpleural distribution.[43] Small, poorly formed peribronchiolar nodules and irregular linear opacities are seen in a smaller percentage of patients. However, the tree-in-bud pattern is clearly uncommon. Areas of ground glass consolidation may be seen in immunocompromised patients with COP.

Decreased Parenchymal Attenuation and Bronchiolar Disease

This category includes patients with constrictive or obstructive bronchiolitis. Conditions associated with

Flow chart 25.2: A stepwise approach to bronchiolar disease. History, physical findings, evidence of hyperinflation on chest radiograph or airflow obstruction on pulmonary function testing suggestive of bronchiolar disease, should trigger a request for obtaining an HRCT scan of the chest performed at the end of inspiration and expiration. A HRCT scan of the chest further classifies bronchiolar diseases. The presence of a tree-in-bud pattern largely suggests either an infectious bronchiolitis, if a focal distribution is noted, or diffuse panbronchiolitis or congenital disease related bronchiolitis, if a diffuse pattern is noted. If centrilobular nodules are predominantly seen, then RB-ILD should be suspected in a smoker or HP in a non-smoker. Mosaic attenuation suggests either a constrictive bronchiolitis or obliterative bronchiolitis. Histology is ultimately required for the final confirmation


Step 1: History and physical examination
(Infection, inhalation exposure,
drug reations, organ transplantation)
Step 2: Chest radiograph and PFT
(Hyperinflation with airflow obstruction)
Step 3: HRCT
Predominant tree-in-bud opacities
Yes
No
Step 4: Predominant
centrilobular nodules
Yes
No
Focal
Disffuse
Smokers
Non-smokers
Infectious bronchiolitis
Viral
Bacterial
mycobacterial
Parasitic
Fungal
Less common:
Juvenile laryngotraction
bronchial papilomatosis
ABPM, rheumatoid arthritis, collagen vascular disease
Diffuse aspiration
bronchiolitis
Diffuse pan bronchiolitis
Congenital diseases
CF
Dyskinetic cilia syndrome
RB/RB-ILD
Less common:
PLCH
CHF
Lymphoma
BAC
Sub-acute HP
Step 5: Mosaic
attenuation/
expiratory airtrapping
Constrictive
bronchiolitis
Obliterative
bronchiolitis
Step 6: Consider tissue diagnosis
(surgical biopsy preferred; however, BAL±TBBX may suffice in some conditions)

ABPM = allergic bronchopulmonary mycosis; BAC = bronchoalveolar cell carcinoma; CF = cystic fibrosis; CHF = congestive heart failure; HP = hypersensitivity pneumonitis; PFT = pulmonary function test; PLCH = pulmonary Langerhans cell histiocytosis; RB-ILD = respiratory bronchiolitis-inetrstitial lung disease; TBBX = transbronchial biopsy

(Devakonda A, Raoof S, Sung A, Travis WD, Naidich D. Bronchiolar disorders. A clinical-radiological diagnostic algorithm Chest 2010;137;938-951)

obstructive bronchiolitis include lung transplant, chronic graft-versus-host disease from allogeneic bone marrow transplant and collagen vascular disease.[44] Clinical symptoms are usually mild, but severe respiratory compromise may result from progressive airway obstruction. Mosaic attenuation is commonly seen in obstructive bronchiolitis with the presence of bronchial dilatation, peribronchial thickening and evidence of air trapping on expiratory HRCT.[45]

Bronchiolar disease should be approached using systematic method as illustrated in Flow chart 25.2.

PARENCHYMAL DISEASES

Solitary Pulmonary Nodule (SPN)

The evaluation of focal lung disease poses a challenge in the diagnosis of pulmonary disorders. There is a lack of consensus leading to several controversies in the definition, assessment and diagnostic techniques, including the imaging and mode of pathologic confirmation of focal lung diseases. For the purpose of this chapter, we will define a solitary pulmonary nodule as a single, rounded lesion in the lung parenchyma, which is not associated with atelectasis or pneumonia. Solitary pulmonary nodules are a common, incidental finding on CT imaging. Characterization of the secondary pulmonary nodule is of utmost importance and may aid in narrowing the differential diagnosis, preventing further unnecessary procedures or missing localized malignancy (Also see Chapter 120A).

Size

The size of a solitary pulmonary nodule on CT has been shown to directly influence the probability of malignancy.[46] Nodules larger than 3 cm are more apt to being malignant. However, smaller lesions, even of less than 1 cm in size have been shown to be malignant in several studies.[47]

Location

Primary lung cancers have been shown to be more commonly located in the upper lobes, particularly on the right side.[48] SPNs have also been reported to be identified in the lung periphery, rather than the medial third of the lung. Metastatic lesions are predisposed to be subpleural in location and are predominantly seen in the lower lobes.[49] Nevertheless, several other lesions, such as lymph nodes are also seen in the subpleural distribution.[50]

Margin and Contour

Benign nodules tend to demonstrate a round, smooth contour with a sharply defined margin. Malignant lesions are more likely to exhibit an irregular lobulated or ragged shape and a vague, irregular or spiculated edge.[51] However, malignant lesions have been reported to demonstrate a smooth appearance and benign condition have shown lobulated or spiculated contours.[52]

Halo Sign

A halo sign is defined as a distinct nodule surrounded by a circular margin of ground glass attenuation.[53] This sign has been most commonly associated with the early course of invasive pulmonary aspergillosis in the correct clinical context. It has however also been reported in Wegener's granulomatosis, Kaposi's sarcoma and bronchoalveolar carcinoma.

Bronchus Sign

The identification of an air bronchogram on CT is of important value. Although non-specific, the present bronchial lumen surrounded by a pulmonary lesion is likely to be malignant. Airways related to lung cancer tend to be abnormal, appearing ecstatic or tortuous.[54]

Cavitation

Several etiologies may result in cysts and cavities, including septic emboli, vasculidities and tumors. CT helps in characterizing cysts and cavities, allowing for the closer evaluation of wall thickness and intracavitary findings such as air-fluid levels. Thin walled cavities tend to be benign, whereas thick walled cavities may be of uncertain etiology.[55]

Feeding Vessel Sign

A focal lesion with an adjacent vessel, known as a feeding vessel sign or vessel-mass sign, has been described in various conditions such as arteriovenous malformations, metastasis or infarcts.[56] Although, it is not reported to be a common finding, a feeding vessel sign is helpful in distinguishing hematogenous metastasis from either primary or granulomatous lesions. It is also useful in diagnosing septic emboli and pulmonary vasculitis is the appropriate clinical situation.

Growth Rates

One of the most important radiographic factors allowing for distinction between benign and malignant disease is the growth rate of the SPN. It is therefore paramount to review prior chest imaging in the evaluation of a SPN. The absence of detectable growth over a two-year period is highly suggestive of a benign etiology.[57] The doubling time of a SPN is the time it takes to double the size, can be determined using the changes in diameter. A 26% increase in diameter will result in a doubling volume of the SPN. A majority of malignant SPNs have a doubling time of 20–400 days.

Calcification

The radiographic presence of calcification reliably suggests that a pulmonary lesion is benign.[58] Furthermore, four patterns of benign calcification have been studied: Laminated and concentric; dense central core; diffuse; and solid and punctuate. In malignant processes, calcifications classically appear speckled or eccentric and usually within large central lesions.[59]

Fat

The appearance of fat is suggestive of two key conditions: Hamartoma or exogenous lipoid pneumonia. A hamartoma is a benign condition, which contains connective tissue, cartilage, smooth muscle, bone and variable amount of fat and represents the third most common cause of a solitary pulmonary nodule.[60] They can be diagnosed by CT as lesions containing fat or fat and calcification, as well as have an even contour with a sharp circumference.[46]

Contrast Enhancement

Due to the fundamental differences in vascularity of focal benign versus malignant lesions, the phenomenon of pulmonary enhancement has been a valuable tool in differentiating the two processes.[61] Malignant lesions are more prone to enhancement following the injection of contrast material. It has been reported that malignant lesion may enhance by greater than 15–20 Hounsfield units.[62]

Diffuse Diseases

Diffuse parenchymal lung diseases are compiled of chronic and acute infiltrative lung diseases and emphysema. These conditions in addition to being diffuse in nature often have patchy or focal distribution. Suggestive findings that indicate parenchymal irregularity in diffuse lung disease include linear and reticular opacities, nodular opacities, and increased attenuation seen as consolidation or ground glass opacities and decreased attenuation seen in emphysema and cystic diseases.

Several acute and chronic pulmonary conditions result in diffuse infiltration of the lungs. They can be classified based on the predominant radiographic pattern on CT (Table 25.6). There are seven distinct histologic types of idiopathic interstitial pneumonias. They include Usual Interstitial Pneumonia/Idiopathic Pulmonary Fibrosis (UIP/IPF), Nonspecific Interstitial Pneumonia (NSIP), Desquamative Interstitial Pneumonia (DIP), respiratory bronchiolitis interstitial pneumonia, Acute Interstitial Pneumonia (AIP), COP/BOOP, and Lymphocytic Interstitial Pneumonia (LIP).[63] High resolution computed tomography evaluation may avoid the necessity for tissue diagnosis and may limit the differential diagnosis in some cases.

Reticular Pattern

Idiopathic pulmonary fibrosis: Idiopathic pulmonary fibrosis has characteristic HRCT findings that can lead to its diagnosis with a high degree of certainty.[64] In the early phase of IPF patchy, the peripheral distribution of ground glass opacities is seen with the areas of normal lung intermingled between the areas of involved lung.

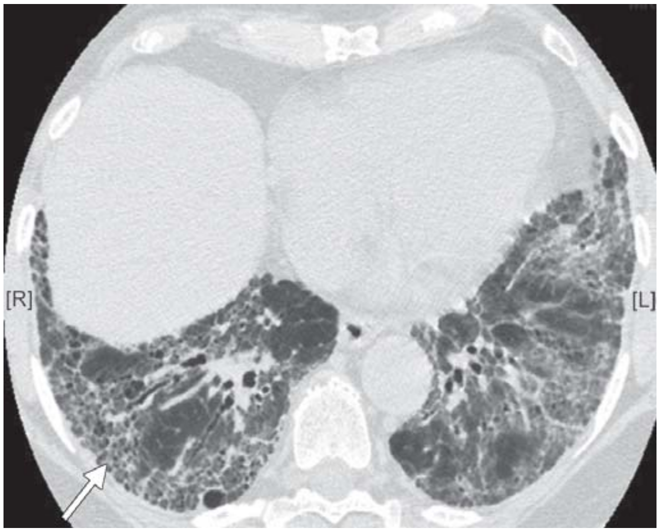


Fig. 25.35: HRCT showing cuts through the lower lobes showing reticular changes including honeycombing, traction bronchiectasis and architectural distortion

The main pattern of abnormality seen on HRCT in a later stage in patients with IPF include intralobular linear opacities, which correspond to histologic areas of fibrosis, a fine reticular pattern, most pronounced at the lung bases and in the subpleural regions and irregular interfaces between the lung and pulmonary vessels, bronchi and pleural surfaces[65] (Fig. 25.35). This progression of fibrosis ultimately results in the dilatation and tortuosity of bronchi and bronchioles, referred to as traction bronchiectasis. The end stage of IPF is illustrated by honeycombing, noted most severely at the lung bases and in subpleural sites.[66] IPF is classically represented as a patchy distributed disease, with spatial and temporal heterogeneity. This refers to the areas of normal lung, reticular changes or honeycombing seen in the same patient within the same lung section.

Nonspecific interstitial pneumonitis: There are two forms of NSIP, which can occur: Cellular or a fibrotic NSIP. HRCT features of NSIP include ground-glass attenuation in a diffuse or patchy distribution with reticular opacities and traction bronchiectasis.[67] In cellular NSIP, there is a prevalence of ground glass attenuation (Fig. 25.36) and in fibrotic NSIP more reticular changes are noticeable (Fig. 25.37). Findings of honeycombing are seldom noted. NSIP, unlike UIP, displays temporal and spatial homogeneity, where there is a uniform pattern of HRCT changes within the same lung segment.

Collagen vascular disease: HRCT features similar to IPF may be seen in various collagen vascular diseases such as

TABLE 25.6: Radiographic patterns in diffuse lung disease

Pattern of opacities		
Consolidation		
	Acute:	Infection, acute respiratory distress syndrome, hemorrhage, aspiration, acute interstitial pneumonia, cyptogenic organizing pneumonia [also called idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP)].
	Chronic:	Chronic infection (tuberculosis fungal), chronic eosinophilic pneumonia, crytogenic organizing pneumonia, lymphoproliferative disease bronchioloalveolar carcinoma, pulmonary alveolar proteinosis, sarciodosis (rarely)
Linear or reticular opacities		
	Acute:	Infections (viral mycoplasma), pulmonary edema
	Chronic:	Idiopathic pulmonary fibrosis (IPF) or usual interstitial pneumonia, connective tissue diseases-associated pulmonary fibrosis, asbestosis, sarcoidosis, hypersensitivity pneumonia, drug-induced lung disease
Small nodules (round opacities <1 cm in diameter)		
	Acute:	Infections (disseminated tuberculous, fungal or viral infections), hypersensitivity pneumonitis (poorly circumscribed centrilobular)
	Chronic:	Sarcoidosis, hypersensitivity pneumonitis, silicosis, coal worker's pneumoconiosis, respiratory bronchiolitis metastases, alveolar microlithiasis
Cystic airspaces		
	Acute:	*Pneumocystis carinii* pneumonia, septic embolism.
	Chronic:	Pulmonary Langerhans cell histiocytosis, pulmonary lymphangioleiomyomatosis, honeycomb lung causes by IPF or other disorders, metastatic disease (rare)
Ground-glass opacities		
	Acute:	Infection (*P. carinii*, cytomegalovirus), pulmonary edema hemorrhage, hypersensitivity pneumonitis, acute inhalational exposures, durg-induced lung disease acute interstitial pneumonia
	Chronic:	Nonspecific interstitial pneumonia (idiopathic or related to underlying disease, e.g. connective tissue disease), respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, drug induced lung disease, pulmonary alveolar proteinosis
Thickened interlobular septa		
	Acute:	Pulmonary edema
	Chronic:	Lymphangitic carcinomatosis, pulmonary alveolar proteinosis, sarcoidosis, pulmonary veno-occlusive disease
Distribution		
Upper lung predominance: Pulmonary Langerhans cell histiocytosis, silicosis, coal worker's pneumoconiosis, carmustine-related pulmonary fibrosis, reactivation tuberculosis, *P. carinii* pneumonia on pentamidine prophylasis		
Lower lung predominance: IPF, pulmonary fibrosis associated with connective tissue diseases, asbestosis, chronic aspiration		
Central (perihilar) predominance: Sarcoidosis, beryllosis		
Peripheral predominance: IPF, chronic eosinophilic pneumonias, cryptogenic organizing pneumonia (or idiopathic BOOP)		
Associated findings		
Pleural effusion or thickening: Pulmonary edema, connective tissue diseases, asbestosis, lymphangitic carcinomatosis lymphoma, lymphangioleiomyomatosis, drug-induced diseases.		
Lymphadenopathy: Infections sarcoidosis silicosis (sarcoidosis and silicosis may be associated with lymph nodes that are calcified in an eggshell patterns), berylliosis, lymphangitic carcinomatosis, lymphoma, lymphocytic interstitial pneumonia.		

(Ryu JH, Olson EJ, Midthun DE, Swensen SJ. Diagnostic approach to the patient with diffuse lung disease Mayo Clin Proc. 2002;77: 1221-1227)

rheumatoid arthritis, scleroderma, mixed connective tissue disease, polymyositis and systemic lupus erythematous.[68] Rheumatoid arthritis may result in fibrosis in a small percentage of patients, with a similar lower lung zone distribution as IPF. More commonly seen are pleural manifestations, but other findings, such as bronchiectasis or rheumatoid nodules can occur.[69] Scleroderma may result in fibrosis with fine reticulation, as well as ground glass attenuation, honeycombing or pleural thickening.[70]

Asbestosis: Asbestosis leads to predominantly basilar and dorsal lung parenchymal fibrosis. Other characteristic findings include: Peribronchiolar fibrosis that forms

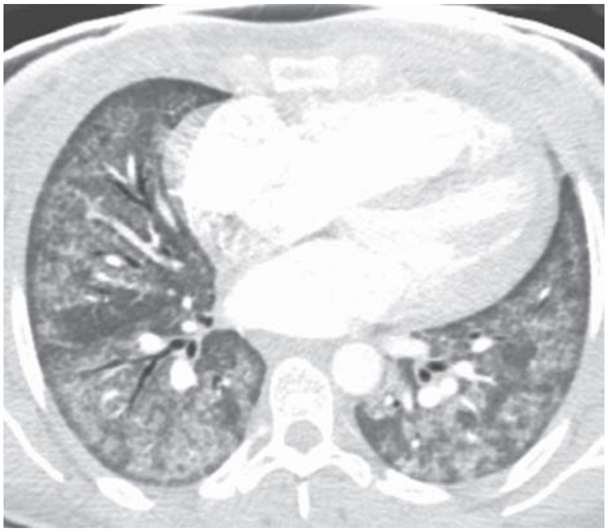


Fig. 25.36: CT chest features of NSIP with diffuse, bilateral ground glass attenuation at the lower lung zones. Note the absence of honeycombing

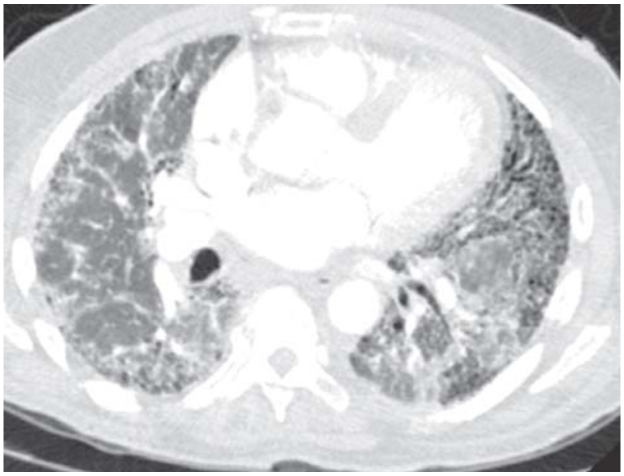


Fig. 25.37: CT Chest through the middle lung zones in a patient with NSIP

centrilobular nodules, intralobular and interlobular septal fibrosis that forms subpleural short lines, coarse parenchymal bands, and subpleural curvilinear bands that parallel the pleura and represent fibrotic bridging from one centrilobular region to the next.[71] Coarse honeycombing can be seen in advanced stages. Coexistent pleural plaques are frequently identified, particularly in patients with curvilinear subpleural lines.[72]

Nodular Pattern

The differential diagnosis of nodular disease includes an extensive list of benign and malignant processes. Nodular disease can be further analyzed based on the predominant distribution of nodules: Perilymphatic; centrilobular or random distribution[10] (Flow chart 25.3).

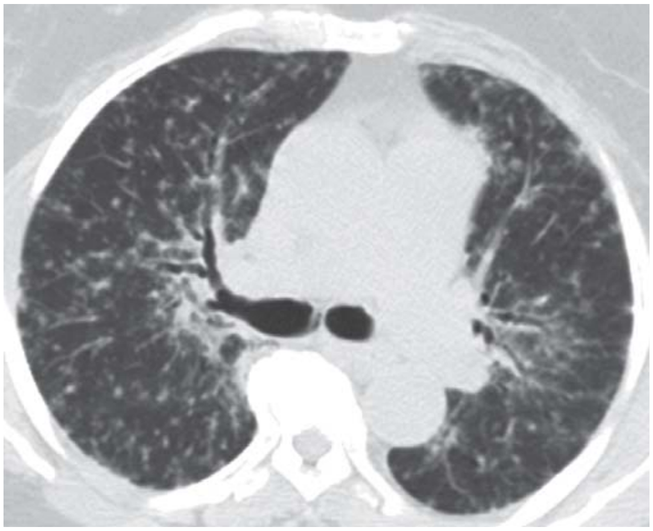


Fig. 25.38: HRCT at the level of the right upper lobe bronchus showing small nodules and nodular thickening along the bronchovascular bundles, interlobular septa, interlobular fissures, and subpleural lung regions in a patient with sarcoidosis

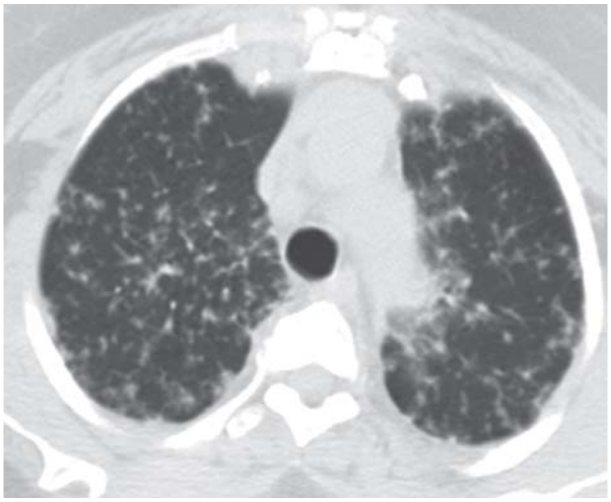
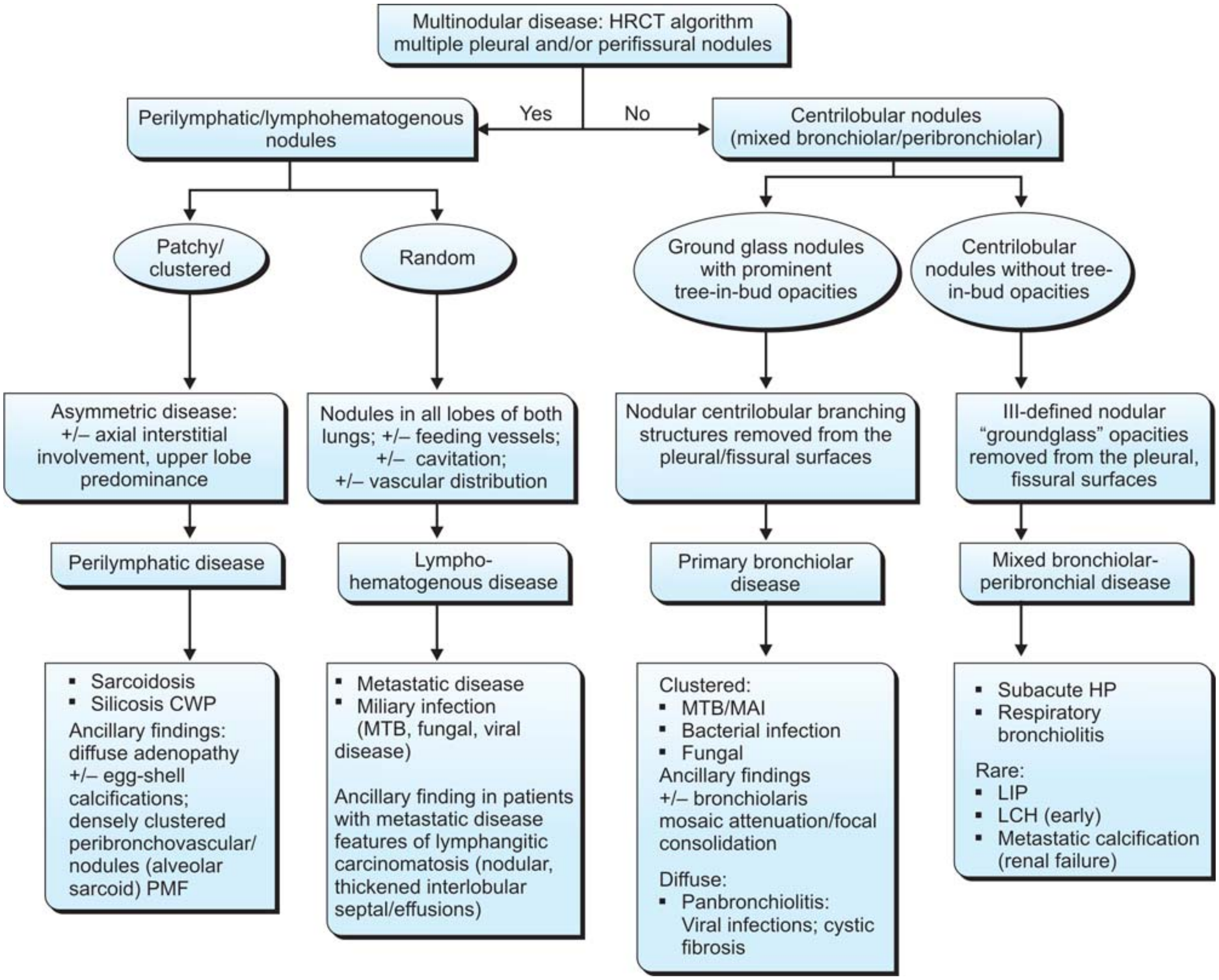


Fig. 25.39: HRCT through the upper lung zones showing multiple small nodules throughout with nodules seen along the subpleural regions and along the interlobular septa and interlobular fissures

Perilymphatic distribution: This includes the following diseases:

Sarcoidosis: The characteristic HRCT finding of sarcoidosis include small nodules and nodular thickening along the bronchovascular bundles, interlobular septa, interlobular fissures and subpleural lung regions[73] (Figs 25.38 and 25.39). The bronchovascular thickening is

Flow chart 25.3: Algorithmic approach to multinodular lung disease[10]


Multinodular disease: HRCT algorithm
multiple pleural and/or perifissural nodules
Yes
No
Perilymphatic/lymphohematogenous nodules
Centrilobular nodules (mixed bronchiolar/peribronchiolar)
Patchy/ clustered
Random
Ground glass nodules with prominent tree-in-bud opacities
Centrilobular nodules without tree-in-bud opacities
Asymmetric disease: +/– axial interstitial involvement, upper lobe predominance
Nodules in all lobes of both lungs; +/– feeding vessels; +/– cavitation; +/– vascular distribution
Nodular centrilobular branching structures removed from the pleural/fissural surfaces
Ill-defined nodular “groundglass” opacities removed from the pleural, fissural surfaces
Perilymphatic disease
Lympho-hematogenous disease
Primary bronchiolar disease
Mixed bronchiolar-peribronchial disease
▪ Sarcoidosis
▪ Silicosis CWP
Ancillary findings: diffuse adenopathy +/– egg-shell calcifications; densely clustered peribronchovascular/ nodules (alveolar sarcoid) PMF
▪ Metastatic disease
▪ Miliary infection (MTB, fungal, viral disease)
Ancillary finding in patients with metastatic disease features of lymphangitic carcinomatosis (nodular, thickened interlobular septal/effusions)
Clustered:
▪ MTB/MAI
▪ Bacterial infection
▪ Fungal
Ancillary findings +/– bronchiolaris mosaic attenuation/focal consolidation
Diffuse:
▪ Panbronchiolitis: Viral infections; cystic fibrosis
▪ Subacute HP
▪ Respiratory bronchiolitis
Rare:
▪ LIP
▪ LCH (early)
▪ Metastatic calcification (renal failure)

Raoof S, Amchentsev A, Vlahos I, et al. Pictorial essay: mulitinodular disease: a high-resolution CT scan diagnostic algorithm. Chest. 2006; 129(3):805-15.

most pronounced at the hila. The nodules appear irregular and represent the coalescence of microscopic granulomas. As fibrosis develops, reticular changes, such as intralobular septal thickening, occur and ultimately lead to architectural distortion, loss of lung volume and traction bronchiectasis.[74] Honeycombing may be seen with sarcoidosis, although it is usually mild and involves primarily the upper and middle lung zones, with relative sparing of the lung bases.[75] Hilar and mediastinal lymphadenopathy is another feature of sarcoidosis seen on CT, with calcification noted in longstanding disease.[76]

Silicosis/coal workers pneumoconiosis: The most characteristic findings in silicosis and coal worker's pneumoconiosis are small nodules predominantly seen in the posterior aspects of the upper lung zones. These nodules vary in size, may be calcified and are distributed largely in the centrilobular pattern.[77] Progressive massive fibrosis is seen as a conglomerate of nodules with an irregular margin, often resulting in architectural distortion.

Lymphangitic carcinomatosis: Pulmonary lymphangitic carcinomatosis refers to the lymphangitic or hematogenous spread of tumor to the lungs resulting in the infiltration and thickening of the interlobular septa, subpleural interstitium and bronchovascular bundles and preservation of the normal lung architecture[78] (Fig. 25.40). The thickening of this structure may be

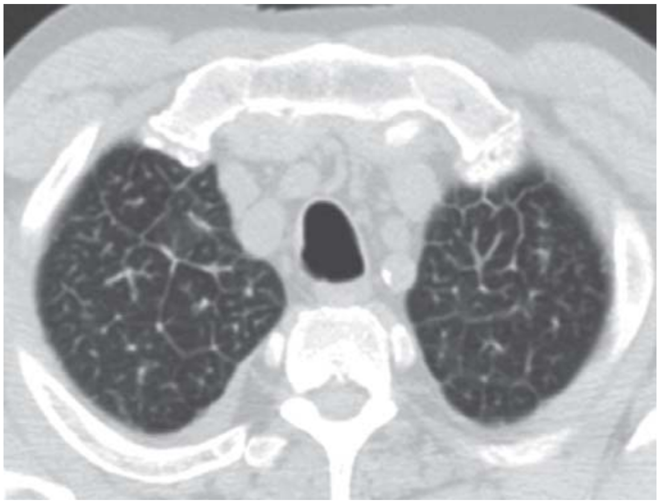


Fig. 25.40: HRCT through upper lobes demonstrating intralobar septal thickening in a patient with lymphangitis carcinomatosis

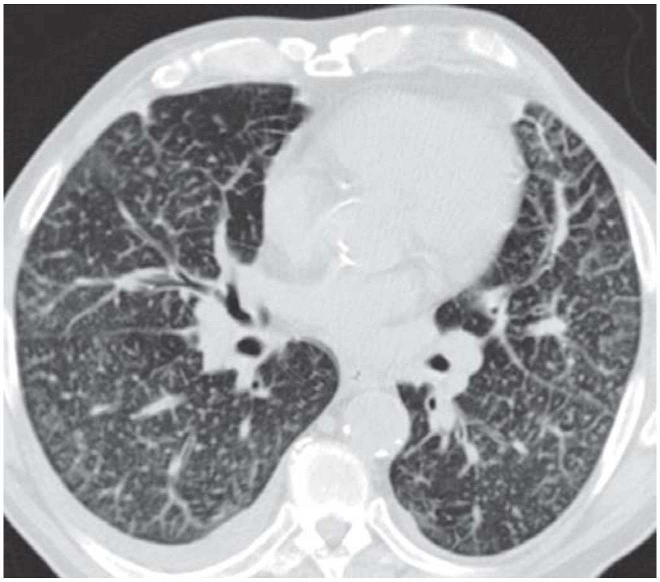


Fig. 25.41: HRCT at the level of the lower lobe bronchi showing a fine reticular pattern from interlobular septal thickening and multiple tiny nodules in a patient with lymphangitic carcinomatosis. Note the extension of the irregular interlobular septal thickening to the pleural surface

smooth or have a nodular appearance and may be diffuse and bilateral or focal and unilateral in distribution (Fig. 25.41). The most common primary malignancies resulting in lymphangitic carcinomatosis are adenocarcinoma of the breast, lung, gastrointestinal tract and prostate.

Centrilobular distribution (ground-glass nodules): This section includes the following diseases:

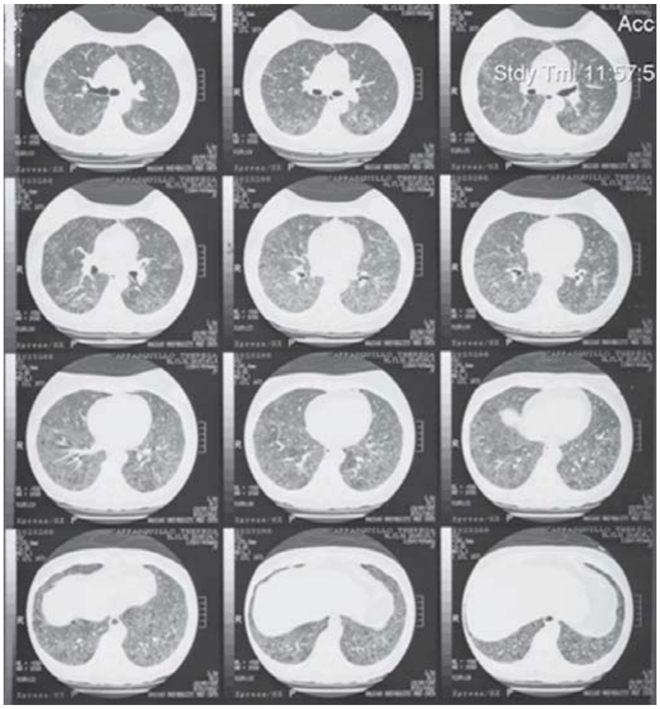


Fig. 25.42: CT chest representing hypersensitivity pneumonitis. Numerous centrilobular nodule which are poorly defined and shown to extend to the periphery are illustrated

Hypersensitivity pneumonitis: Hypersensitivity pneumonitis, also known as extrinsic alveolitis represents a type 3 allergic reaction or immune complex disease. HRCT is most useful in diagnosing subacute hypersensitivity pneumonitis, where it displays diffuse or patchy ground-glass opacification with lobular sparing, lobular air-trapping and centrilobular poorly defined airspace nodules.[79] The ground-glass attenuation is noted predominantly in the middle and lower lung zones and may be present in combination with mosaic attenuation (Fig. 25.42). In chronic hypersensitivity pneumonitis, fibrosis, represented by a reticular pattern, architectural distortion and ultimately honeycombing is seen with relative basilar sparing.[80]

Lymphocytic interstitial pneumonitis: Lymphocytic interstitial pneumonitis can be seen in patients with Sjögren's syndrome and is seen commonly in children with acquired immune deficiency syndrome. Dense infiltration of monoclonal or polyclonal T lymphocytes occurs in the interstitium. It can lead to lymphoma of the lung parenchyma. The characteristic features on HRCT include ground-glass opacities, reticular opacities and perivascular cysts[81] (Figs 25.43 and 25.44).

Centrilobular distribution (tree-in-bud): This section includes the following diseases:

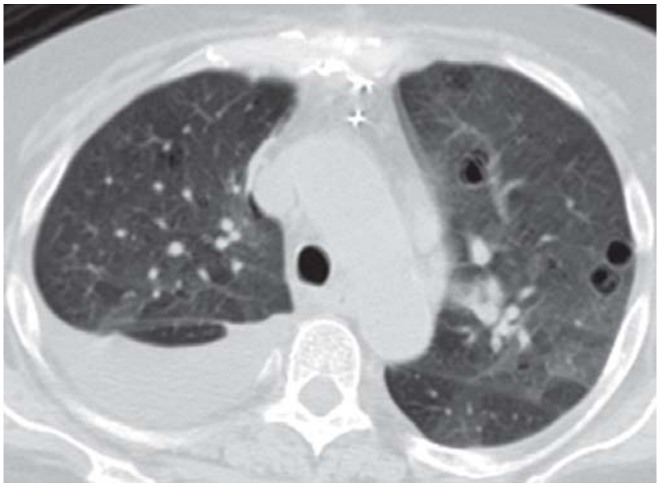


Fig. 25.43: CT chest through the upper lobes demonstrating cystic changes in a patient with LIP. Also noted is a pleural effusion on the right

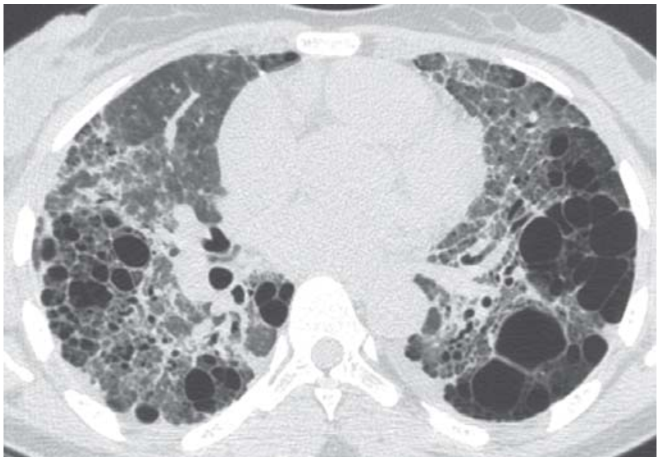


Fig. 25.44: CT Chest through the lower lungs demonstrating cystic changes in a patient with lymphocytic interstitial pneumonitis

Panbronchiolitis: Panbronchiolitis is a form of diffuse bronchiolitis found in Asia, especially Japan and Korea.[82] The characteristic CT features of diffuse tree-in bud pattern are seen mainly affecting the lower lung zones, with complete resolution after macrolide therapy. Typically seen are centrilobular nodular and linear opacities corresponding to thickened and dilated bronchiolar walls with intraluminal mucous plugs, mosaic attenuation, as a result of peripheral air trapping and bronchiectasis, especially in advanced disease.[83]

Infectious etiology: The tree-in-bud pattern is frequently seen in several airway infections from viral etiologies; bacterial infections, such as MTB or MAI; and fungal etiologies such as Allergic Bronchopulmonary Mycosis (ABPM).[41]

Random distribution: This section includes the following disease:

Hematogenous metastasis: Hematogenous tumor metastasis most commonly results in localized tumor nodules, rather than lymphatic infiltration. Multiple, large, well-defined nodules involving the lower lung zones are seen in a randomly distributed fashion.[84]

Pulmonary Opacities

Ground-glass opacities: This section includes the following diseases:

Desquamative interstitial pneumonitis/respiratory bronchiolitis interstitial lung disease: These diseases are exclusively found in smokers. The major HRCT finding in patients with respiratory bronchiolitis is the presence of ill-defined, centrilobular ground-glass nodules, primarily in the upper lobes. DIP may be distinguished from RBILD by the presence of ground glass attenuation, which is predominantly found in the middle and lower lung zones[85] (Fig. 25.45). Mild fibrosis is indicated by irregular linear opacities, architectural distortion and honeycombing may be seen in the subpleural and lower lung regions. DIP and RBILD are likely to be related or even part of the same pathologic process, differing only in the severity, location and extent of the abnormality.

Acute interstitial pneumonitis: Acute interstitial pneumonitis is also known as Hamman-Rich syndrome and is characterized by an acute onset and rapid progression. HRCT findings are of diffuse ground-glass attenuation and

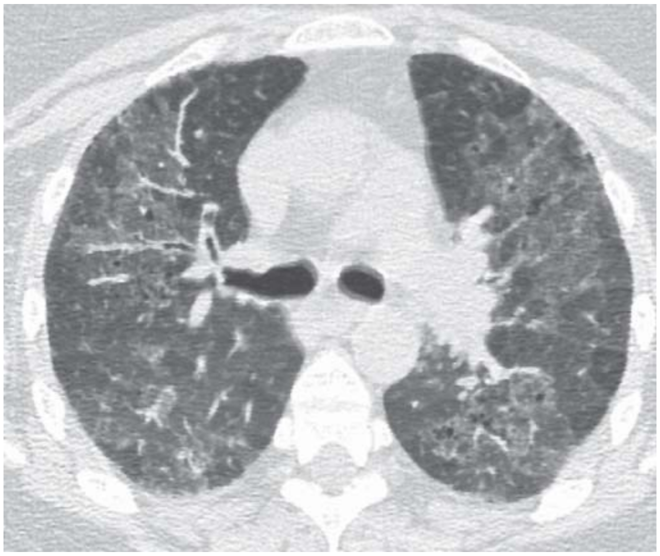


Fig. 25.45: CT chest through the upper lobes in a patient with desquamative interstitial pneumonitis showing a diffuse ground-glass attenuation

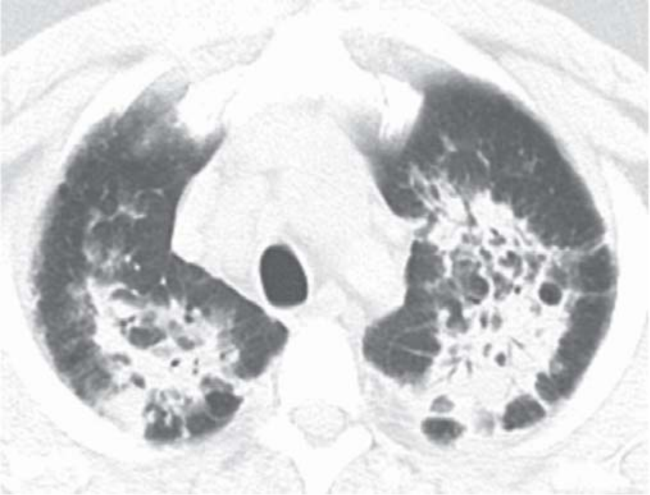


Fig. 25.46: CT chest showing bilateral dense consolidation in the upper lobes in cryptogenic organizing pneumonia

consolidation with abnormalities suggestive of fibrosis such as traction bronchiectasis.[86]

Pulmonary alveolar proteinosis: Pulmonary Alveolar Proteinosis (PAP) results from the ineffective clearance of surfactant from alveoli. The predominant HRCT features of PAP consist of the bilateral areas of ground-glass opacification with smoothly thickened interlobular septal lines.[87] This pattern is also called “crazy paving.” There may be lobular or geographic sparing. Other features seen on HRCT include poorly defined nodular opacities and consolidation.[88]

Consolidation

BOOP/COP: HRCT typically shows the peribronchial and peripheral areas of consolidation[89] (Figs 25.46 and 25.47). Another suggestive finding is the presence of rings or crescents of consolidation surrounding ground-glass opacities, which has been called a reverse halo sign.[90]

Bronchoalveolar Carcinoma (BAC): Bronchoalveolar carcinoma may present with three distinct patterns,[91] as well as as a small solitary nodule, which has a characteristic ground-glass appearance on CT, suggestive of a good prognosis. It may also present as lobar consolidation resembling bacterial pneumonia, where the CT features typically show air bronchograms. BAC may also be represented as multifocal pulmonary nodules.

Cystic Diseases

There are many pulmonary conditions that may result in cystic changes on CT. Flow chart 25.4 illustrates the classification of multiple hypolucent lesions according to the distributive pattern.

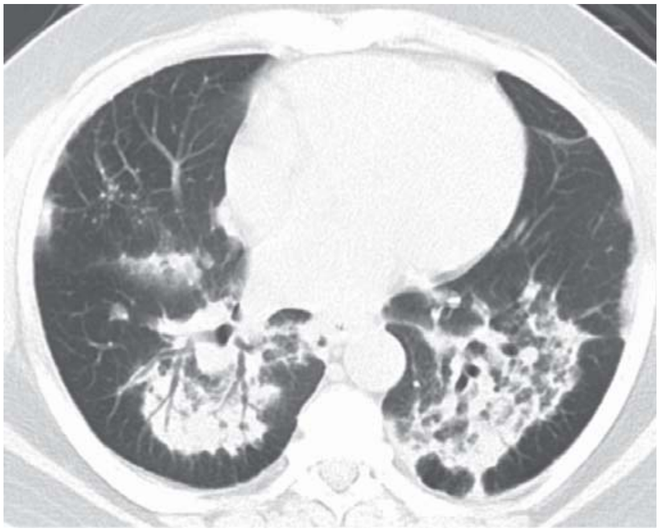


Fig. 25.47: CT chest through the lung bases showing dense bilateral consolidation with air bronchograms in a patient with cryptogenic organizing pneumonia

Lymphangioleiomyomatosis (LAM): LAM affects the women of reproductive age and results from a smooth muscle proliferation within the pulmonary interstitium causing thickening of the walls of the lymphatics, blood vessels and bronchioles. Patients are present with spontaneous pneumothorax, chylothorax, hemoptysis and marked hyperexpansion of the lungs. HRCT demonstrates multiple thin walled cysts diffusely throughout the lung[92] (Fig. 25.48). The cysts are rounded

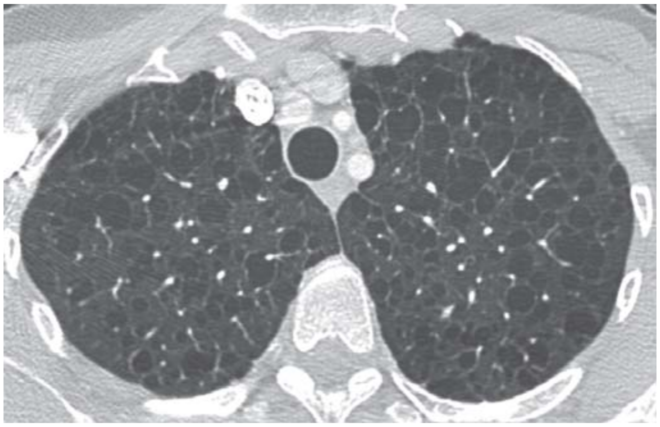
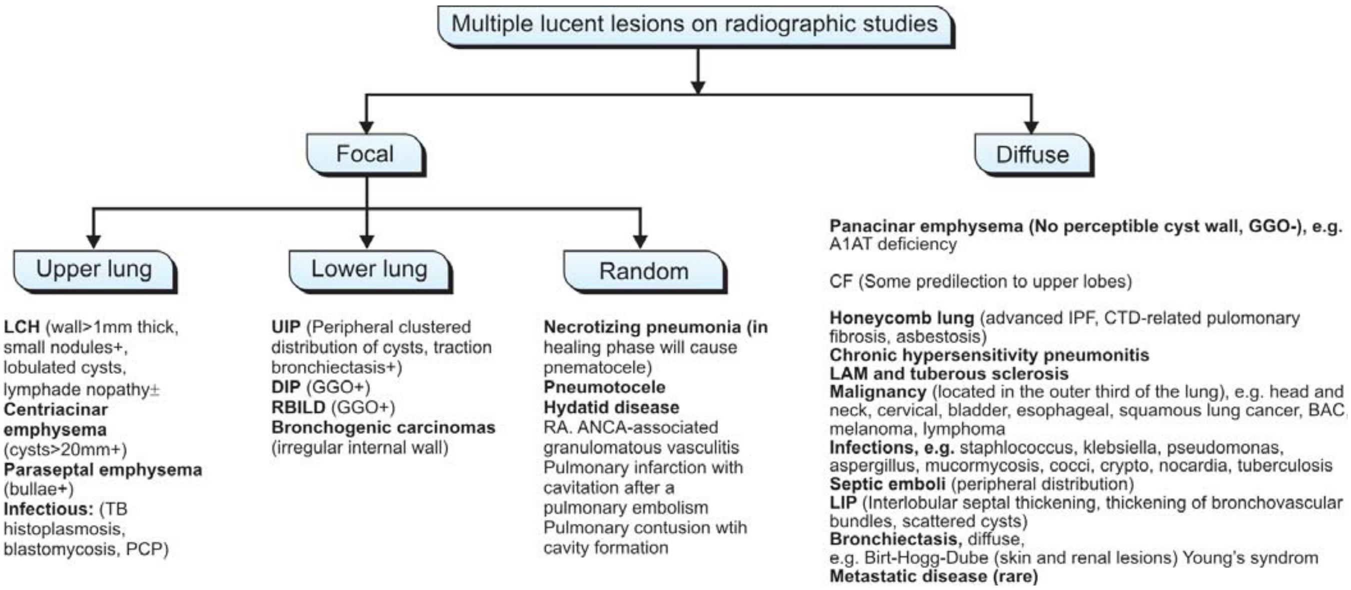


Fig. 25.48: CT chest through the upper lobes showing diffuse cystic changes in a patient with lymphangioleiomyomatosis. The cysts are evenly distributed and have thin, definable walls. Note the absence of nodules

Flow chart 25.4: Multiple lucent lesions are classified according to their distribution pattern as either focal or diffuse. The focal lucencies can further be distinguished into upper lobe, lower lobe or random distribution. Examples of diffuse lucent lesions include panacinar emphysema, LAM, LIP or congenital disease related diffuse bronchiectasis. Examples of focal upper lung lucent lesions include centrilobular or paraseptal emphysema, LCH with presence of small nodules and infectious etiologies. Focal lower lung lucencies are usually seen in interstitial lung diseases, such as UIP, DIP and RBILD as cystic changes with ground glass opacities also seen in DIP and RBILD. Randomly distributed focal lucencies may be seen in a braod group of conditions, such as rheumatoid arthritis, necrotizing pneumonia and cavitating infarctions after a pulmonary embolism


Multiple lucent lesions on radiographic studies
Focal
Diffuse
Upper lung
Lower lung
Random
LCH (wall>1mm thick, small nodules+, lobulated cysts, lymphade nopathy±
Centriacinar emphysema (cysts>20mm+)
Paraseptal emphysema (bullae+)
Infectious: (TB histoplasmosis, blastomycosis, PCP)
UIP (Peripheral clustered distribution of cysts, traction bronchiectasis+)
DIP (GGO+)
RBILD (GGO+)
Bronchogenic carcinomas (irregular internal wall)
Necrotizing pneumonia (in healing phase will cause pnematocele)
Pneumotocele
Hydatid disease
RA. ANCA-associated granulomatous vasculitis
Pulmonary infarction with cavitation after a pulmonary embolism
Pulmonary contusion wtih cavity formation
Panacinar emphysema (No perceptible cyst wall, GGO-), e.g. A1AT deficiency
CF (Some predilection to upper lobes)
Honeycomb lung (advanced IPF, CTD-related pulomonary fibrosis, asbestosis)
Chronic hypersensitivity pneumonitis
LAM and tuberous sclerosis
Malignancy (located in the outer third of the lung), e.g. head and neck, cervical, bladder, esophageal, squamous lung cancer, BAC, melanoma, lymphoma
Infections, e.g. staphlococcus, klebsiella, pseudomonas, aspergillus, mucormycosis, cocci, crypto, nocardia, tuberculosis
Septic emboli (peripheral distribution)
LIP (Interlobular septal thickening, thickening of bronchovascular bundles, scattered cysts)
Bronchiectasis, diffuse,
e.g. Birt-Hogg-Dube (skin and renal lesions) Young's syndrom
Metastatic disease (rare)

LCH: Langerhans cell histiocytosis; TB: tuberculosis; PCP: *Pneumocystic jiroveci*; UIP: usual interstitial pneumonitis, DIP: desquamative interstitial pneumonitis; RBILD: respiratory bronchiolitis-inetrstitial lung disease; RA: rheumatoid arthritis; A1AT: alpha-1-antitrypsin; CF: cystic fibrosis; IFP: idiopathic pulmonary fibrosis; CTD: connective tissue disease; LAM: lymphangioleiomyomatosis; BAC: bronchoalveolar carcinoma; LIP: lymphocytic interstitial pneumonitis

and may vary in size, but bizarre-shaped cysts as those seen in Langerhans cell histiocytosis, are unlikely (Fig. 25.49).

Langerhans cell histiocytosis: Langerhans cell histiocytosis (LCH) also known as eosinophilic granuloma or histiocytosis X is recognized on CT by the presence of cysts showing an upper lobe predominance, especially in the early stages. The initial changes include small nodular opacities with sharply defined or stellate centrilobular nodules seen on HRCT. Multiple thin-walled cysts of varying sizes are usually present in scattered form throughout the upper and middle lung zones with the relative sparing of the bases. The cysts have bizarre, irregular shapes, which can appear in combination with nodules in the intermediate stages of the disease[93] (Fig. 25.50).

Pneumocystis pneumonia: Pneumocystis Jiroveci Pneumonia (PJP, previously called pneumocystis carinii pneumonia)

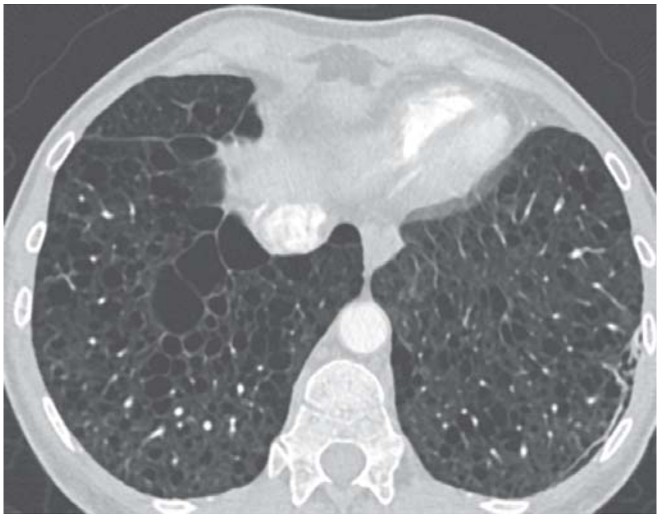


Fig. 25.49: CT chest in a patient with lymphangioleiomyomatosis showing well defined, multiple cysts with uniform distribution at the lung bases

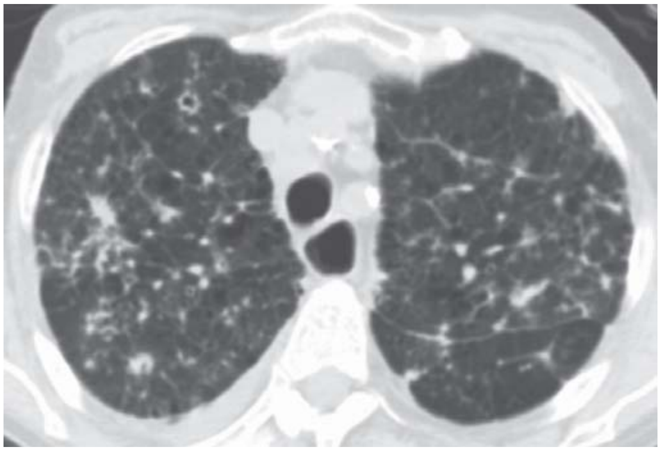


Fig. 25.50: HRCT through the upper lobes in a patient with langerhans cell histiocytosis. There are nodules present with irregular cysts with thin and thick walls

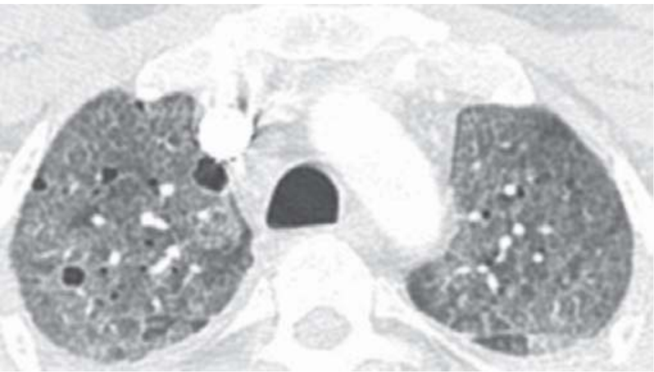


Fig. 25.51: A classic CT chest representation of diffuse ground glass attenuation in a patient with *pneumocystic carinii* pneumonia

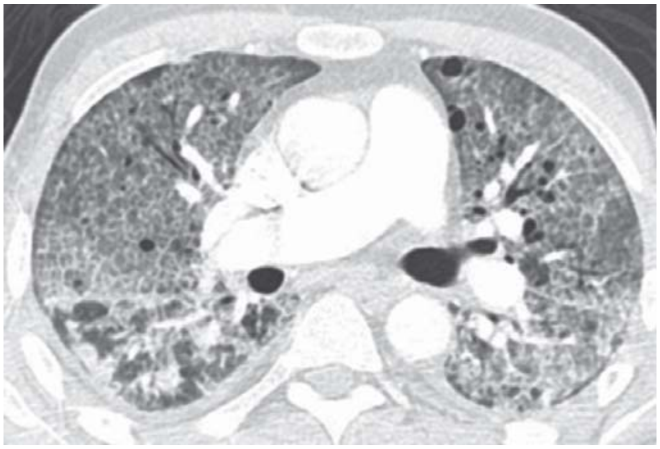


Fig. 25.52: CT chest showing a diffuse ground glass pattern with a crazy paving appearance in a patient with *pneumocystic carinii* pneumonia

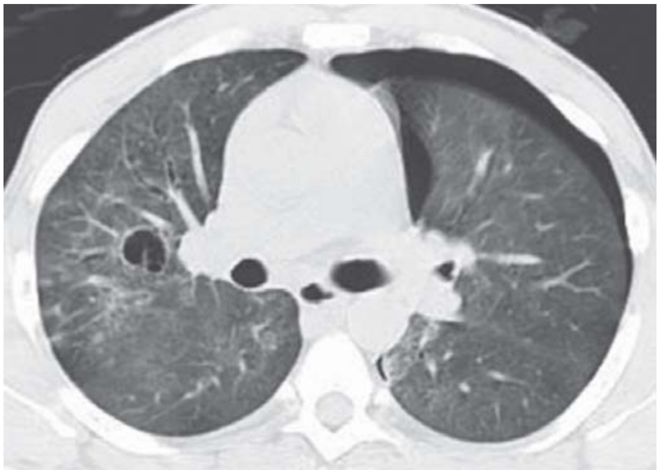


Fig. 25.53: CT Chest in a patient with *pneumocystic carinii* pneumonia with evidence of pneumothorax and bilateral diffuse haziness

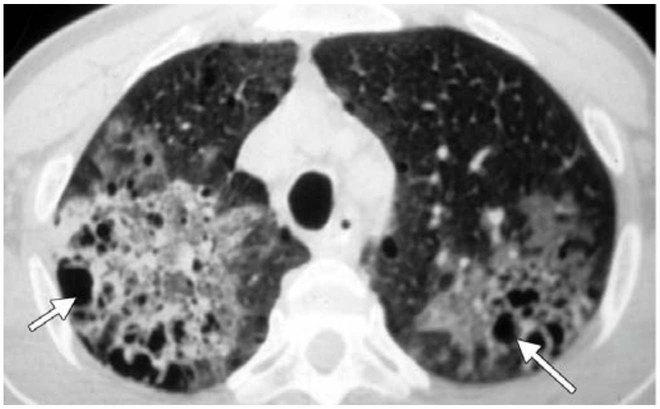


Fig. 25.54: HRCT through the upper lung zones showing a dense opacity in the right upper lobe, ground glass opacities in the left upper lobe, small and large (arrows) cysts in a patient with *Pneumocystic jiroveci* pneumonia

is one of the most common pulmonary infections in patients with AIDS. The HRCT findings of PJP have been well studied. These findings consist of bilateral ground-glass attenuation, which appear consolidated with severe disease and a distinct mosaic pattern with the areas of normal lung interspersed between the areas of ground-glass opacities[94] (Figs 25.51 and 25.52). Other associated findings include pneumothoraces or cystic lung changes (Figs 25.53 and 25.54).

MEDIASTINAL DISEASES

The mediastinum is bounded laterally by the lungs, anteriorly by the sternum, and posteriorly by the vertebral bodies. Several focal and diffuse conditions may occur within the mediastinum. The mediastinum can be divided into compartments based on CT landmarks to facilitate the differential diagnosis of various findings. These include the anterior mediastinum, which includes the retrosternal clear space and the cardiophrenic angle; the middle mediastinum, which includes the retrosternal clear space, subcarinal region and retrocardiac clear space; and the posterior mediastinum. It should be pointed out that there are no physical boundaries between compartments that may limit any mediastinal disease.

The Retrosternal Clear Space

This region is bordered anteriorly by the sternum and posteriorly by the aorta and the great vessels. The normal structures located in this region include the thymus gland, lymph nodes and fat. Abnormalities involving the retrosternal clear space include thymoma, thymic cyst, lymphoma, teratoma, aortic aneurysm or lipoma. Thymomas represent a majority of anterior mediastinal lesions in adults. The CT appearance of a thymoma shows a homogenous soft-tissue rounded or lobulated mass, which is sharply demarcated and does not conform to the normal shape of the thymus.[95] Thymic cysts appear thin walled, with air fluid levels on CT (Fig. 25.55). Teratomas are seen with a combination of fluid-filled cysts, fat, soft tissue and calcification.[96]

The Cardiophrenic Angle

The cardiophrenic angle is the space anterior and to the right of the heart, usually involves benign lesions such as fat, lipoma, pericardial cyst or Morgagni hernia.

The Retrotracheal Clear Space

The retrotracheal space includes structures posterior to the trachea, anterior to the thoracic spine and superior to the aortic arch. The normal structures in this area include the esophagus and lymph nodes. Abnormalities affecting the esophagus, such as tumor, achalasia, Zenker's diverticulum are seen in this region. Vascular structures, such as an aberrant right subclavian or thyroid masses, such as goiters, may also be seen in this area.[97]

The Subcarinal Region

This region is situated below the carina and above the left atrium. Normal structures include fat, lymph nodes and the esophagus. The differential diagnosis of lesions in this location consists of lymphadenopathy, bronchogenic cysts, esophageal diverticulum or tumors (Fig. 25.56).

The Retrocardiac Clear Space

This retrocardiac space exists behind the heart and in front of the thoracic spine. The structures located in this

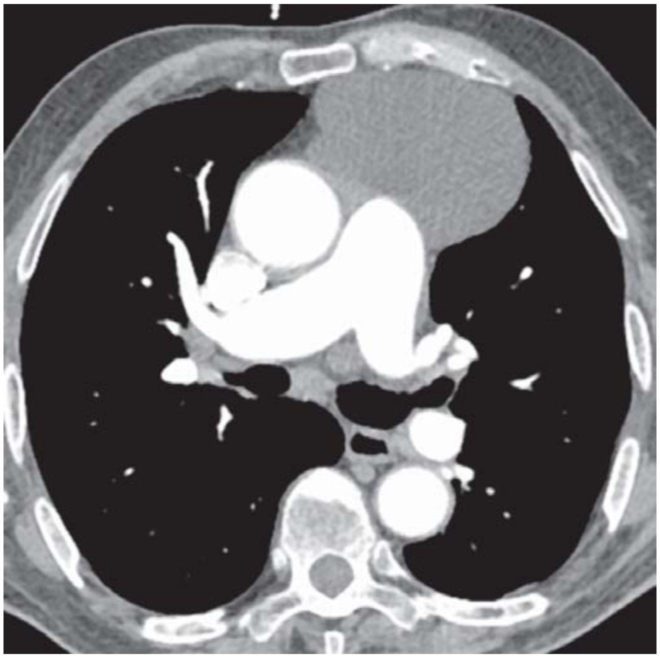


Fig. 25.55: CT chest (mediastinal window) illustrating a large mediastinal mass in the retrosternal clear space. Note the homogenous appearance. This is representative of a thymic cyst

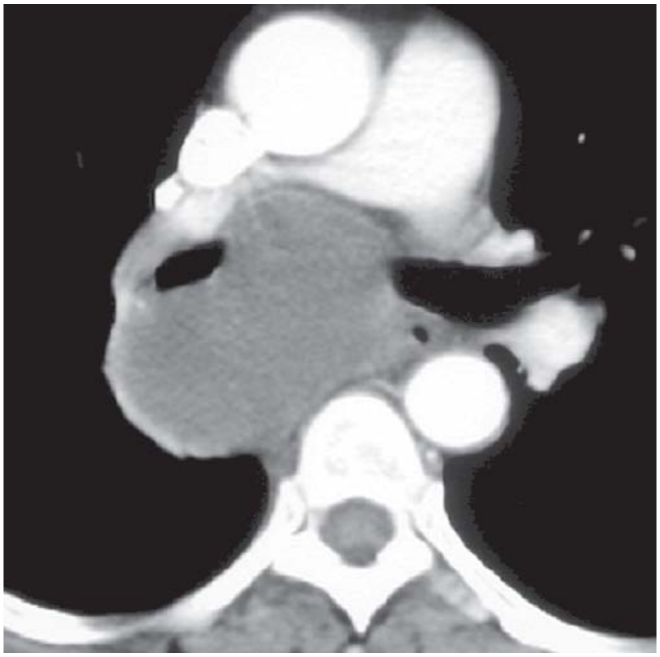


Fig. 25.56: CT chest (mediastinal window) demonstrating a large bronchogenic duplication cyst in the subcarinal region

space are the esophagus, aorta, azygous vein, fat and lymph nodes. Esophageal lesions, such as duplication cyst, varices, hiatal hernia and tumor, aortic aneurysm and lymphadenopathy may arise in this location.

The Posterior Mediastinum

The posterior mediastinum covers the region posterior to the anterior border of the vertebral bodies, where the vertebral column, fat and nerves are situated. The most common lesions in the posterior column are neurogenic and best imaged with MRI.

MISCELLANEOUS

Allergic Bronchopulmonary Mycosis

CT findings of ABPM include central airway abnormalities where there is bronchial dilatation with mucus-filled centrilobular bronchioles resulting in a tree-in-bud pattern[98] (Fig 25.57). Parenchymal abnormalities, such as consolidation, cavitation, bullae or scarring, as well as pleural abnormalities, including focal pleural thickening may also be evident.[99] Central bronchiectasis and mucoid impaction are specific findings in ABPM (Fig. 25.58).

Chronic Eosinophilic Pneumonia

The classic HRCT picture of chronic eosinophilic pneumonia is consolidation in a peripheral distribution confined primarily to the outer third of the lung and with an upper lobe distribution (Figs 25.59 and 25.60).

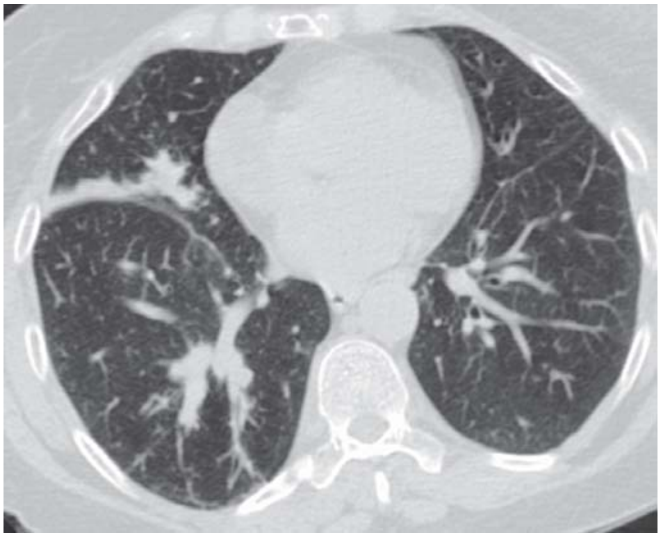


Fig. 25.57: CT chest showing insipation of bronchi in a patient with allergic bronchopulmonary aspergillosis

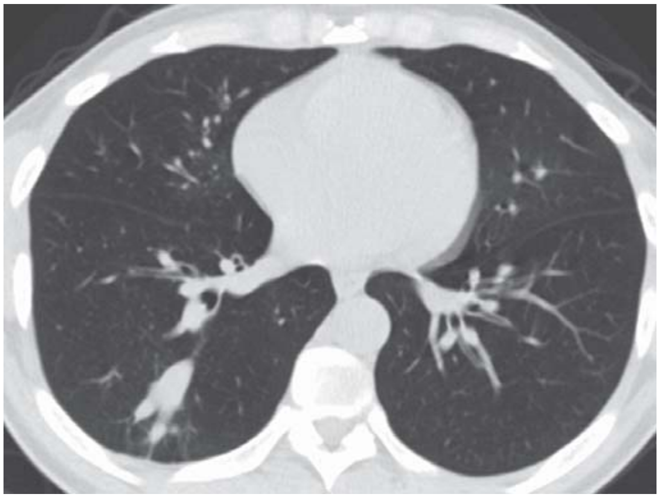


Fig. 25.58: CT chest in a patient with allergic bronchopulmonary aspergillosis showing insipation of the lower lobe bronchi

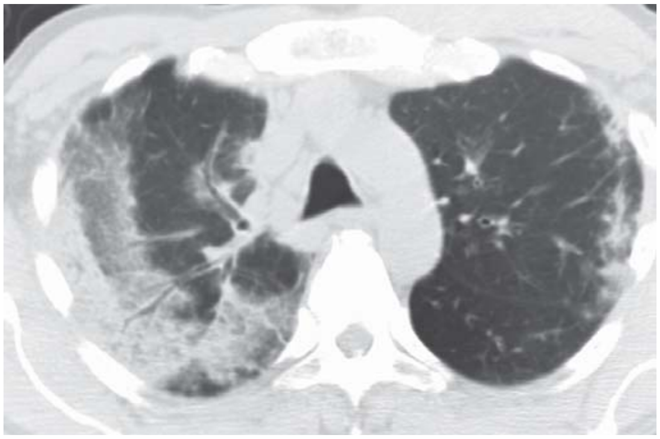


Fig. 25.59: CT chest with peripherally distributed opacities in a patient with chronic eosinophilic pneumonitis

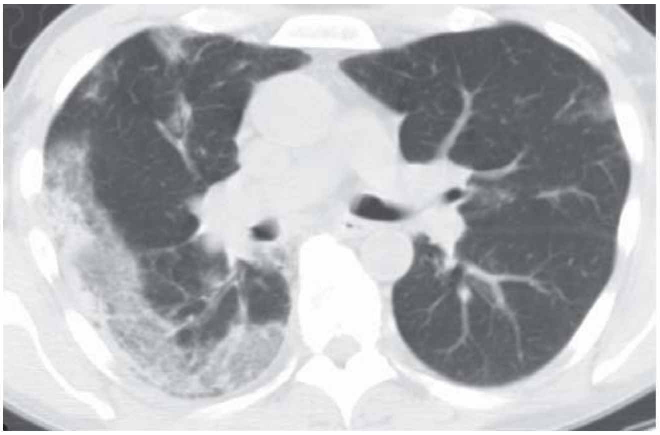


Fig. 25.60: CT chest in a patient with chronic eosinophillic pneumonitis with peripherally distributed opacities

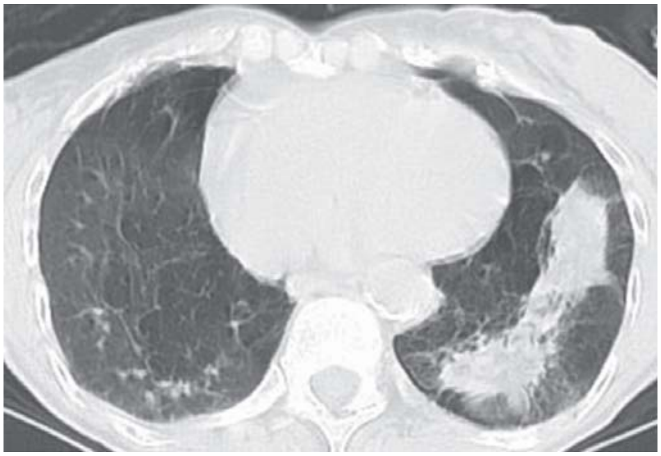


Fig. 25.61: CT chest representation of lipoid pneumonia

Lipoid Pneumonia

CT findings of lipoid pneumonia have been studied in a small number of cases. In the appropriate clinical context, CT may demonstrate solitary nodule resembling carcinoma, the localized area of consolidation or extensive bilateral opacities.[100] HRCT findings of lipoid pneumonia show parenchymal nodules or opacities containing fat (Fig. 25.61)

Drug-Induced Lung Disease

There are several manifestations of drug-induced lung disease. The most common include noncardiogenic pulmonary edema, hypersensitivity pneumonitis and chronic pneumonitis.[101] Noncardiogenic pulmonary edema had been described to occur after the administration of cytosine arabinoside, methotrexate and cyclophosphamide, resulting in a widespread airspace consolidation with predominance in the dependent lung regions. Hypersensitivity pneumonitis has been seen after methotrexate, cyclophosphamide and bleomycin administration. The HRCT findings of bilateral ground-glass attenuation in either patchy or diffuse distribution are seen. Chronic pneumonitis is the most common drug-induced lung disease reported with all cytotoxic drugs and causes reticular changes in the lower lungs as seen with IPF (Figs 25.62 and 25.63).

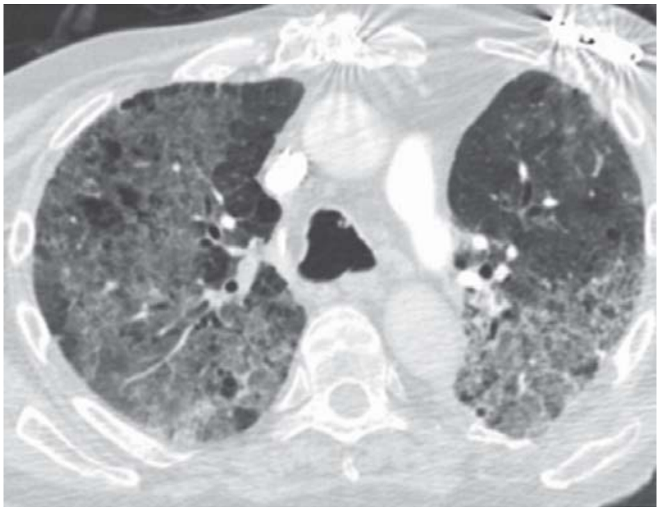


Fig. 25.62: CT chest showing diffuse fibrosis with ground glass attenuation in a patient with drug-induced lung disease

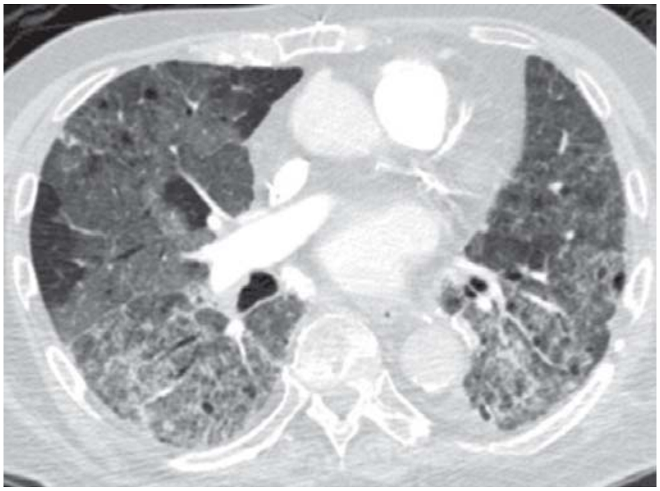


Fig. 25.63: CT chest showing diffuse fibrosis, increased density in drug-induced lung disease

CONCLUSION

The indications and role of CT imaging in the diagnoses of various thoracic diseases has been immensely influenced by a variety of technologic advancements. CT has become a fundamental part of the clinical decision making in a number of conditions involving the lung parenchyma, airways, vasculature and the mediastinum. Several characteristic features, such as ground-glass opacification, honeycomb changes, nodular features help narrow the differential diagnosis in many situations. These features depict the extent of disease processes and guide the course of management, eliminating the need for invasive diagnostic testing. It is therefore of paramount importance to understand and recognize the different CT features in thoracic conditions.

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26A

Pulmonary Function Testing

Ashutosh N Aggarwal

INTRODUCTION

Pulmonary function tests are designed to assess how well the lungs are able to perform their intended role. There is as yet no single test that can provide sufficiently detailed information on all the aspects of lung function. Instead, depending on the clinical scenario, one must do one or more procedures to answer a particular question. Further, the available options vary greatly in the terms of the ease of conducting the test, equipment and technician requirements, test performance characteristics, and procedure cost. As a result, not all investigations may be feasible, or even necessary, in a given setting. Of all pulmonary function tests available, spirometry is by far the most commonly used procedure, in the view of its relative simplicity, easy equipment availability, and the good standardization of test performance and interpretation algorithms. This chapter provides an overview of the physiologic principles, conduct, and interpretation of commonly used pulmonary function tests. The abbreviations and terminology used herein are outlined in Table 26A.1.

SPIROMETRY

Spirometry is the commonest and most widely used lung function test, although its true potential still needs to be realized. In many ways, its utility can be compared to blood pressure measurement or electrocardiography, in routine cardiac evaluation. However, one needs to pay careful attention to following standard procedures, while performing and interpreting the test. Because the residual volume in lungs cannot be exhaled, spiromteric measurements are limited to the vital capacity and its subdivisions (Fig. 26A.1).

Indications and Contraindications

There are multiple scenarios in which information obtained from spirometry may prove useful. The most common indication for doing the test is a functional evaluation of patients with lung disease. The presence of spirometric abnormalities, as well as the degree of impairment, provides useful information about the disease severity and pulmonary reserve of the patient. Often, the test is conducted to narrow the differential diagnosis of a patient being assessed for pulmonary disorder. For instance, the documentation of airflow limitation in a smoker being evaluated for breathlessness would increase the probability of the patient having Chronic Obstructive Pulmonary Disease (COPD). Because the test can be easily repeated, and the results are quite reproducible for a given patient, serial measurements can provide information about disease progression, as well as response to prescribed treatment.

The test also has an important role in clinical trials, as it is the best standardized objective surrogate for true pulmonary function. Spirometry is also used as a screening tool for studies in epidemiologic surveys, as it may provide an objective definition of disease state (such as bronchial asthma). It can also be used to screen at-risk populations for subclinical disease (for example pre-operative assessment or detecting COPD among asymptomatic smokers). The test is also utilized in occupational setting, both for detecting work-related respiratory disorders and for disability assessment in

TABLE 26A.1: Glossary of abbreviations and terms describing lung volumes and air flow

ERV	Expiratory reserve volume	Difference between the volume of air in lungs at end expiration during quiet breathing (functional residual capacity) and after forced exhalation (residual volume)
$FEF_{25\%-75\%}$	Forced midexpiratory flow	The average air flow in the middle half of a forced expiratory maneuver
FEV_1	Forced expiratory volume in first second	Volume of air exhaled during the first second of a forced vital capacity maneuver
$FEV_1\%$	FEV_1/VC	Ratio of forced expiratory volume in first second to the vital capacity (either forced or slow)
FEV_t	Forced expiratory volume in first 't' seconds	Volume of air exhaled during the first 't' seconds of a forced vital capacity maneuver (e.g. FEV_6 is the volume in first six seconds)
FRC	Functional residual capacity	Volume of air remaining in lungs at end expiration during quiet breathing
FVC	Forced vital capacity	Volume of air exhaled from a position of full inspiration to full expiration during a forced expiratory maneuver
IRV	Inspiratory reserve volume	Difference between the volume of air in lungs at end inspiration during quiet breathing and after maximal inspiration (TLC)
MVV	Maximal voluntary ventilation	Maximal volume of air that can be breathed in (or out) in one minute
PEF	Peak expiratory flow	The maximal air flow generated during a forced expiratory maneuver
RV	Residual volume	Volume of air remaining in lungs even after complete forced expiration
SVC	Slow vital capacity	Volume of air exhaled from a position of full inspiration to full expiration during a slow (or relaxed) expiratory maneuver
TLC	Total lung capacity	Volume of air within lungs at the end of full inspiration
VC	Vital capacity	Volume of air exhaled from a position of full inspiration to full expiration
V_E	Minute ventilation	Volume of air exhaled in one minute
V_t	Tidal volume	Volume of air breathed in (or out) in each respiratory cycle during quiet respiration

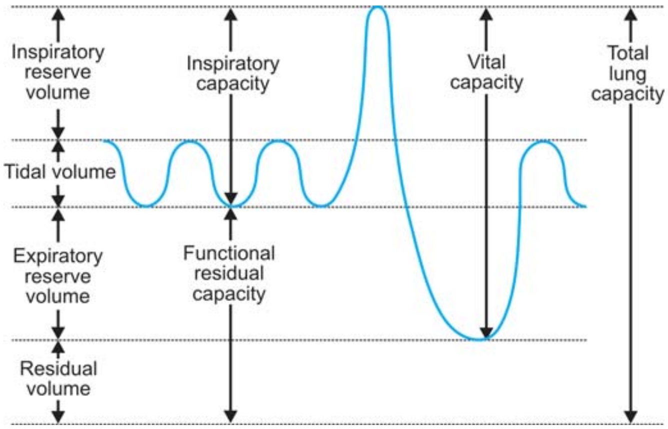

Fig. 26A.1: Various lung volumes and capacities in relation to the spirometry tracing. Note that residual volume cannot be determined through conventional spirometry

symptomatic people (for example as part of compensation procedures). Finally, spirometry is an important research tool for understanding pathophysiology and temporal course of several diseases, as well as for the derivation and validation of reference equations.

It is also important to understand when not to perform spirometry. Any benefit from the information obtained through this test should be carefully weighed against patient discomfort and risk. The test is better avoided in pregnant and severely dyspneic patients. It should also not be carried out in patients where pressure swings due to a forced expiratory maneuver can worsen existing conditions (such as ruptured tympanic membrane, bronchopleural fistula, ongoing hemoptysis, etc.). Uncooperative patients and those on life support systems, should also not undergo the test.

Equipment

A wide range of apparatus, ranging from handheld portable devices to large equipment, and from predominantly manual to completely automated systems, is available to perform spirometry. Although many factors, such as cost, patient load, clinical requirements, etc., determine the choice of machine, it is important to use one that confirms to some minimum technical specifications necessary to obtain valid results. Such recommendations for equipment performance were laid out by the American Thoracic Society, and have recently been updated as a joint recommendation from the American Thoracic Society and the European Respiratory Society.[1,2] The important performance criteria relate to accuracy (degree of conformity to the true value), precision (degree of repeatability of the same measurement) and resolution (minimum measurable incremental quantity). It is also advisable to have a system that can be calibrated periodically to ensure optimum performance.

Most commercially available spirometers nowadays are computerized systems that employ a transducer to convert a mechanical signal to an electrical one, and display the output in a fashion understood by the operator. These equipment can be divided into two broad categories: Volume displacement spirometers and flow-sensing spirometers. The former work with volume as the primary output, and flow is a derived parameter. Such machines can have a water seal, a dry-rolling seal or a bellows type design. Flow sensing devices can either be electronic turbines, or use electronic pneumotachometers (sensors that estimate airflow from the change in pressure occurring across a suitable resistance), which in turn can have a flow-resistive, a heated wire, or an ultrasonic design. As opposed to volume displacement spirometers, these machines measure flow as the primary signal, which is time-integrated to yield volume estimates.

Technique

The basic steps in patient preparation are outlined in Table 26A.2. Briefly, the patient is instructed to breathe gently through the mouthpiece from and into the spirometer. This accustoms him to breathing through the machine, and also generates a recording for tidal volume. Thereafter, a maximal inspiratory maneuver starting at tidal end expiration, followed by a forced expiratory maneuver, defines the forced vital capacity. It is extremely important that the technician supervising the test constantly encourages the patient throughout this procedure, to generate the best possible effort. Failing

TABLE 26A.2: A typical spirometry session

Pre-procedure preparation

- Ensure equipment integrity (electrical power, tubings, filters, etc.)
- Calibrate spirometer
- Verify indications/contraindications to the test
- Obtain informed consent for procedure
- Check personal and clinical details (age, gender, smoking habits, medications, diagnosis, previous tests, results of other investigations, etc.)
- Measure weight and standing height
- Explain (and preferably demonstrate) test procedure to the subject

Forced expiratory maneuvers

- Apply nose clip
- Place appropriately sized mouthpiece in the mouth, and ask subject to tightly close lips around it
- Ask subject to breathe gently from and into the mouthpiece for a few breaths
- At end-tidal expiration, ask subject to inhale as completely as possible
- Ask subject to exhale as rapidly, as completely, as forcefully, and for as long as possible, till no more air can be expelled out from the lungs; provide constant encouragement throughout
- Repeat for a minimum of three maneuvers

Optimize test quality

- Verify that each maneuver is technically acceptable
  - Satisfactory start of test (no hesitation)
  - Good duration (expiratory time preferably more than six seconds)
  - Free from artifacts (such as cough, submaximal effort, early glottic closure, premature termination of expiration, etc.)
- Check repeatability from among at least three acceptable maneuvers
  - Two largest FVC values within 150 mL of each other
  - Two largest FEV_1 values within 150 mL of each other
- Perform additional maneuvers if necessary, till repeatability criteria are satisfied

Check for bronchodilator reversibility (optional, but recommended)

- Ask patient to inhale 400 μg of salbutamol, preferably through a spacer attached to inhaler
- Wait for 15-30 minutes
- Repeat forced expiratory maneuvers as above, and verify test quality

Interpretation and reporting

- Compare observed values to predicted norms
- Look at shape, size and pattern of flow-volume loop
- Review available clinical information
- Categorize spirometry data into normal, obstructive or restrictive patterns
- Assess the severity of pulmonary function impairment (if any)
- Generate report, with comments on test quality and interpretation

this, not only will the test remain of poor quality, but the end-result may also be a falsely abnormal spirometry report. Several centers routinely perform postbronchodilator assessment as well. Although time-consuming, the additional information from this procedure is quite helpful, especially in the characterization of airflow limitation.

Quality assessment involves confirming the acceptability and reproducibility of multiple tests in same session. Detailed guidelines are available in this regard, and are summarized in Table 26A.2.[2] Acceptability should be tested for each individual maneuver in any spirometry session, whereas reproducibility assesses how well the results of individual "acceptable" maneuvers in any spirometry session match with each other. Each spirometry session should have at least three acceptable maneuvers from which reproducibility can be assessed. If three maneuvers do not meet reproducibility criteria then testing can be continued till these criteria are met. Normally, no more than eight maneuvers are recommended, as patients get fatigued beyond that.[3] If reproducibility criteria are not met even after eight attempts, testing should be concluded and interpretation performed from three best tests, making a note of this fact in the final report.

The start of expiration is usually defined by the back-extrapolation of the steepest portion of the volume-time curve to zero volume. The end of expiration is reached when the expired volume is less than 25 mL in one second or the subject cannot continue exhaling further. Normally, expiratory time should exceed six seconds. All measurements should be reported at Body Temperature and Pressure, Saturated (BTPS) conditions. This standardizes the readings to barometric pressure at sea level, body temperature, saturated with water vapor. Nomograms are available to derive correction factors based on the ambient atmospheric conditions.

Reference Values

The basic purpose of pulmonary function testing is to identify persons with abnormal lung function. To know what is abnormal, we must first define what is normal. Predicted normal values can be obtained from studies carried out in healthy subjects. They are usually in the form of a regression equation describing the predicted value as a function of gender and anthropometric data (e.g. height, weight, etc.), and differ greatly with ethnicity. For instance, the predicted value of FEV_1 among men is expressed as FEV_1 (L) = $-1.90 - 0.025A + 0.00006A^2 + 0.036H$ (*A age in years, H height in cm*) from the regression equation for north Indian adults being used at our laboratory.[4] Any value below the predicted normal is not necessarily reduced, since the normal value is a range rather than a fixed point. This introduces the concept of "lower limit of normal" or LLN, which can be defined in several ways. The simplest (and most widely used) method is to use a fixed percentage of predicted value. For example, a value less than 80% of predicted FEV_1 can be considered abnormal. However, there is very little statistical or physiological basis for such an approach.

A more valid approach is to use lower 95% confidence limits of the regression equation, or subtract 1.645 times the standard error of estimate of the regression equation from the predicted value, to define the LLN.[5] Any value below the corresponding LLN is considered abnormal. It is very important to use norms derived from individuals largely similar to the patients being generally tested at any pulmonary function laboratory. Therefore standard Caucasian norms, often incorporated into spirometer software, should be avoided, and locally appropriate reference equations applied wherever available. Reference equations for use in different geographic areas of India are available and should be preferably used.[4,6-13] Due to significant ethnic variability, these equations should not be interchanged with each other.[14] The common practice of using 85% or 90% predicted Caucasian values as the corresponding predicted value for north Indians is also statistically not valid.[15]

Interpretation and Patterns in Common Disorders

Interpreting lung function data is not just about looking at numbers generated by the spirometer. Both the volume-time curve and the flow-volume loop should also be evaluated with regard to their technical quality, size and shape, and various components, before making a final interpretation. Often such graphical analysis provides additional important information not obtainable from the numerical data. If available, the postbronchodilator graphs should also be similarly evaluated and compared to baseline curves. The clinical data provided in the requisition form is equally important in helping to reach any conclusion, especially in the borderline situations.

The most important action is to turn off computer-based interpretation, even if such software is offered with the machine. The initial step in interpretation is confirming that the test is of reasonably good quality (see above). Broadly, the interpretation of spirometric data involves only three numerical variables: FEV_1, VC and FEV_1/VC.[16] The largest observed values of FEV_1 and VC available from among at least three acceptable and reproducible tests should be used as the key parameters for interpretation, even if these individual observations are derived from different test maneuvers. If both forced and relaxed VC maneuvers have been performed, the larger value of VC amongst the FVC and SVC measurements should be used for the interpretation. The large number of other variables, often available from computerized spirometer outputs, usually provide no additional information, and are best excluded from a standard interpretative algorithm. It is well recognized that increasing the number of tests for interpretation is likely to increase the probability of falsely abnormal results.[17] These readings may however be used to arrive at a conclusion in borderline or difficult situations. Values clearly above or clearly below their respective LLNs can be interpreted confidently. Borderline values need interpretation with caution, often supplementing clinical information and/or other test results to make decisions.

Any spirometry record with normal FEV_1, VC and FEV_1/VC (i.e. all values more than their corresponding LLN values) should be interpreted as normal. Any spirometry record with FEV_1/VC value below its predicted LLN should be interpreted as having an obstructive abnormality (Fig. 26A.2). In situations where statistically valid LLN figures are not available (or not practical to use, as in field settings), FEV_1/VC ratio less than 70% is often used to define airway obstruction. However, this practice is likely to yield false positive results, especially in the elderly.[18] An obstructive defect is commonly seen in disorders associated with airflow limitation such as asthma and COPD. It may also be observed in diseases with small airway obstruction (such as bronchiolitis), cystic fibrosis, bronchiectasis, airway tumors, etc. Patients with upper airway obstruction can be further characterized based on appearance of flow volume loops.

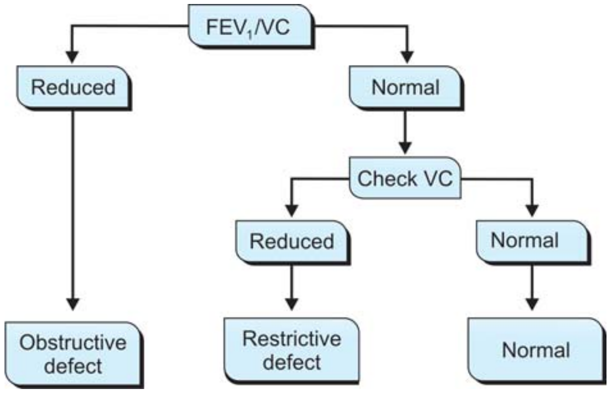

Fig. 26A.2: A basic algorithm for spirometry interpretation

Any spirometry record with a normal FEV_1/VC (i.e. value above corresponding LLN), coupled with a reduced VC (i.e. value below corresponding LLN), is suggestive of a restrictive abnormality. In situations where statistically valid LLN figures are not available (or not practical to use, as in field settings), observed VC ratio less than 80% of predicted value is often used to define reduction in VC. However, such an approach may result in the substantial misclassification of results.[19] Restrictive defects are common in conditions with the loss of functioning lung parenchyma (e.g. diffuse parenchymal lung diseases, lung collapse/atelectasis, pneumonia, after lung resection). Such defects are also observed in neuromuscular diseases (due to reduction in generation of force needed for a FVC maneuver), as well as disorders of chest wall and pleura (e.g. massive pleural effusion, pleural fibrosis, obesity, kyphoscoliosis).

It is important to note that spirometry can only suggest, but not confirm, a restrictive defect. True restriction is defined as reduction in total lung capacity. A mixed (obstructive plus restrictive) defect also cannot be diagnosed solely based on spirometry. A disproportionately low VC in the face of a reduced FEV_1/VC can either represent air trapping (with consequent increase in RV at the expense of VC, as in severe emphysema), or a true reduction in TLC (as in COPD with pneumonia). In such situations, it is advisable to estimate TLC (see below) for better characterization. FEV_1, expressed as a percentage of predicted normal value, is used to describe the severity of both obstructive and restrictive abnormalities. There is no universally accepted scheme of severity categorization.

More recently, some laboratories are shifting to FEV_6 as a substitute for FVC. Forced exhalation up to six seconds is a lot easier to perform for many patients. There are much less technical issues with the accurate measurement of low flow during prolonged expiratory maneuver, and the end of test can be more easily defined. FEV_6 may be more reproducible in several patients, especially those with airflow limitation. Reference equations for FEV_6 have also become available.[20,21] There is data to suggest that FEV_6 may be an acceptable surrogate for FVC in diagnosing both obstructive and restrictive defects on spirometry.[22,23]

The flow-volume loop may also provide a clue to underlying pathology (Fig. 26A.3). A small and concave or scooped curve suggests obstructive disorder. A small curve with steep slope suggests restriction. A small and flat curve suggests central airway obstruction. In disorders with variable intrathoracic obstruction, only the expiratory component of the loop is flat, whereas in

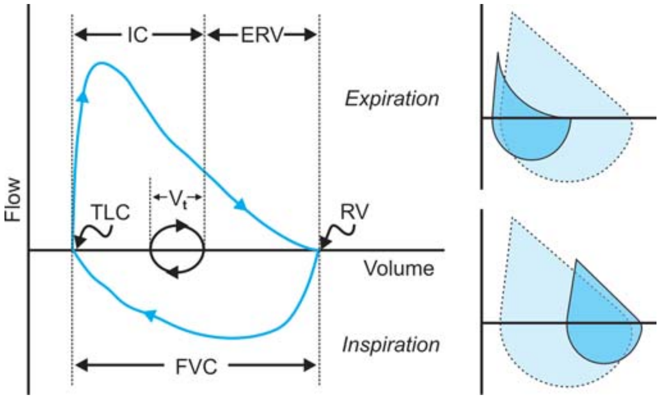

Fig. 26A.3: The left panel shows a typical flow-volume loop and the various subdivisions of lung volume. The right panel shows changes in the shape of flow volume loop in obstructive (top) and restrictive (bottom) defects, with the dotted line representing the normal loop

disorders with variable extrathoracic obstruction, only the inspiratory component is flat. Both components are flat in lesions causing fixed airway obstruction.

Bronchodilator Responsiveness (BDR) is considered to be present, if the increase in FEV_1 and/or VC (15–30 minutes after the inhalation of 400 µg salbutamol) in the post-bronchodilator study is both greater than 12% and greater than 200 mL over baseline values. Although an oversimplification, patients with asthma tend to have BDR much more frequently than those with COPD. It must be noted that the lack of BDR does not necessarily imply poor clinical response to bronchodilators in either condition.

PEAK EXPIRATORY FLOW

Peak Expiratory Flow (PEF) is defined as highest flow achieved from a maximum forced expiratory maneuver started without hesitation from a position of maximal lung inflation.[24] It can be measured either as a part of the spirometry procedure on the same instrument (with values derived from the flow volume curve), or separately using peak flow meters. The first meter specifically designed to measure this index of lung function was developed more than 50 years ago (Wright meter). Subsequently, a more portable, lower cost version (the ‘Mini-Wright’ peak flow meter) was developed, and other designs and copies have since then become available across the world.

Although PEF is fairly well reproducible for an individual, the normal range of PEF in healthy individuals is rather wide. As a result, predicted values of PEF cannot be used to detect lung disease, since there is substantial overlap between values in patients with lung diseases and normal persons. Further, since PEF recordings are both flow and volume dependant, they tend to get reduced in both obstructive and restrictive disorders. Hence the general notion that diminished PEF is a marker of airway obstruction is also not correct. While a normal PEF can reliably rule out airway obstruction, a low PEF does not necessarily indicate the same. The degree of reduction in PEF does not correlate well with the severity of obstruction described by the degree of reduction in FEV_1. PEF measurements generally underestimate the degree of airway obstruction, as determined from FEV_1 measurements.[25] This is partly because PEF predominantly reflects large airway function, while FEV_1 reflects both large and peripheral airway function. On the other hand, PEF is an extremely good tool for personal monitoring, especially among patients with bronchial asthma. Once a patient has established his/her personal best value, daily PEF monitoring can provide early clue to worsening airflow limitation due to impending exacerbation or poor control.

To measure PEF using a Mini-Wright meter, the indicator is moved to the bottom of the numbered scale. The subject then inhales deeply, and places the mouthpiece in his/her mouth, tightly closing the lips around it. The mouthpiece should be gripped between the teeth and over the tongue. A noseclip is not necessary. He/she then blows out as hard and fast as possible in a single blow. The procedure is repeated two more times and the highest reading from three successive blows is recorded. The largest two readings should be within 40 L/min of each other. It has been known for some time that the linear scale on the standard Mini-Wright PEF meter is an oversimplification, since the scale actually has nonlinear characteristics. As a result, the standard scale can over-record PEF in the mid-range by as much as 30%. However, this scale has continued to be used for diagnosing and managing asthma worldwide for nearly half a century. More recently, the requirements for equipment accuracy have been refined in a European Commission standard adopted in 2004.[26] The corresponding new Mini-Wright meters have an alinear scale that better reflects the true PEF (Fig. 26A.4). As predicted values for PEF have been obtained with meters with the old scale, these need to be converted to the new scale for data interpretation using the new meters. Nomograms and online converters are available for this purpose.

STATIC LUNG VOLUMES

Since spirometry cannot measure RV, it is not possible to determine FRC and TLC from this test. Other techniques are needed for the purpose. These methods

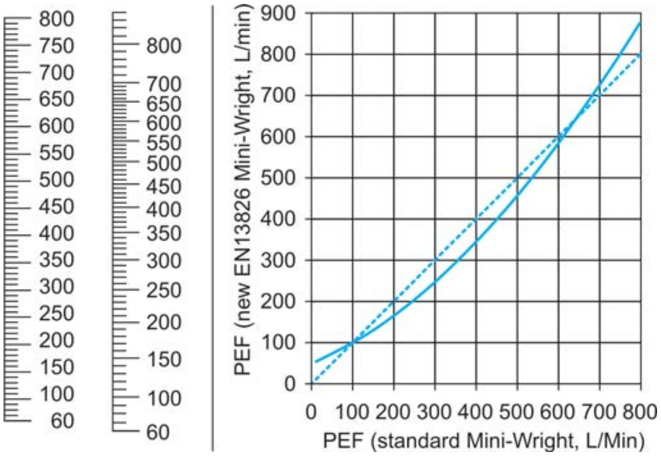

Fig. 26A.4: The left panel compares the standard and the newer (based on the EN13826 standard) scales used in Mini-Wright peak flow meters. Note that the standard meter (left) has a linear scale whereas the newer scale (right) is alinear. The right panel shows the direction and magnitude of error with the use of the standard scale, in comparison to the newer scale

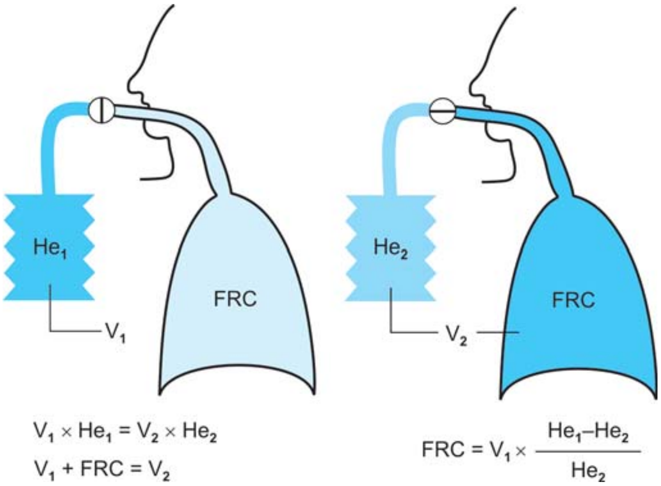
He_1
FRC
V_1
He_2
FRC
V_2
$V_1 \times He_1 = V_2 \times He_2$
$V_1 + FRC = V_2$
$FRC = V_1 \times \frac{He_1 - He_2}{He_2}$

Fig. 26A.5: Helium dilution technique to estimate functional residual capacity (FRC). Gas laws can be used to calculate FRC from initial and final helium concentrations (He_1 and He_2 respectively), and the known volume of helium mixture reservoir (V_1). See text for procedure details

are generally based on principles in which airflow velocity plays no role (in contrast to spirometry), and hence the term "static lung volumes" is often used for these measurements. Three techniques may be used: (a) open circuit nitrogen washout, (b) closed circuit inert gas dilution, and (c) whole body plethysmography. Determination of static lung volumes is helpful in ascertaining true restrictive physiology, and differentiating between obstructive and restrictive disorders. Comparison between TLC estimated through gas dilution and plethysmographic methods can also quantify the extent of air trapping within the lungs.

Open Circuit Nitrogen Washout Technique

In this method, the subject breathes 100% oxygen, starting from end-tidal expiration. This results in the washing out of nitrogen from the lungs. The exhaled gas is collected over the next 5–7 minutes, and its volume determined. Nitrogen concentration is measured through an analyzer in the breathing circuit and test stopped once a low plateau (concentration 1 to 2% for at least three successive breaths) is reached. The initial nitrogen concentration in the lungs is assumed to be similar to that in air. FRC can then be easily computed from the initial and final nitrogen concentrations, and the final collected volume. The technique has the drawback that any lack of precision in measuring nitrogen concentrations or expired volume will result in significant errors.

Closed Circuit Inert Gas Dilution Technique

The method is based on the equilibration of air in the lungs with a known volume of gas mixture containing a specified proportion of an inert gas (usually helium). The subject begins by tidal breathing through the mouthpiece. At end expiration of one such breath, he is connected to a reservoir containing a gas mixture with known helium concentration. Thus the point of starting the maneuver corresponds to the FRC. The subject continues to breathe in and out from this reservoir for about ten minutes, till the equilibration of gas between the reservoir and the lungs. The final concentration of helium is measured, and a simple calculation is used to derive the FRC (Fig. 26A.5). A vital capacity maneuver is performed at the same session to define the other lung volumes, which helps in computing the TLC and RV by addition or subtraction of the spirometrically determined IC and ERV respectively from the FRC. In view of the simple principles and technique, this method is widely used to determine static lung volumes.

Whole Body Plethysmography

In contrast to gas dilution techniques, plethysmography measures the total volume of air in the thoracic cavity, including gas trapped in bullae and other noncommunicating spaces (e.g. air within pleura or esophagus). Plethysmographically determined FRC is therefore often referred to as thoracic gas volume (TGV). Although several different types of body plethysmographs are available, the "volume constant" type is the most widely used. The equipment consists of a large air-tight chamber of known (and constant) volume. The subject sits inside this cabin and breathes through a mouthpiece till a stable end-expiratory level is obtained. At end-tidal expiration, a solenoid-operated shutter is used to occlude airway at the mouthpiece for 2–3 seconds, and the subject is asked to gently pant against the closed shutter with glottis open. As he breathes, chest expansion and retraction cause small pressure changes within the plethysmograph and at mouthpiece, which are recorded using pressure transducers (Fig. 26A.6). Since the plethysmograph volume is constant, these changes can be used to derive changes in the volume of air within the plethysmograph, and indirectly within the lungs. Pressure changes at the mouthpiece can be considered to directly reflect alveolar pressure changes, as the glottis is open and there is no net gas flow (due to the closed shutter). TGV can be computed from the slope of these pressure-volume curves using Boyle's law. Although the technique is cumbersome, it provides more reproducible measurements than dilution methods.

Interpretation

Reference equations for static lung volumes are used in a fashion similar to spirometry to define population limits of normality. In contrast to spirometry, an increase in TLC beyond the upper limit of normal is also considered pathological. A few regression equations are available in this regard from India as well.[6-11]

A decrease in TLC is diagnostic of a restrictive defect. In parenchymal restriction (e.g. lung fibrosis), RV and TLC are reduced proportionately, resulting in a normal RV/TLC ratio. In extrapulmonary restriction (e.g. chest wall or neuromuscular disorders), RV is usually normal (or sometimes even increased), resulting in an increased RV/TLC ratio. On the other hand, TLC might be increased in acromegaly, or in conditions like emphysema, as a result of air trapping. An increase in RV/TLC ratio, with an obstructive defect on spirometry, is a good indicator of air trapping. In conditions characterized by noncommunicating air in the lungs (e.g. emphysema, bullae, etc.), whole body plethysmography provides a better estimate of the lung volume, since gas dilution techniques measure only the volume of air that is freely exchanged during breathing. In fact, the difference in volumes calculated by the two techniques may provide some indication to the volume of noncommunicating air present in the lungs.[27] Estimation of static lung volumes is also necessary to diagnose mixed obstructive-restrictive defects, with a combination of reduced FEV_1/VC ratio and reduced TLC.

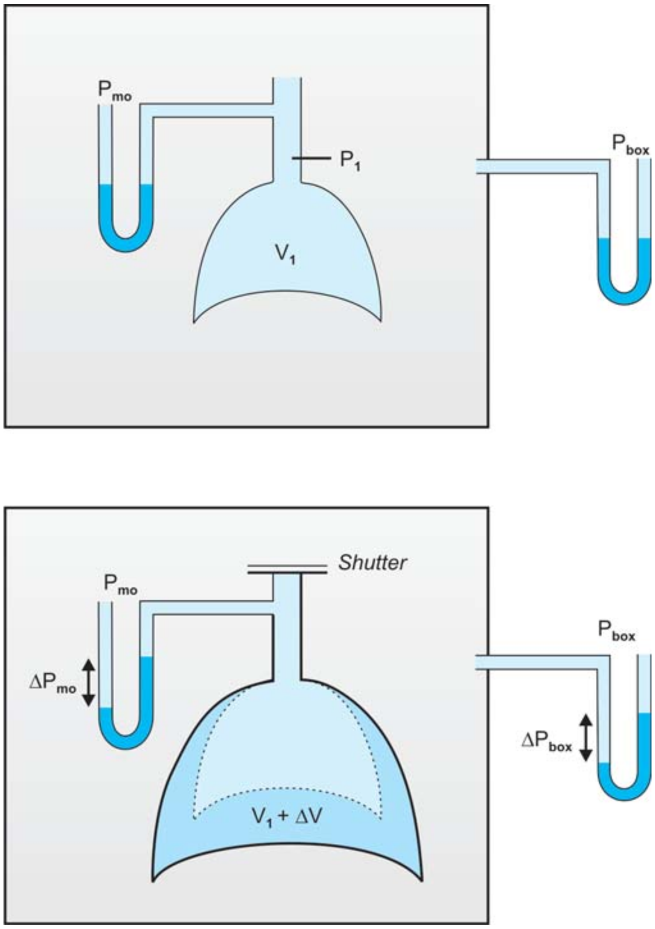

Fig. 26A.6: Whole body plethsmography to calculate static lung volumes using a constant volume apparatus. Under static conditions, pressure at mouth (P_{mo}) corresponds to the alveolar pressure (P_1), which is atmospheric at baseline. As the subject pants against a closed shutter, small fluctuations in mouth pressure (ΔP_{mo}) reflect alveolar pressure changes, while small fluctuations in lung volume (ΔV) are recorded as corresponding changes in pressure inside the plethysmograph chamber (ΔPb_{box}). A standard constant, specific to the plethysmograph being used, can be applied to compute ΔV from ΔPb_{box}. If the shutter is closed at tidal end-expiration, then gas laws can be used to compute functional residual capacity (V_1) from these data. See text for procedure details

DIFFUSING CAPACITY OF LUNGS

Measurement of pulmonary diffusing capacity allows us to assess the ability of lungs to transport gas from inspired air to the red blood cells in pulmonary capillary network. It is however, a misnomer, since gas transfer does not depend solely on diffusion across the alveolo-capillary membrane, and it is not a "capacity" in that there is no theoretical maximal limit. Many laboratories therefore employ the term "transfer factor" instead.

The Diffusing Capacity for Carbon Monoxide (DLCO) is the generally measured index. This is because carbon monoxide uptake is easily measurable, and the gas essentially follows the same pathway as oxygen during transport from alveolar air to red blood cells, and ultimate binding to hemoglobin. DLCO is the uptake of carbon monoxide from lungs per unit time per unit of carbon monoxide driving pressure. The test is usually performed for the screening of diffuse lung diseases and pulmonary vascular disorders; precise characterization of airflow limitation; differential diagnosis and severity assessment of restrictive ventilatory defects; disability evaluation; and preoperative assessment. There are no absolute contraindications. However, for technical reasons, most machines cannot measure DLCO in individuals with an extremely low VC (usually <1.5 liters) or severely dyspneic patients unable to hold breath for a sufficient time. The test cannot be performed on many patients receiving supplemental oxygen, as this needs to be discontinued before and throughout the test procedure.

Methodology

DLCO can be measured using a single-breath method, an intrabreath method or a rebreathing technique. The first is most commonly used, as it is simpler and better standardized (Fig. 26A.7). The gas mixture used contains 0.3% carbon monoxide, a tracer gas (helium, methane or neon), 21% oxygen, and balance nitrogen. The subject first gently breathes room air through a mouthpiece. Once comfortable, he is instructed to exhale completely (though not forcefully). At RV, he is connected to a reservoir containing the gas mixture, and instructed to inhale fully up to TLC, in less than two seconds. At this point he is asked to hold his breath for approximately ten seconds, without straining. Thereafter, he exhales fully, smoothly and quickly, and the expired gas is collected. The initial 0.75 to 1.0 liter is discarded as it represents dead space, and the next 0.5 to 1.0 liter is collected for analysis. Some instruments use rapid analyzers that provide real-time gas concentration curves from the exhaled gas, and allow washout till the tracer gas concentration reaches a plateau and collection subsequently. The collected mixture is analyzed for final tracer gas concentration and carbon monoxide uptake. For the purposes of analysis, the breath hold time is more than the actual breath holding period. The Jones-Meade method measures breath-hold time starting at 30% of inspiratory time and extending to half of the sampling time.[28]

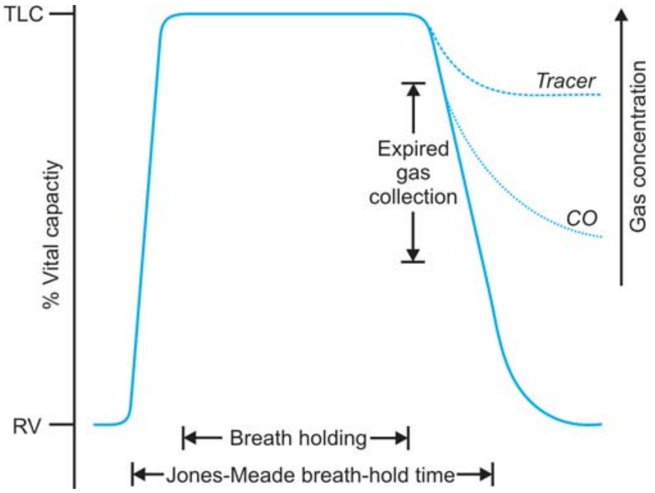

Fig. 26A.7: Schematic representation of the estimation of pulmonary diffusing capacity using the single breath technique. The subject inhales the gas mixture deeply residual volume (RV) to total lung capacity (TLC), and holds breath for ten seconds. Expired gas is collected after discarding that from dead space. Note that breath holding time used for calculations (see reference 28) is slightly longer than actual breath-hold. See text for procedure details

DLCO is calculated from the total lung volume, breath-hold time, and the initial and final alveolar carbon monoxide concentrations. It is a product of the subject's total lung capacity and rate of carbon monoxide uptake during the breath-hold time. An estimate of the total lung capacity and the initial alveolar carbon monoxide concentration is obtained from the tracer gas concentration in exhaled gas.

The test can be repeated after an interval of at least five minutes. Generally, a mean value is reported from two acceptable tests whose results agree within 2 mL/min/mm Hg.

Interpretation

In contrast to other pulmonary function tests, observed DLCO values must be normalized to key nonrespiratory variables. Hemoglobin concentration is important as it removes the carbon monoxide from the blood, thus providing a nearly constant gradient for gas transfer. Anemic patients may thus have a lower DLCO, and the measurement should therefore be corrected for this factor in such patients.[29,30] Smokers tend to have a small baseline level of blood carbon monoxide, and thus the transfer gradient may be less than for nonsmokers. If available, blood carboxyhemoglobin levels may be used to compensate for this anomaly.[30,31]

As with other lung function tests, the patient's result is interpreted by comparing it with a corresponding reference value. Regression equations for use in Indian subjects are available.[10,11,32] It must be noted that the degree of variability of DLCO (both for a given subject and for the population) is much higher than the results of other lung function tests. In case serial tests are performed, a DLCO result can also be compared to previous values to detect any sizeable change. Normalizing the DLCO to patient's alveolar volume may provide additional information about the reason for an abnormal result. When alveolar volume is reduced (either because of true restriction or due to noncommunicating air spaces), the ratio of DLCO to alveolar volume is relatively preserved. The ratio is however decreased if alveolar volume is increased (as in emphysema) or normal (as in anemia or nonperfusion of ventilated alveoli).

EXERCISE TESTING

Exercise testing is generally indicated for (a) evaluation of exercise intolerance, (b) evaluation of unexplained breathlessness, (c) preoperative assessment, and (d) formulation of exercise prescriptions. Detailed evaluation can give some clue about whether the underlying disorder is predominantly cardiovascular or respiratory in origin. Exercise testing can range from gross and crude assessments to highly detailed and standardized evaluation using computerized equipment. The two most regularly employed types of exercise testing for evaluating pulmonary diseases are the Six-Minute Walk Test (6MWT) and a formal complete Cardiopulmonary Exercise Testing (CPET).

Basic Modalities

Stair climbing remains the most basic exercise test that asks patients to climb stairs till they get limited by symptoms.[33] There is, however, no consensus on how to standardize the procedure, and several variations (such as climbing at own pace or at brisk pace, climbing with or without holding handrails) are used. Results are generally reported as number of stairs or number of flights of stairs.

Step tests ask the subject to walk up and down on a stool or bench at a specified rate. Several variations exist with regard to the height of steps, number of steps, and the frequency of step-ups. The most popular is the Master's two-step test.[34] The test is well suited to field use, and subjects can achieve close to their maximal exercise capacity.

The 6MWT is a simple procedure that assesses the maximum distance that a subject can walk on flat surface at his/her own pace in six minutes. The test provides a global estimate functional capacity, but does not give any specific information on individual systems (cardiac, pulmonary, hematologic and musculoskeletal) involved in exercise. The test is also sensitive to patient effort. The 6MWT is the most popular among the basic exercise tests as it is simple, practical and well standardized, and involves an activity familiar to almost everyone. A measured corridor, usually about 30 meters, is used, and the subject walks to and fro in this space at a self-determined pace. If a long corridor is not available, the test can be performed on a treadmill, although pacing and control are not as optimal and the distance walked is usually less.[35] Guidelines are available regarding the standardization, performance, and interpretation of the 6MWT.[36] The test has good reproducibility and good correlation with other measures of functional status.[37] For this reason, the 6MWT is the preferred investigation when a complete CPET is not available.

The shuttle walk test uses an audio signal from a metronome to dictate the walking pace.[38] Walking speed is incrementally increased every minute while the subject walks to and fro on a ten meter straight path. The test is terminated when the subject can no longer maintain the required speed. Hence the test correlates better with maximal symptom limited tests, such as the CPET, rather than the submaximal tests like 6MWT.[39] However, the test is more complicated than 6MWT, and may result in more frequent cardiac complications in the absence of electrocardiographic monitoring.

Exercise testing may sometimes be used to diagnose airway hyperreactivity due to exercise in patients with unexplained dyspnea. Exercise-Induced Bronchospasm (EIB) is described as a self-limiting bronchospastic event occurring immediately after strong exercise. Typically, greater than 10 to 15% reduction in FEV_1 and/or FVC is observed.[40] EIB is caused by the loss of heat, water or both, from the airways during exercise.

Cardiopulmonary Exercise Testing

The CPET is a more complex investigation that involves exercise at incrementally increasing intensity. The test is terminated when symptoms limit further exercise, or the maximal exercise capacity is achieved. A computerized protocol provides breath-by-breath information on respiratory gas exchange, airflow, oxygen consumption, carbon dioxide production, and cardiac variables (such as heart rate, blood pressure, etc.). The subject exercises on either a treadmill or on a bicycle ergometer; the latter may however be preferable as work rate can be directly measured.

Electrocardiographic and noninvasive blood pressure monitoring accompanies the test. In addition, oxygen saturation is continuously monitored through pulse oximetry. Real-time data on ventilatory and gas exchange parameters is obtained by asking the subject to breathe through a mouthpiece connected to a spirometer and metabolic cart. Flow, volume, and exhaled oxygen and carbon dioxide concentrations are measured. Either incremental or constant work protocol can be used. The test is terminated when the subject (a) gets exhausted, fatigued or distressed; (b) develops signs of cardiovascular instability (ischemia, arrhythmia, substantial blood pressure elevation, etc.); or (c) develops significant hypoxemia.

Although data for a large number of monitored and calculated variables is generated, interpretation and clinical correlation depends on the judicious integration of all available information. No single parameter is diagnostic of a cause for exercise limitation. Four basic measurements are critical in describing the response to exercise: oxygen consumption, carbon dioxide production, heart rate and minute ventilation. Under steady state conditions, measured oxygen uptake (Vo_2) equals metabolic oxygen consumption, and measured carbon dioxide output (Vco_2) is the same as its metabolic production. Both Vo_2 and Vco_2 can be mathematically computed from expired gas concentrations. Vo_2 increases linearly with work intensity until limitations in cardiac output and/or tissue extraction result in a plateau. This level is termed Vo_{2max} and is the best index for aerobic capacity. At lower work levels, Vco_2 increases at a rate similar to Vo_2. However, at higher work levels, the bicarbonate buffering of increased lactic acid production (resulting from anaerobic metabolism) causes Vco_2 to rise more steeply. The point where the Vco_2 begins to rise disproportionate to the Vo_2 is termed "anaerobic threshold" (Fig. 26A.8), and is a marker for the onset of metabolic acidosis during exercise. It usually occurs at 50 to 60% of Vo_{2max} with a wide range of normal values. The ratio between Vo_2 and heart rate reflects the amount of oxygen consumed in each cardiac cycle, and is often termed "oxygen pulse."

CPET is used to find whether or not a subject's maximal exercise capacity is decreased. A reduction in Vo_{2max} is the starting point for evaluating impaired exercise capacity. The quantum of this reduction is a rough indicator to the severity of exercise limitation. If Vo_{2max} is reduced, the other variables are then integrated into decision making to arrive at the most probable cause. In this regard, CPET is not clearly diagnostic of any individual disease process, but can rather only suggest the likely physiologic mechanism of dyspnea or exercise limitation. The cardiovascular response is assessed through anaerobic threshold, oxygen pulse, and relationships of Vo_2 to heart rate and work intensity. The ventilatory response is assessed through respiratory reserve (peak V_E/MVV), maximal respiratory rate, and arterial Pco_2 (if available). Gas exchange is assessed through physiological dead space assessment, oximetry, arterial oxygenation (if available), and calculating alveolo-arterial oxygen gradient ($P_{A\text{-}a}O_2$). Based on these assessments, and taking into account the overall clinical information, the etiology of exercise limitation can be deduced. The three basic causes for exercise limitation are cardiovascular disorders, respiratory disorders and physical deconditioning (Table 26A.3). However, one must be careful as significant overlap exists between response patterns in different disease conditions.

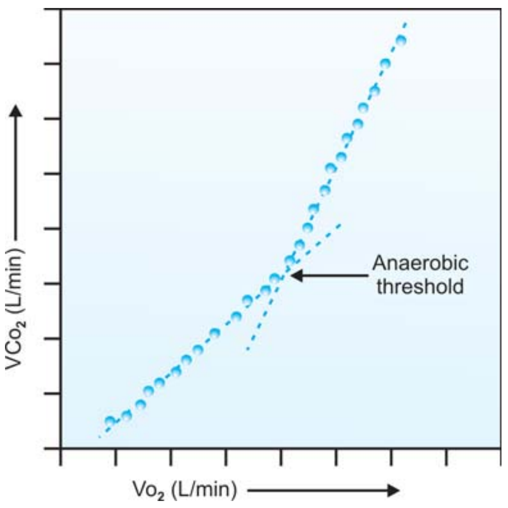

Fig. 26A.8: Anaerobic threshold determined from a plot of oxygen uptake (Vo_2) and carbon-dioxide production (Vco_2) during cardiopulmonary exercise testing

The test is highly sensitive in the identification of subclinical disease than other lung function tests conducted at rest. Therefore, CPET can be performed for preoperative assessment, disability evaluation, and the selection of candidates for heart and/or lung transplantation. The test is also useful in determining whether breathlessness results from cardiac or pulmonary component among patients who have disorders of both organ systems.

TABLE 26A.3: Typical responses during cardiopulmonary exercise testing

Parameter	*Normal value*	*COPD*	*ILD*	*Pulmonary vascular disease*	*Heart failure*	*Obesity*	*Decondition*
Vo_{2max}	>84% predicted	↓	↓	↓	↓	↓	↓
Anaerobic threshold	>40% of predicted Vo_{2max}	↔/↓	↔/↓	↓	↓	↔	↔/↓
Peak heart rate	>90% of age predicted	↓	↓	↔/↓	Variable	↔/↓	↔/↓
Oxygen pulse	>80%	↔/↓	↔/↓	↓	↓	↔	↓
Peak V_E/MVV x 100	<85%	↑	↔/↑	↔	↔/↓	↔/↑	↔
V_E/Vco_2 (at AT)	<34	↑	↑	↑	↑	↔	↔
Dead space/Tidal volume	<0.30	↑	↑	↑	↑	↔	↔
P_aO_2	>80 mm Hg	↔/↓	↓	↓	↔	↔	↔
$P_{A\text{-}a}O_2$	<35 mm Hg	↑	↑	↑	↔	↔/↓	↔

AT: Anaerobic threshold; COPD: Chronic obstructive pulmonary disease; ILD: Interstitial lung disease; MVV: Maximum voluntary ventilation; $P_{A\text{-}a}O_2$: Alveolo-arterial oxygen gradient; P_aO_2: Partial pressure of arterial oxygen; Vco_2: Carbon-dioxide production; V_E: Minute ventilation, Vo_{2max}: Maximal oxygen consumption

OTHER TESTS

Airway Hyperresponsiveness

Airway Hyperresponsiveness (AHR), a characteristic feature of bronchial asthma, is an increased sensitivity of airways to a variety of inhaled agents. AHR is classically measured using inhalation challenges with airway constrictor agonists, such as histamine or methacholine, which result in direct bronchoconstriction. Recently, inhaled mannitol solution has also become available for this purpose and acts by inducing osmotic changes in the airway.[41] Exercise can also be used to test for AHR (see above).

In general, histamine or methacholine solution is freshly prepared in doubling dilutions. After baseline spirometry, the subject inhales progressively increasing concentrations of the provocative agent through a dosimeter or nebulizer. Spirometry is repeated 30–90 seconds after each inhalation, and a rest of up to five minutes is provided between two successive inhalations. Several dosing protocols are in vogue, but the two most commonly used are (a) two-minute tidal breathing method and (b) five-breath dosimeter method.[40] The results are reported as percentage decrease in FEV_1 from the baseline, and summarized through an index termed PC_{20} (provocative concentration causing 20% reduction in FEV_1). PC_{20} is interpolated from a graph plotting FEV_1 values against the logarithm of provocator concentration. For methacholine, values higher than 20 mg/mL are normal, and values less than 4 mg/mL suggest AHR.[40] Resuscitation equipment should be available during testing, as sometimes life-threatening bronchospasm can result from the procedure.

Airway Resistance

Airway resistance can be clinically estimated using several approaches such as interrupter technique, forced oscillation technique and whole body plethysmography. The interrupter technique is the simplest, and requires monitoring airway pressure and airflow. Flow is abruptly interrupted, and airway resistance is obtained by dividing the pressure change after interruption by the flow obtained immediately before the interruption. Forced oscillation technique measures airway resistance by imposing flow oscillations on the airways during spontaneous breathing. These cyclical waves result in slight shifts in airflow, and consequent changes in airway pressure. Airway resistance is computed from pressure and flow changes, and frequency. The technique can provide added information about contributions from central and peripheral airways to the total airway resistance. When using the plethysmograph, the subject instructed to pant slowly, before and after the shutter at mouth is closed. Airway resistance is computed as the ratio between the slopes of mouth pressure-plethysmograph pressure and air flow-plethysmograph pressure changes.[42] This value can also be standardized to the lung volume by multiplying it by the simultaneously determined TGV. The resultant index is called specific airway resistance, and its reciprocal is termed as specific conductance.

Airway resistance is not normally determined for clinical purposes, but may provide additional information in the evaluation of patients suspected to have obstructive disorders. The range of normal airway resistance is not well defined, and generally values higher than 2.8 cm $H_2O/L/s$ are considered abnormal.

Pulmonary Mechanics

The elastic properties of the lungs are determined by relating alterations in the volume of air in the lungs to the corresponding changes in the lung's recoil. A body plethysmograph is usually used to determine the static pulmonary mechanics. Lung recoil force is measured as the transpulmonary pressure. This is the difference between the alveolar and pleural pressures; the former is measured at mouth under static conditions with shutter at mouth closed and glottis open, and the latter is quantified through pressure measurement from a thin balloon placed in the lower third of esophagus and connected to a pressure transducer. The subject sits in a whole body plethysmograph. After a few tidal breaths, he inspires fully to TLC, then exhales to FRC and again inspires to TLC. During the subsequent exhalation, a shutter at mouth occludes the airway intermittently. Mouth and esophageal pressures are recorded at each occlusion. Since mouth pressure equals alveolar pressure under static conditions, the transpulmonary pressure can be calculated at each shutter closure. This data is integrated with volume measurements to plot the relationship between transpulmonary pressure and lung volume. The slope of this curve over a range corresponding to the tidal volume is the static lung compliance. The whole plot can also be analyzed through a monoexponential analysis to yield a shape constant for the curve.[43] Unlike lung compliance, the shape constant is largely independent of ethnicity, patient effort and lung size. In patients with restrictive ventilatory defects, exponential analysis helps to differentiate restriction due to reduced elastic properties from that due to the loss of lung volume.[44]

Respiratory Muscle Function

Estimation of maximal respiratory pressures are a simple technique to assess global respiratory muscle function. A manometer is used to record highest pressures during maximal inhalation and exhalation, which can be sustained for at least one second.[45] Maximal Expiratory Pressure (MEP) is roughly twice as much as Maximal Inspiratory Pressures (MIP). The test is commonly used during the evaluation of respiratory muscle weakness in patients with neuromuscular disorders. It is also used as one of the several parameters to assess weaning potential in patients receiving mechanical ventilation. Abnormal muscle strength is identified by comparing observed values to reference data; such data is also available for the Indian population. Values are generally higher among men, and decline with age. A reduction in both MIP and MEP indicates generalized skeletal muscle weakness. A low MIP with normal MEP suggests isolated inspiratory muscle weakness (usually diaphragmatic). Isolated expiratory muscle weakness (normal MIP and low MEP) is rare.

The Sniff Nasal Inspiratory Pressure (SNIP) is a noninvasive test of inspiratory strength. The test is performed by wedging a catheter into one nostril and asking the subject to sniff through the other nostril. Pressure is measured in the obstructed nostril. The SNIP correlates strongly with transdiaphragmatic pressure and the MIP, but provides no information on expiratory muscle function.

Transdiaphragmatic pressure can be measured after the insertion of esophageal and gastric balloon catheters. This allows functional assessment during inspiration, expiration, a sniff, a cough or phrenic nerve stimulation. Although the technique is highly complex and invasive, it is the best measure of respiratory muscle strength. However, a wide normal range limits its clinical utility.[45]

Control of Breathing

The tests available to assess the respiratory control system include (a) inhalation of hypoxic or hyperoxic gas mixtures to stimulate chemoreceptors and (b) sleep studies to monitor behavior of the control system during sleep.[45] The hypoxic ventilatory response is evaluated by administering an hypoxic gas mixture to the subject over four to six minutes through a rebreathing circuit. This results in progressive hypoxemia, stimulation of peripheral chemoreceptors and an increase in respiratory drive. Blood CO_2 is maintained at the same level by removing CO_2 from the rebreathing bag. The ventilatory response is biphasic, with an initial rapid increase in ventilation followed by a gradual decline to a plateau. Ventilatory response to hypercapnia is determined by asking the subject to rebreathe a hyperoxic gas mixture, thereby causing progressive hypercapnia over four to six minutes. This results in the stimulation of central chemoreceptors, as well as an increase in the respiratory drive. End-tidal carbon dioxide tension is also monitored. The rise in ventilation in response to hypercapnia is linear. In either test, the measurements of ventilation or occlusion pressure are used to assess motor output. Occlusion pressure is assessed using $P_{0.1}$, which is the pressure generated in first 100 milliseconds of inspiration against an occluded airway.

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26B

Respiratory Muscle Function

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INTRODUCTION

Breathing, which is essential for life, requires the repetitive contractions of the muscles of respiration. Proper functioning of respiratory muscles is essential and unlike limb muscles, the muscles of breathing have no opportunity to rest and have to work throughout life. Besides breathing, respiratory muscles also play a role in other functions like sneezing, coughing, defecation, urination and parturiition. The respiratory muscles are an important component of the "respiratory pump" which consists of the respiratory center, and the conducting nerves, the thoracic cage and the muscles of breathing.[1] Till a few years ago, little attention was paid to respiratory muscles in the field of pulmonary medicine. A better understanding of respiratory muscle pathophysiology, the realization of the important role of respiratory muscles that they play in different diseases and the development of newer tests to more accurately assess respiratory muscles function have lead to an increased interest in this area.[2-4] Respiratory muscle training has also emerged as a treatment modality in patient with chronic respiratory diseases. A basic knowledge of the anatomy and physiology of the respiratory muscles is therefore important to properly understand their actions and the tests used to assess their functions.

Respiratory Muscles – Anatomical Considerations

The respiratory muscles can broadly be divided into two categories; those that take part in inspiration and those that are predominantly expiratory in function. In a normal person, during quite inspiration, the respiratory muscles contract in a coordinated manner so that the diaphragm moves down like a piston and the rib cage move upwards and outwards in a bucket handle manner. This increase in the size of the thoracic cage creates a more negative pleural pressure and air is drawn into the lungs. Besides this, during inspiration, as the airway pressure becomes negative, other muscles also act and prevent collapse of the conducting structures mainly in the upper airways. These muscles are the pharyngeal constrictor muscles, the genioglossus and the neck strap muscles.[5] These muscles ensure patency of the upper airways during inspiration. Also, the laryngeal abductor muscles contract and open the vocal cords during inspiration. All these muscles must act in synchrony to ensure adequate breathing during inspiration.

Expiration during normal breathing is usually passive. At the end of inspiration the inspiratory muscles relax and the normal elastic recoil of the lung facilitates expiration. During activities such as exercise and in patients with underlying lung disease, expiratory muscles may be recruited for a more active and forceful exhalation.

Inspiratory Muscles

Diaphragm: The diaphragm is the main muscle of inspiration and during quiet breathing, accounts for about 70 to 80% of the work of breathing.[6] The diaphragm is composed of two distinct muscle components, the costal portion and the crural portion.[7] Both of these are inserted into a central tendon. The costal portion arises anteriorly from the xiphoid process and from the upper margin of the lower 6 ribs. The thick crural portion consists of muscle fibers that arise from the arcuate ligaments and are inserted into the upper three lumbar bodies on the right side and the upper two lumbar vertebrae on the left side.[8] The costal and crural parts of the diaphragm may be recruited differently especially when an individual is breathing at a high ventilatory rate.

The diaphragmatic curvature is like that of a hemisphere. If the radius of this hemisphere were to be r, than as per Laplace's law the pressure inside the sphere (P) would be equal to 2 T/r, where T is the tension in the wall. If T is kept constant and r increases, as would happen if the diaphragm flattens and the curvature of the diaphragm decreases, it will lead to a decrease in pressure.[9] This commonly occurs in patients with Chronic Obstructive Pulmonary Disease (COPD) where flattening of the diaphragm due to emphysema or air trapping occurs and decreases the efficiency of the diaphragm to generate pressure. Also, the dome shape of the diaphragm increases diaphragmatic function through the zone of apposition. The zone of apposition is that part of the diaphragm that lies next to the inner aspect to the rib cage. When the diaphragm contracts and descends, it increases intra-abdominal pressure. This increased intraabdominal pressure is transmitted laterally to the rib cage and through the zone of apposition it facilitates the expansion of the lower rib cage.[8,9]

Besides the diaphragm, other muscles also contract during normal inspiration. These are mainly the scalene muscles, the intercostals and the triangularis.[54] The scalene muscle originates from the transverse process of the lower five cervical vertebrae. It is inserted on the upper surface of the first and second ribs. These muscles act by lifting and expanding the rib cage during inspiration.

This muscle was initially thought to be an accessory muscle of inspiration, but studies have clearly shown that the scalene are primary and not accessory muscles of inspiration.[10] The intercostals muscles consist of the external and internal intercostals, these muscles run between the ribs. The external intercostals and the parasternal part of the internal intercostals also contract during inspiration. Contraction of these muscles lifts the ribs and thereby increases the anteroposterior diameter of the rib cage.[11]

Accessory Inspiratory Muscles

As the ventilatory demand increases, the accessory muscles of inspiration come into play. The sternocleidomastoid is the most important accessory muscle of inspiration.[11] This muscle runs from the mastoid process and attaches to the medial third of the clavicle, the ribs and the manubrium sterni. Contraction of this muscle leads to the elevation of the first rib and lifting of the sternum. This results in an increase in the anteroposterior diameter of the upper part of the rib cage. The external intercostal muscles may also contract as ventilatory demand increases. Other muscles like the Pectoralis major and minor, latissmess dorsi, anterior serratus and trapezius, though not muscles of respiration, actively contract in patients with severe obstructive lung disease.[5]

Expiratory Muscles

Expiration in a normal individual is a passive process, achieved by the elastic recoil of the lung when the muscles of inspiration relax. The abdominal muscles assist expiration. These include rectus abdominis, external and internal oblique and transverse abdominis.[6] Contraction of these muscle decreases the size of the rib cage and the end expiratory lung volume also decreases. Also, as these abdominal muscles contract, the intra-abdominal pressure increase, the abdominal contents get compressed and the diaphragm is pushed upward.[6]

Both the inspiratory and expiratory muscle function in a coordinated manner in a number of activities that an individual performs in day-to-day life. Activities like sneezing, coughing or defecation require the synchronous activity of these muscles to generate a large intrathoracic pressure. In coughing, a deep inspiratory effort is required. After this, the glottis closes and a very high intrathoracic pressure is generated due to the powerful contraction of the diaphragm and the abdominal muscles. The glottis than opens and this pressure is suddenly released and it leads to an explosive expiratory effort. This causes a very high flow and generates a shearing force in the airways. This helps in removing secretions and other foreign particles, which may be present in the airways.

RESPIRATORY MUSCLES—BASIC PHYSIOLOGY

Respiratory muscles generate pressure differences during the cycle of breathing, which allow ventilation to occur. It is important to remember that respiratory muscles differ from other skeletal muscles in certain key ways. Firstly, they are the only skeletal muscles on which life depends. Secondly, they are under both voluntary and involuntary control. Also, respiratory muscles contract mainly to overcome elastic and resistive loads. This is unlike other skeletal muscles, which cope mainly with inertial load. They are also by far the most extensively used skeletal muscles. The force generated by the respiratory muscles, as for any muscle, depends upon its level of excitation, the initial resting length and the mode of contraction.[12]

One important component in the functioning of the respiratory muscles is the length tension relationship. In a muscle, the active force developed is a function of the length of the muscle. As the length of muscle fibers decreases, its capacity to generate pressure also decreases. On the other hand, lengthening of a muscle fiber, up to a point, increases its capacity to generate force.[12] This concept is important to understand in relation to the diaphragm. In patients with COPD as the lung hyperinflates, the diaphragm is pushed down and the length of the muscle fibers decrease. This significantly decreases the efficiency of the diaphragm to generate force and thereby increases the work of breathing.

Whenever a muscle is stimulated, it contracts and generates a force. As the frequency of the stimulus increases, there occurs an associated increase in the force the muscle can generate. As the stimulus is further increased, the force that the muscle can generate continues to increase until it reaches a plateau and above this frequency the force does not increase.[5] This plateau is reached at a frequency above 50 Hz and this association between stimulus and the force that a muscle generates is known as force – frequency relationship. Another mechanical property, which is important, is the relationship between the force a muscle generates and the velocity of muscle fiber shortening. The greater the force a muscle generates, the slower the velocity of contraction. There is therefore an inverse relationship between the velocity of muscle contraction and the force generating capacity of a muscle.[6]

It has been shown that the respiratory system has been designed in such a way that after some time as the inspiratory demand increases, rather than increasing the force of contraction, newer inspiratory muscles of respiration get recruited. In this way muscle function is coordinated so that the respiratory muscles are always shortening at a velocity that will lead to optimum function.

EVALUATION OF RESPIRATORY MUSCLE FUNCTION

Assessment of respiratory muscle function should form a part of routine respiratory system diagnostic work-up. Dyspnea occurring when no other pulmonary cause is apparent may occur due to respiratory muscle weakness. Broadly, evaluation of respiratory muscle function would be indicated in two situations: (i) When clinical features suggest respiratory muscle weakness and (ii) if the patient is suffering from a disease where respiratory muscle weakness is known to occur. Respiratory muscle assessment is also being done where muscle weakness may affect other disease processes, as may occur with steroid therapy, prolonged mechanical ventilation and severe malnutrition.[13-16]

History and Examination

Breathlessness is the main symptom of patients with respiratory muscle weakness. In patient with generalized neuromuscular diseases, respiratory muscles are usually involved and these patients may show wasting and fasciculation of the limb muscles. Patients with significant diaphragmatic weakness classically complain of breathlessness when supine, or sitting or standing in water.[2] Breathlessness which occurs immediately on lying supine or on entering a swimming pool is very suggestive of severe diaphragmatic weakness. As the respiratory muscle weakness progresses, it lead to nocturnal hypoventilation and disturbed sleep. This leads to day time somnolence and impaired intellect.[17] Ultimately, ventilator failure and cor pulmonale develop. Patients with weakness of bulbar and expiratory muscle have poor cough and these patients have a higher chance of developing recurrent aspiration and pneumonia.

Physical examination may at times be helpful. Increase in respiratory rate may occur due to respiratory muscle weakness. Use of accessory muscles and intercostals recession may suggest respiratory distress and muscle weakness. Patients with diaphragmatic weakness or paralyses show a typical paradoxical inward inspiratory abdominal movement. Normally, as the diaphragm contracts during inspiration, the abdominal contents are pushed down and the abdominal wall moves outwards. In patients with diaphragmatic weakness or paralysis, during inspiration, the pleural pressure becomes more negative and the weak or paralyzed diaphragm gets sucked into the thoracic cage. This leads to the paradoxical inward abdominal movement during inspiration. This movement is better appreciated in the supine position.[3] These physical findings are usually only appreciated when diaphragmatic weakness has progressed to more than 75% and therefore significant respiratory muscle weakness may be missed on clinical examination.[18]

Imaging to Assess Respiratory Muscle Function

A plain chart radiograph may show an elevated hemidiaphragm and this may suggest hemidiaphragmatic paralysis. In patients with bilateral diaphragmatic paralysis, both hemidiaphragms are elevated and the X-ray may appear relatively normal.[19] Fluoroscopy is a commonly used test in suspected hemidiaphragmatic palsy and is positive in about 90% of cases.[5] An upward or cephalad movement of the diaphragm is seen. This test can be falsely positive and does not provide information about the extent of diaphragmatic weakness. A short sharp submaximal sniff during fluoroscopy is a useful maneuver to assess for diaphragmatic weakness.

Ultrasound has emerged as a useful tool to assess movement, thickness and zone of apposition of the diaphragm.[20] Besides this subpulmonary or subdiaphragmatic collections, traumatic rupture and pleural masses can also be detected.[21] It is also a safe method with no radiation exposure and is simple to perform. Ultrasound has also been used for assessing hemidiaphragmatic movements, zone of apposition and the thickness of the diaphragm.[22] Hemidiaphragmatic movement has been evaluated in normal individuals and in patients with underlying respiratory diseases. By this technique, the normal range of craniocaudal excursion of the posterior hemidiaphragm has been established and an acceptable reliability has been obtained in the terms of interobserver and intraobserver reproducibility. It has also been found to be a reliable quantitative as well as qualitative method for assessing posterior diaphragmatic excursions. Ultrasound has been also used to see the thickness and length of the zone of apposition with good results.[23] The thickness of the zone of apposition at different lung volumes has been measured. This measurement has shown good repeatability in most subjects although it may be difficult to perform in obese individuals.[23] Ultrasound has also been used to evaluate the thickness of the diaphragm in different neuromuscular and respiratory diseases.[22,24]

Function Testing

At times, conventional spirometry provides the first suspicion of respiratory muscle weakness. As spirometry is routinely done and easy to perform, it is often used to assess the severity, progression and functional consequence in patients with confirmed respiratory muscle weakness. Patients with inspiratory muscle weakness classically have low vital capacity, decreased Total Lung Capacity (TLC) and near normal Residual Volume (RV).[23] The Functional Residual Capacity (FRC) is also relatively preserved in patients with respiratory muscle weakness. Usually the total lung capacity is less markedly reduced than the vital capacity and therefore the RV/TLC ratio and FRC/TLC ratios are often increased.[23] A normal vital capacity makes respiratory muscle weakness highly unlikely. Diffusion capacity to carbon monoxide is reduced, but normal or raised when adjusted for volume and this helps to distinguish respiratory muscle weakness from alveolar disorders like pulmonary fibrosis.

In patients with diaphragmatic palsy, the vital capacity falls when the patient is supine, and this fall should be more than 25% to be definitely abnormal.[25] Regular monitoring of vital capacity is also useful in patient with progressive muscle weakness or paralysis, i.e. Guillain–Barré syndrome.[26,27] If the vital capacity falls below 50% from baseline, the patient may need ventilator support. It must be remembered that in patient with long-standing respiratory muscle weakness, vital capacity will also fall due to reduced chest wall and lung compliance, possibly due to microatelectasis.[5] Vital capacity maneuver is a patient-dependant maneuver and therefore, the result depends upon patient's motivation and ability. Moreover, a number of other diseases can lead to a decreased vital capacity. This test is therefore neither specific nor diagnostic.[28]

Flow Rates and Dynamic Spirometry

In patients with pure respiratory muscle weakness, airway resistance is normal. A decrease in both inspiratory and expiratory flow rates occurs in patients with respiratory muscle weakness. These flows are decreased more in the effort dependant part of the flow volume loop. The decrease in expiratory flow rates is less as compared to inspiratory rates and the ratio of maximum mid inspiratory flow rates to maximum mid expiratory flow rates, which is usually greater than one, is less than one in cases of respiratory muscle weakness.[23] However, a similar decrease can occur in extrathoracic upper airway obstruction. Flow volume loop shows a decrease at high lung volumes than at low lung volumes and peak flow is markedly decreased. As residual volume is approached, expiratory muscles cannot overcome the outward elastic recoil of the chest wall, flow rapidly decreases and ceases at high residual volume. Because of this, the descending loop of the flow volume curve tends to be convex rather than concave, with an abrupt drop off of flow at the end of expiration.[23]

Maximum Voluntary Ventilation (MVV) is also reduced.[5] This test is also done and in the past was recommended to assess respiratory muscle weakness. However, it is not a sensitive test and is not useful to diagnose respiratory muscle weakness.[5]

Oximetry

Monitoring overnight pulse oximetry may help in providing evidence to the severity of respiratory muscle weakness.[2] A normal nocturnal oximetry suggests that the muscle weakness is not severe enough to cause ventilatory failure. On the other hand, demonstration of nocturnal hypoventilation suggests severe respiratory muscle weakness, which may cause ventilatory failure. Patients with moderate-to-severe respiratory muscle weakness show fall in oxygen saturation during rapid eye movement sleep.[5] This fall in oxygen saturation is mainly due to hypopneas and these may appear to either central or obstructive or a mixture of both.[29] In patients with pure respiratory muscle weakness substantial nocturnal desaturation occurs only if respiratory muscle strength is less than one-third of normal.[2] As respiratory muscle weakness progresses hypercapnia starts occurring initially during sleep. Many of these patients may have coexisting respiratory disorders, which may also contribute to hypoventilation.

Mouth Pressures

These tests give a good estimate of global respiratory muscle strength. The tests most widely used to assess inspiratory and expiratory muscle strength are static Maximum Inspiratory Pressures (MIP) and static Maximum Expiratory Pressure (MEP) at mouth. These tests are simple to perform, fairly accurate, noninvasive and well tolerated by the patients. Also, normal values for MIP and MEP have been established in different ethnic groups.[30-33] Portable and inexpensive devices are now available, which allows one to measure MIP and MEP at beside, in the Outpatient Department (OPD) and in the Intensive Care Unit (ICU)[34] (Fig. 26B.1).

Both MIP and MEP are measured at different lung volumes so that the maximum muscle strength of the muscle can be measured. The length of the respiratory muscles and therefore their contractile force vary with lung volume. The force a skeletal muscle can generate depends on the force-velocity and force-length relationship (see section on respiratory muscle physiology above). The expiratory muscles are longer at high lung volumes and so expiratory muscles contractile force is highest at or near total lung capacity. Conversely inspiratory muscles are longer at low lung volumes and so inspiratory muscle force is greatest between functional residual capacity and residual volume.

Devices used to measure MIP and MEP measure inspiratory and expiratory pressures at mouth when the patient makes a maximum effort against a closed airway.

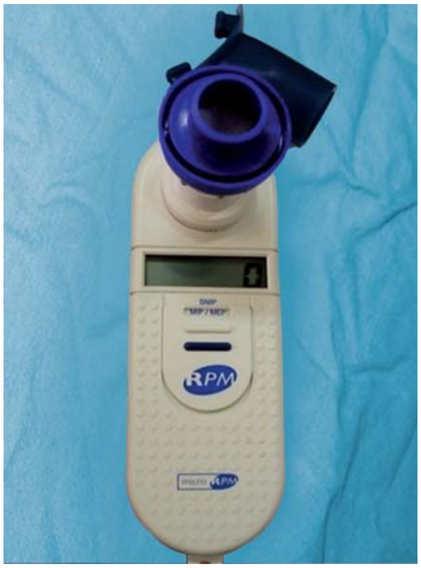

Fig. 26B.1: Simple portable device to measure mouth pressures and sniff nasal inspiratory pressure

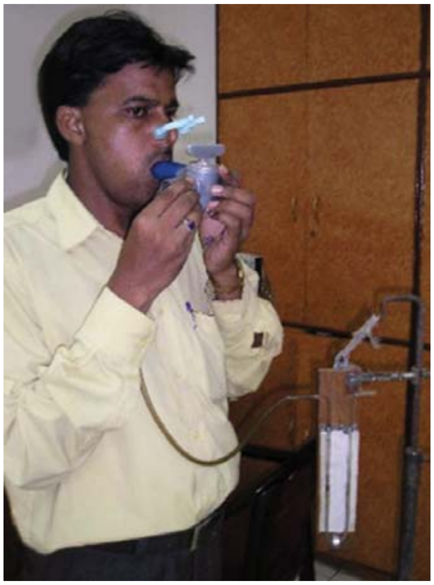

Fig. 26B.2: Traditionally used method to measure mouth pressure using a mercury manometer

Initially a mercury manometer was used to measure MIP and MEP (Fig. 26B.2), but this has been replaced by a pressure gauge, which is now used to measure the pressure (Fig. 26B.3). Lips are pursed inside a wide bore mouth piece. This contracts the facial muscles and prevents the cheeks from ballooning during expiration.[30,33] The inspiratory and expiratory pressure must be maintained for at least 1.5 seconds, so that the maximum pressure sustained for at least one second can be recorded. For

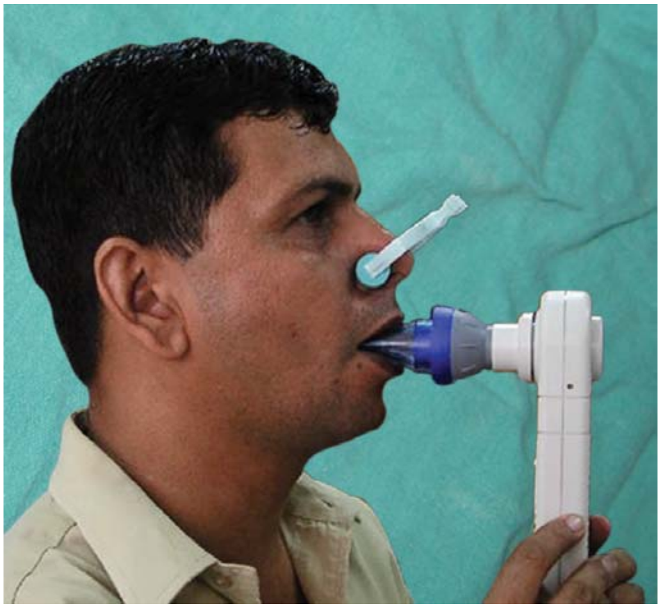

Fig. 26B.3: Pressure meter being used to measure mouth pressure

reasons explained above, to get the best readings of respiratory muscles strength, MEP is measured at or near total lung capacity and MIP between residual volume and functional residual capacity. In females, MIP and MEP are about 65% to 70% less than that of males. Over the age of 50 years in both sexes, the pressure values are about 85% to 90% of that for younger adults. Also, a much greater degree of intrasubject variability in pressure is present as compared to variation in spirometry.

Like the vital capacity, a normal or high MIP (more than 80 cm of H_2O) rules out clinically significant respiratory muscle weakness.[2] Both MIP and MEP are subject dependant and at times it is difficult to ensure that the patient is making a truly maximum effort. Therefore, patient's cooperation is very important. A low value may, therefore, be due to poor effort and may underestimate the strength of the respiratory muscles. As this test is easy to perform and normal values are available it is widely used to rule out respiratory muscle weakness. Serial measurements over time may give valuable information about progression or improvement in muscle weakness in patient with chronic neuromuscular disease. Also, MIP is useful to assess respiratory muscle strength in the ICU in patients on mechanical ventilator to determine fitness to wean off the ventilator. Patients with an MIP less than in 20 cm H_2O are usually unfit for a weaning trial.[35]

Nasal Pressures

Another method used to assess respiratory muscle strength is by doing the sniff test.[36,37] A sniff is an inspiratory maneuver, which is short and sharp in performed through one or both unoccluded nostril. During a sniff, there occurs a sharp contraction of the diaphragm and other inspiratory muscles. Sniff is a natural maneuver, is simple and noninvasive and may patients find it easy to do. It has been shown that in normal subjects, the pressure developed in the esophagus during a sniff closely relates to the pressure in the nasopharynx, mouth and nose.[38] Therefore, measurement of the Sniff Nasal Inspiratory Pressure (SNIP) provides a good estimate of inspiratory muscle strength. Normal value of SNIP have been established and it has been evaluated in patients with COPD and interstitial lung disease.[39,40]

The tests consists of asking the subject to perform a short sharp maximal sniff through one unobstructed nostril while measuring nasal pressure through a catheter wedged in the contralateral nostril (Fig. 26B.4). Various methods for wedging and occluding the nostril with a small tube are used. These include foam, rubber bung and dental molding material. This test is easy and natural and allows patients to activate inspiratory muscles completely. This test is also relatively reproducible and has a smaller range of normal values than mouth pressures.[37,38] Simple portable devices are available for SNIP recording and this test can now be done at the bedside.[41]

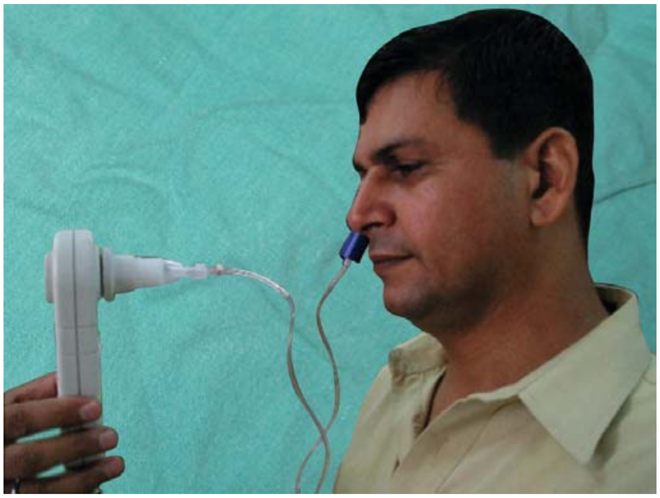

Fig. 26B.4: Sniff nasal inspiratory pressure being measured using a catheter and a nasal bunge to occlude one nostril

Invasive Tests

i. Transdiaphragmatic Pressure

Sometime noninvasive tests do not help in confirming the absence of respiratory muscle weakness and at times a more accurate estimation of the degree of muscle weakness is needed for treatment purpose in patients with underlying respiratory muscle weakness. In such situations tests, which are more precise, but invasive and where patients' own effort is not required, are used. These tests require the introduction of two small latex balloons, which are sealed over a catheter into the esophagus and stomach. These balloons are thin walled, usually 5 to 10 cm long and have a 3.5 to 5 cm perimeter.[23] The catheter is about 70 to 100 cm long. The catheter is attached to a transducer, which records the pressure. Using local anesthesia, these small esophageal and gastric balloons are introduced through the nose and gradually passed through the phyranx into the esophagus. One catheter is positioned at the lower end of the esophagus (esophageal balloon) and the other is positioned in the stomach (gastric balloon). A very small amount of air is introduced into these balloons. One balloon lies just above (reflects pleural pressure) and the other just below the diaphragm (reflects abdomen pressure).[23] This allows one to measures the pressure difference across the diaphragm when it contracts and therefore the transdiaphragmatic pressure (Pdi) can be measured.

ii. Maximum Transdiaphragmatic Pressure (Pdi max)

Measurement of Pdi max gives an idea of the strength of the diaphragm. Transdiaphragmatic pressure is calculated as the difference in the Gastric Pressure (pga) and the Esophageal Pressure (Pes) measured when the subject makes an isotonic contraction during a maximal voluntary effort. The transphragmatic pressure will vary with lung volume and should therefore be recorded at a known lung volume (usually FRC). Normal value for Pdi max and in patients with different lung diseases have been established.[42]

iii. Transdiaphragmatic and Esophageal Pressure During Sniff

Sniff is easy to perform and most subjects are easily able to perform a maximal sniff effort. With the gastric and esophaged balloons in place, the subject is asked to perform a maximum sniff at FRC without using a nose clip.[2] The Sniff Transdiaphragmatic Pressure (Sniff Pdi) is recorded. Usually the patient is asked to perform a number of these maneuvers till three reproducible tracings are obtained. Sniff Pdi has been studied in normal and in different diseases. It has a narrow normal range and better between day coefficient of variation than MIP.[37]

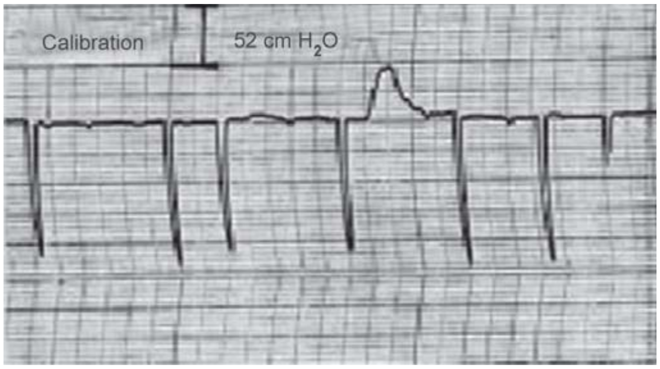

Fig. 26B.5: Tracing of sniff esophageal pressure recorded in a patient using an esophageal balloon catheter. Patient has performed multiple sniff maneuvers. The upward positive wave is due to swallowing

Studies suggest that clinically useful information about diaphragmatic strength can be obtained by using a single esophageal catheter and measuring Sniff Esophageal Pressure (Sniff Poes)[43]. A single esophageal catheter is routinely used in many respiratory laboratories for measuring lung compliance. Esophageal pressure is measured, with a pressure transducer, while the patient makes a short, sharp, maximal sniff. This esophageal pressure during a sniff (Sniff Poes) closely relates to Sniff Pdi and is simpler to do (Fig. 26B.5).

All these tests, i.e. Pdi max, Sniff Pdi and Sniff Poes, are useful, accurate and reproducible tests. They provide reliable assessment of the diaphragmatic strength. However, like previous tests they also are dependent on patient's cooperation and low values become difficult to interpret at times.

iv. Tests Where Subject's Cooperation Not Needed

Phrenic nerve stimulation: The diaphragm is innervated by the phrenic nerves only. Thus stimulating the phrenic nerve provides a unique way of assessing diaphragmatic function without the cooperation of the patient. Besides pressure measurement, phrenic nerve stimulation also allows to record electromyogram of the diaphragm and phrenic nerve conduction time.[44] Phrenic nerve stimulation super imposed on a naturally occurring or voluntary contraction is an important research tool and provides information about the maximal voluntary pressure that the diaphragm can generate.[45]

Electrical stimulation: Electrical stimulation of the phrenic nerve can be done in the neck and the diaphragmatic contraction can be measured by the esophageal and gastric balloons.[23] The contraction, which is the twitch transdiaphragmatic pressure (twitch Pdi) has the advantage that it does not need patient's motivation or cooperation. Both unilateral and bilateral electric stimulation of the phrenic nerve can be done. The phrenic nerve is usually located just beneath the posterior border of the sternocleidomastoid muscle at the level of the cricoid cartilage. Precise location of the nerve is required for electrode placement and to achieve this, repeated stimulation near the site is frequently required. Once the nerve is identified, the spot is marked and the orientation of the electrode in the neck is observed by the operator.[23] The operator usually stands behind the seated subject and the current intensity is increased to obtained supramaximal stimulation. The procedure is usually done on each side separately and after that bilateral electrical stimulation is applied and twitch Pdi is recorded with the esophageal and gastric balloons. Twitch Pdi has been measured in normal subject and in patients.[46,47] This test can be uncomfortable as the stimulus intensity is increased to achieve supramaximal stimulation. Also, sometimes it is difficult to locate the exact site of the nerve and reliable supramaximal stimulus is not obtained. This test is useful when there is severe weakness or the results of the previous tests are not definite as the patient is unwilling or unable to cooperate.

Magnetic stimulation: It has been known for long that magnetic fields can stimulate the nervous structures.[48] The last decade has seen the extensive use of magnetic stimulation in neurology.[49] Magnetic stimulation by a magnetic coil creates brief and intense magnetic field.[23] This field is only mildly hampered by structures on the surface of the body like skin and bones. It therefore reaches the deeper nervous structures and the rapidly changing magnetic field causes current to flow in the nervous tissue within the field.[50,51] This in turn causes the muscle to contract. Magnetic stimulation overcomes a lot of problems associated with electrical stimulation.[52,53] It is relatively painless and easy to apply in a clinical setting. By placing a circular magnetic over the cervical phrenic nerve routes one can achieve supramaximal bilateral phrenic nerve stimulation once this coil is activated.[54,55] The magnetically measured Pdi is slightly greater than the electrical Pdi possibly due to the activation of accessory muscle, which may get activated due to the spread of the magnetic field.[2]

For the assessment of respiratory muscle function, bilateral phrenic nerve stimulation can be achieved by stimulating the phrenic nerve roots in the cervical spine.[54,55] More localized phrenic nerve stimulation can be achieved by using a figure of eight-shaped magnetic coil in the neck. This coil can be used unilaterally for unilateral stimulation of the phrenic nerve or bilaterally for bilateral phrenic nerve stimulation.[56,57] This allows easy and accurate assessment of hemidiaphragmatic function. Bilateral anterior stimulation also has the advantage that it can be done in supine position.[56,57] Respiratory muscle assessment using magnetic stimulation is now done as an OPD procedure, in the ward and even in an ICU setting.[58] This has largely replaced and electric stimulation has become well established in clinical practice.

Magnetic stimulation of the respiratory muscle is being increasingly used to assess respiratory muscle function and endurance.[56,59] The role of abdominal muscle and the pressure changes that occur during abdominal muscle stimulation is being better understood.[60] Also, the mechanism of diaphragmatic fatigue, cough, etc. are also evaluated.[56,61,62]

Electrophysiological Assessment of Respiratory Muscles

Electromyography (EMG)

Electromyography has traditionally been used to assess various aspects of skeletal muscle function. Stimulation of the phrenic nerve causes the diaphragm to be activated and the electrical signal generated by this activation is recorded.[63] Recording EMG of the respiratory muscles can help to assess the level and pattern of activation of these muscles. This helps in the diagnosis of neuromuscular diseases and when combined with other tests, helps to assess the efficacy of the contractile function of the muscle. To record EMG of the diaphragm, electrodes can be placed at different sites. Surface electrodes can be placed in the neck, over the chest wall muscles or next to the area of apposition of the diaphragm on the chest wall. Electrodes wound around a small catheter can be swallowed and placed in the lower esophagus to measure a more pure crural diaphragm EMG. Electrodes can also be inserted into the respiratory muscle of interest using wire, needles or hook electrodes.

Surface electrodes are commonly used because they are noninvasive, easy to apply and a large number of motor units can be assessed. Surface electrodes have been used to assess activity of the diaphragm, scalene, intercostals, abdominal muscles and accessory muscles. The electrodes are placed over or as close as possible to the muscle to be evaluated. The site is determined by palpation and knowledge of the surface anatomy of the respiratory muscles.

Diaphragmatic EMG can be obtained by needle electrodes introduced with reasonable safety through the 10th intercostals space in the mid axillary line. Placement of surface electrodes in the 7th, 8th and 9th intercostals space can also be used to record diaphragm EMG. Esophageal electrodes are used more for research purpose. They provide a more accurate and pure diaphragm EMG. Electromyography is useful in distinguishing neuropathic and myopathic diaphragmatic dysfunction. It may also help in detecting diaphragmatic fatigue.

Respiratory Muscle Endurance

Muscle endurance can be defined as the ability to sustain a specific muscular task over time.[23] Although respiratory muscle strength and endurance appear to be closely linked, there are many conditions where the endurance of the respiratory muscles cannot be predicted by measuring maximum pressures or maximum ventilator capacity. For example, certain respiratory muscle training protocols used in normal individuals and in patients has a greater effect on endurance than on muscle strength.[64,65] Similarly some asthmatic patients show an inherent elevation in endurance properties as a faction of strength.[66] Also, patients with COPD or those on acute steroid treatment show significant reduction in endurance properties relative to strength.[67,68] Therefore, measurement of endurance of the respiratory muscles can have important clinical implications. It may also have an important utility in assessing the efficacy of a rehabilitation program. Unfortunately no uniformly accepted and simple method exists for the estimation of endurance.

Endurance may be measured as ventilator endurance or endurance to an applied load.[23] Traditional approach for evaluating ventilator endurance has been to measure the Maximum Sustainable Ventilation (MSV), i.e. the maximum ventilation that can be maintained for 10–15 minutes. Maximum sustainable ventilation is usually expressed as a fraction of maximal voluntary ventilation (MMV). Normal subjects can achieve a MSV, which is 60% to 80% of MMV.[69] Various techniques have been used to calculate MSV. The maximum effort technique requires the subject to breath at a ventilation of approximately 70% to 90% of their MMV using a visual feedback from either a spirometer or an oscilloscope.[23] Another method that has been used utilizes a 10% incremental increase in target ventilation, every three minutes, beginning at 20% of maximum voluntary ventilation until the subject cannot sustain the target ventilation. MSV is calculated from the last 10 breaths of the last minute of the highest target ventilation. Tests for MSV have been found to be exhaustive and time consuming and are largely impractical.

Various devices have been used to assess endurance against an applied load. Early methods utilized orifice type flow resistance applied to the inspiratory circuit, but these have been replaced by threshold resistive loading devices, which make it possible to more accurately control the pressure the subject inspires against, independent of flow.[23] Inspiratory threshold devices have also been used to test endurance.[23,70,71] Technique involves inspiring through a device that contains a weighted plunger. To initiate inspiration, enough pressure must be generated to lift the plunger out of the socket. Thereafter inspiration remains constant for the entire inspiration.

A negative pressure device and a three-minute incremental protocol has also been described to measure endurance and fatigue.[61,72] The ability to sustain such a breathing effort during an endurance test depends upon the force and the duration of the inspiratory muscle contraction. It has been demonstrated that intense diaphragmatic contractions of brief duration can be sustained for as many breath as could less intense diaphragmatic contractions of brief duration that occupied a larger fraction of breath.[23] Therefore, the Tension Time Index of the Diaphragm (TTIdi) is calculated to predict fatigue and is a better marker than either contractile force or duration of contraction. TTIdi is the product of the contractile force and duration and contraction. Force is expressed as Pdi breath/Pdi maximum. The duration of contraction is the inspiration duty cycle (this is TI/TTOT, i.e. the duration of inspiration divided by the duration of a complete breath). It has been shown that the human diaphragm becomes fatigued when the TTI di exceeds 0.15.

CONCLUSION

Respiratory muscles are essential for life. Their assessment and early detection of weakness becomes important. The diaphragm, which is the main muscle of respiration, is unique that it can be assessed by the volume displaced (spirometry), pressure generated (muscle strength) and by the Electrical Activity of the Muscle (EMG). Many different tests have therefore been used to assess diaphragm function. Tests for diaphragmatic endurance and fatigue are also used. Besides respiratory diseases, many systemic illnesses and disorders cause weakness of the respiratory muscles and their assessment becomes important in these diseases.[14,16,68,73,74] It is therefore important to know when to suspect respiratory muscle weakness in a given patient and how best to test for such weakness.

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27

Respiratory Disability and Preoperative Evaluation

Gyanendra Agrawal, D Gupta

INTRODUCTION

Both disability assessment and preoperative evaluation focus on the accurate assessment of the functional state of the respiratory system. The initial part of this chapter is intended to provide a framework for the evaluation of impairment and disability caused by respiratory diseases, including common occupational and environmental respiratory diseases. The later part focuses on a comprehensive clinical assessment and appropriate standardized tests, to objectively assess the risks and the outcomes of patients with lung disease undergoing specific surgeries.

EVALUATION OF RESPIRATORY DISABILITY

The ability of an individual to take part in the gainful employment and activities of daily living are profoundly affected by the respiratory impairment. The common reasons for the evaluation of impairment/disability are to assess fitness for a particular job, to decide compensation on a litigation following a workplace injury, and to assess the eligibility for government entitlement programs in certain countries.

Evaluating physicians generally fit into two categories such as treating (personal) physician and Independent Medical Examiner (IME). Treating physicians know better about health of their patients, however, they may be biased. IME, generally appointed by the referring agency, is supposed to provide an unbiased objective evaluation. Evaluation of impairment/disability is a multistep process in which the physician assesses impairment, the award of benefits is decided at an administrative level. Although the physician's input is important, the patient must understand that the physician does not have control over the acceptance of claims or level of benefits awarded.

Impairment, Disability and Handicap

Impairment is defined as "a loss, loss of use, or derangement of any body part, organ system or organ function." This is purely a medical condition that objectively measures any loss or abnormality of psychological, physiological, or anatomical structure or function.[1,2]

Disability is a term that indicates the total effect of impairment on a patient's life. It is affected by diverse factors such as age, gender, education, economic and social environment and energy requirements of occupation. Thus, two people with an identical impairment may have different disability.[1,2]

Handicap is "the disadvantage for a given individual, resulting from impairment or disability, which limits or prevents fulfilment of a role that is normal (depending upon age, sex, and social and cultural factors) for that individual."

CLINICAL METHODS OF EVALUATING IMPAIRMENT

Accurate assessment of respiratory impairment requires a medical diagnostic evaluation. Decreased lung functions may result totally or in part from nonrespiratory diseases either directly (e.g. neuromuscular diseases, arthritis of the spine) or indirectly (e.g. congestive cardiac failure). Moreover, the accurate diagnosis and staging of the disease is the basis for sound prognosis and medical prescriptions, which later may bear importantly on the determinations of disability and impairment. The evaluation of respiratory diseases must include a chest radiograph, in addition to indicated laboratory tests.[2]

History

The most common symptoms that lead to pulmonary disability evaluation are dyspnea, cough and wheezing. Dyspnea or shortness of breath is a distressing sensation of difficult, labored or unpleasant breathing. Dyspnea is entirely subjective and fairly sensitive, but not specific, symptom. In all patients, an attempt should be made to rate the severity of the patient's dyspnea by the means of a scale or classification scheme, such as that suggested by the Medical Research Council (MRC).[3] In the context of disability evaluation only the chronic forms of cough (i.e. lasting for more than four weeks) and sputum production are relevant. It is difficult to quantitate the severity of cough and therefore, it is not easy to integrate them into a system of progressive gradation of disability. A history of wheezing may provide important clues during disability evaluation. The temporal correlation of the onset of wheezing, as well as its association with the workplace (or with particular exposures), may help to identify a specific cause of impairment. Wheezing that occurs primarily on workdays and improves during weekends or during vacations is highly suggestive of work-related asthma.

A comprehensive medical history, including the documentation of hospitalizations, allergies and medications, should be obtained, so conditions other than respiratory diseases that contribute to or likely to modify any impairment can be identified. A detailed history of the applicant's employment in chronologic order is required for both attribution and disability evaluation purposes. This history should include even part-time jobs and hobbies. History of exposure to specific respiratory agents at the workplace, like dusts, fumes and vapors should prompt further questioning to clarify the timing, duration and dose of exposure when possible, and the use of respiratory protection. Many work-related abnormalities resemble other diseases and cannot be diagnosed correctly without a validated exposure history. Presence of similar complaints or diseases also in coworkers, is helpful in establishing an occupational etiology.

Inquiries should be made into avocational activities to uncover any potential contributing exposure (e.g. pigeon breeding). An environmental exposure history should include a discussion of potential environmental triggers that include pets in the household, exposures to birds or other organic antigens, such as molds, as well as seasonal or temporal variability of symptoms. Smoking can be the primary cause or a major contributing factor to many respiratory diseases; therefore, a detailed smoking history should be obtained. This includes the age at which the patient started to smoke, estimates of both the average and maximum amount of tobacco smoked per day, whether and when smoking was stopped, as well as second-hand smoke exposure. The cumulative dose of cigarette smoke exposure should be characterized in terms of pack-years (i.e. the number of packages smoked per day multiplied by the number of years of smoking).

Physical Examination

A physical examination that is primarily focused on the cardiopulmonary system should be performed. The patient also should be evaluated for clinical evidence of right heart failure associated with advanced and chronic respiratory disease (cor pulmonale). The physical examination is probably more useful for detecting the signs of nonrespiratory organ system dysfunction that could be contributing to a disability than for characterizing the level of respiratory impairment.

Imaging Studies

The chest radiograph is the most widely used element in the clinical evaluation of patients with respiratory disease. It is more useful in determining the etiologic diagnosis than the level of impairment, because the correlation between radiographic abnormality of the chest and physiologic dysfunction is imperfect, especially among patients with obstructive lung diseases. An asthmatic patient with severe, partially irreversible airflow obstruction may have only minimal abnormality of the chest radiograph. Conversely, patients with a significant amount of bullous emphysema may not have a comparable degree of airflow limitation.[4]

Among patients with pneumoconioses (inorganic dust-related pulmonary interstitial diseases, such as asbestosis, silicosis and coal workers' pneumoconioses), the chest radiographic findings are very important. In fact, the International Labor Organization (ILO) has devised a classification scheme for the standardized interpretation of chest radiographs to objectively characterize and communicate the extent of radiographic abnormalities in the pneumoconioses.[5]

Computed tomography of the chest is a more sensitive tool than plain radiographs in detecting both parenchymal and pleural abnormalities. They offer considerable insight into the precise anatomic changes that accompany a disease state, but offer little to the evaluation of physiologic impairment. However, there are no recommendations at present for CT-screening of populations at risk for occupational interstitial lung disease.

Pulmonary Function Testing

Simple pulmonary function tests like spirometry and diffusing capacity measurements are the most commonly used objective measures of respiratory limitation for disability assessment. The equipments used for these tests are widely accessible and adequate standards for repeatability and reproducibility can be easily met. Both these tests should be performed carefully according to the ATS/ERS guidelines.[6,7] Spirometry can distinguish obstructive from restrictive lung physiology and provide the quantification of the degree of pulmonary dysfunction. On the basis of FVC, FEV_1, and diffusing capacity, classification of degree of respiratory impairment can be made. The diffusing capacity has particular usefulness in the evaluation of restrictive ventilatory defects and is more sensitive than lung volume measurement as a screening tool for patients at risk for pneumoconiosis.[8]

Arterial Blood Gas Analysis

Arterial blood gas studies are rarely used as a criterion of impairment and should be reserved for selected patients. Because of the variability of arterial blood gas measurements even in stable patients, arterial hypoxemia should be documented by a minimum of two measurements, at least four weeks apart. Resting arterial hypoxemia is considered as a "modifying condition" in the ATS statement; for example, in a patient whose spirometry and DL_{CO} results straddle the border between the two categories of impairment, the presence of a low arterial PaO_2 can justify a rating of the higher category of impairment.[2]

Cardiopulmonary Exercise Testing

Majority of the patients being evaluated for respiratory disability do not require exercise testing because there is a good relationship between FEV_1 and DL_{CO} and oxygen consumption and work capacity.[9,10] The physician should consider Cardiopulmonary Exercise Testing (CPET) only when there are grounds for believing that the routine tests have underestimated the impairment. The aim of exercise testing in such cases is to determine first, whether or not the person is significantly impaired, and secondly, whether the cause of impairment is due to respiratory disease or some other cause.[2] Because of the later need, the testing must at a minimum include the measurement of Ventilation (V_E), maximal oxygen consumption (VO_2 max) and anaerobic threshold. The measurement of oxygen consumption during CPET is considered to be the "gold standard" assessment of the subject's ability to perform work[4] (See Chapter 26A for CPET).

Bronchoprovocation Testing

Bronchoprovocation testing is an important method in the assessment of impairment and disability in the cases of occupational asthma, because routine pulmonary function testing performed between attacks may not reveal the abnormality. The presence of bronchial hyperreactivity may have significance in judging ability to continue certain types of employment.

DISEASE-SPECIFIC IMPAIRMENT ASSESSMENT

Asthma

Evaluation of impairment in the setting of asthma is a problematic aspect of disability assessment, since asthma is a disorder characterized by variability over time, with airflow obstruction that may revert toward normal, either spontaneously or as a result of medication administration. On the day of evaluation, patient's lung function may not show an accurate reflection of his usual condition, but may be atypically bad or atypically good.[4] Patients with history that is suggestive of asthma and have normal spirometry in the absence of medication for asthma, may be tested for airway hyperresponsiveness with nonspecific bronchodilator challenge.

Workplace exposures frequently exacerbate an underlying asthmatic condition (work-related asthma) or cause sensitization of the respiratory tract to materials found uniquely in the workplace (occupational asthma). Occupational asthma is the most frequently reported occupational lung disease in the industrialized world. It is important to distinguish immunologic occupational asthma from irritant-induced asthma, where continued work may be possible, if irritant exposures are reasonably controlled. Evaluation of impairment in patients with occupational asthma is almost similar to that for patients with atopic asthma. In addition to the pharmacotherapy, nonpharmacologic interventions must be addressed such as the control of environment triggers, patient and family education.[11]

Pneumoconiosis

A variety of inorganic dust exposure produces pulmonary fibrosis (e.g. asbestosis, silicosis and coal worker's pneumoconiosis) or both granulomatous disease and fibrosis (e.g. beryllium), each with fairly characteristic radiographic appearances. The diagnosis of pneumoconiosis is associated with an increased risk of future impairment, despite normal lung function at the time of testing, because further exposure to the causative agent may increase the risk of progression. Therefore, the recognition of radiologic manifestations of these diseases should prompt removal from mining employment, particularly in relatively young individuals. Such a prohibition is not obviated by showing that current exposure is within legally permissible limits, because such limits are not presumed to provide adequate protection for persons who already manifest the disease.[2]

Hypersensitivity Pneumonitis

With hypersensitivity pneumonitis, continued exposure to the offending agent is likely to lead to either acute attacks or insidious progression of disease, depending on the dose of exposure. Therefore, patients with hypersensitivity pneumonitis should be considered 100% impaired on a permanent basis for any job that involves future exposure to the causative agent.

Obstructive Sleep Apnea

Only some individuals with sleep apnea develop a functional impairment that affects work activity. In severe cases, it can result in the deterioration of daytime cognitive performance, which may interfere with work activities that require constant vigilance like vehicle and machine operators. The development of cor pulmonale indicates 'severe' impairment.[2]

Lung Cancer

Patients with lung cancer are presumed to be severely impaired for at least 1 year following diagnosis, even if surgical resection appears to have been successful in curing the disease.

DISABILITY EVALUATION

Disability evaluation is the determination of the impact of impairment on an individual's ability to meet the demands of his or her own life. Disability evaluation has a broader focus than impairment because factors like the essential requirement of a job, specific tasks, educational level of the individual, individual skills, and potential for retraining must be taken into consideration in determining a specific individual's disability. The American Medical Association (AMA) has developed guidelines for assessing physical impairment that are widely accepted by governments and legal systems as the standard of evaluation for loss of physical function.[12]

Varying percentages of lost function are grouped into four severity classes: Class one constitutes 0% functional loss (for instance, an observable abnormality caused by an anatomic variation); class two indicates that there is objective evidence for a 10% to 25% impairment of the whole person as result of organ dysfunction; class three indicates a 26% to 50% impairment of the whole person; and class four is 51% to 100% impairment of the whole person.

According to the AMA Guides, impairment rating requires that the evaluator first recognize that an abnormality is present, then identify the cause of the abnormality and objectively evaluate the severity of deviation from normal function, and finally, translate the severity of dysfunction into a numerically based classification that estimates how much of an effect the organ dysfunction has on the individual's ability to carry on the activities of daily living. Other steps that may be difficult for the evaluating physician are the work relatedness of the impairment (attribution) and the percentage of the total impairment due to work-related causes (apportionment). Regardless of the evaluating physician's opinions, the final decision concerning the level of disability is made administratively by the responsible agency after the consideration of nonmedical factors.

The evaluation of respiratory disability/impairment is a multistep process. Knowledge of these components of disability evaluation will help physicians to better serve their patients and supply appropriate data to the adjudicating system. Different programs under the social security systems in various countries provide financial and rehabilitative benefits to disabled individuals. However, such programs or specific entitlement systems are lacking in this country. With the introduction of such programs, the community will be better served, ultimately contributing to the growth of nation.

PREOPERATIVE EVALUATION OF RESPIRATORY SYSTEM

Pulmonary physicians are often requested to do the preoperative evaluation of patients by various surgical departments. The goals of this consultation are to estimate the risk of postoperative pulmonary complications, to optimize the patient's condition, and to propose strategies to decrease the postoperative pulmonary complications. The second part of this chapter is an attempt to encompass all aspects of preoperative pulmonary evaluation prior to both thoracic and nonthoracic surgeries. It focuses the approach to risk stratification based on patient- and procedure-related risk factor analysis, detailed preoperative pulmonary evaluation, and strategies to reduce postoperative pulmonary complications.

Pulmonary Physiology in the Postoperative Period

The knowledge of changes in pulmonary physiology is mandatory to understand the mechanisms of various pulmonary complications that occur in the postoperative period, since many postoperative respiratory complications are related to exaggerations of the expected postoperative changes in pulmonary function that occur as a result of the surgery itself, anesthesia, or various pharmacologic interventions.

The pulmonary functions in the postoperative period are characterized by moderate-to-severe reductions in Vital Capacity (VC) and smaller reductions in Functional Residual Capacity (FRC). While the Forced Expiratory Volume in 1 Second (FEV_1) is decreased, the ratio of FEV_1 to the forced vital capacity (FEV_1/FVC %) remains unchanged, indicating that the overall pattern of pulmonary function abnormalities is restrictive. A significant reduction with up to 70% decrease in VC and up to 50% decrease in FEV_1 and FRC is seen, leading to a high risk of atelectasis and hypoxia, especially in the first 24 hours. This severe reduction in lung function is seen more often with thoracic and upper abdominal procedures than with surgery involving the lower abdomen or extremities; and it gradually recovers within three weeks.[13] Reductions in other lung volumes, including Total Lung Capacity (TLC), Inspiratory Capacity (IC), Expiratory Reserve Volume (ERV), and Residual Volume (RV) have also been noted.[14] The proposed mechanisms for the reduction in lung volumes consist of the postsurgical pain and associated muscle splinting, which impair lung mechanics; and the diaphragm dysfunction.

The reduction of FRC is of major physiological significance postoperatively, since the decrease of FRC below the Closing Capacity (CC) leads to the closure of the alveolar units causing atelectasis. FRC is the lung volume at the end of a normal tidal expiration; and CC is the lung volume at which small airways in the lung bases begin to close during expiration because of a reduction in airway radial traction. When CC exceeds FRC, lung volume fails to increase sufficiently during tidal breathing to open all the airways and, consequently, some alveolar units remain closed. This creates an area of low ventilation relative to perfusion, which is the main mechanism of hypoxemia in postoperative patients. Elderly patients, smokers and COPD patients are at higher risk of getting such complications since the closing capacity is increased in these subset of patients.

Diaphragmatic dysfunction is an important factor, which contributes to the postoperative reduction in lung volumes. Postoperative pain, spasm and paralysis are all known to reduce diaphragm function, although relief of pain does not completely restore function. Rather, diaphragmatic dysfunction has been found to persist even with adequate pain relief.[15] Decreased central nervous system output to the phrenic nerves, possibly as a result of inhibitory reflexes arising from sympathetic, vagal or splanchnic receptors is the proposed mechanism of diaphragmatic dysfunction.

Postoperative hypoxemia is a quite common event and prophylactic oxygen therapy is routinely given to all patients undergoing thoracic and upper abdominal surgeries. The underlying mechanisms are multiple and are largely related to the residual effects of the anesthesia. This includes ventilation-perfusion mismatch, alveolar hypoventilation, anesthetic-induced inhibition of hypoxic pulmonary vasoconstriction, right-to-left shunting, and depressed cardiac output. Micro-thromboemboli, altered FRC-CC relationships and increased dead space ventilation due to rapid shallow breathing are other mechanisms contributing to postoperative hypoxemia. Respiratory depression either due to the anesthetic agents or narcotic drugs given for postoperative analgesia is a common feature of the postoperative period. These drugs reduce the ventilatory response to hypercapnia and hypoxia, resulting in decreased tidal volume and thereby increasing $PaCO_2$.

Several lung defense mechanisms are compromised after surgery, contributing to an increased risk of pulmonary infection. Ciliary damage from endotracheal intubation and inhalation of dry gases; and reduced tracheal mucus velocity leads to significantly reduced mucociliary clearance. Ineffective cough reflex due to postoperative pain, excessive use of narcotics or altered lung mechanics contributes to the retention of secretions and atelectasis.

Physiologic Changes After Thoracic Surgery

Resection of pulmonary tissue for various indications leads to a number of physiologic changes. Vital capacity decreases by about 15% after lobectomy and 35% to 40% following pneumonectomy.[16] The decrease in lung function is usually less than expected from the number of segments removed, suggesting that the disease had already decreased the function of the resected lung and/or that expansion of the remaining lung had occurred. Serial studies have shown that FEV_1 decreases within the first several months following lung cancer resection, but tends to recover to a small extent by six months after surgery.[17] The lung becomes stiffer and elastic recoil pressure and transdiaphragmatic pressure at TLC increases after thoracic surgeries. Maximum effort tolerance decreases after pneumonectomy with a normal pulmonary artery pressure at rest and an increase in pulmonary artery pressure and in pulmonary vascular resistance on effort, compared to preoperative values.

Lung Volume Reduction Surgery (LVRS) does not affect the postoperative pulmonary arterial pressure at rest or during exercise.[18] The patients also develop the decrease in arterial oxygen saturation on effort after pneumonectomy, possibly due to the absolute decrease in diffusing capacity. The patients also develop a decrease in oxygen consumption, cardiac output, stroke volume and heart rate at maximum exercise, and they were not able to achieve their preoperative maximal workload.[16] The changes seen after lobectomy are almost similar to the changes seen after pneumonectomy, but the differences are less pronounced.[19]

POSTOPERATIVE PULMONARY COMPLICATIONS

Postoperative pulmonary complications are at least as common as are postoperative cardiac complications and contribute similarly to morbidity, mortality and the length of stay.[20] Pulmonary complications may even be more likely than cardiac complications to predict long-term mortality after surgery.[21] A number of definitions have been proposed for postoperative pulmonary complications. A practical and clinically relevant approach is to include only those complications that contribute directly to morbidity or prolonged length of stay,[22] which will exclude minor complications such as fever and productive cough. Included are the clinically important postoperative pulmonary complications, which are pneumonia, atelectasis, bronchospasm, respiratory failure with prolonged mechanical ventilation, and exacerbation of underlying obstructive lung disease (Table 27.1). The reported incidence of these complications ranges from 5% to 90% depending on the variability of the definitions used. In general, pulmonary complications associated with thoracic surgeries are more common and more severe, as compared to nonthoracic surgeries. The mechanisms of postoperative impairment in lung function are multiple, interactive, and at present, incompletely understood.

TABLE 27.1: Postoperative pulmonary complications

*Nonthoracic Surgery**	*Thoracic Surgery*
Atelectasis	Bronchopleural fistula
Pneumonia and tracheobronchitis	Empyema
Respiratory failure with prolonged MV	Mediastinitis, osteomyelitis of sternum
	Phrenic nerve damage
Exacerbation of COPD	Anastomotic leak during esophagectomy/gastrectomy
Thromboembolism	

*May be associated with thoracic surgeries also.
MV: Mechanical ventilation; COPD: Chronic obstructive pulmonary disease

Risk Factors for Postoperative Pulmonary Complications (Table 27.2)

A number of risk factors have been associated with the development of postoperative pulmonary complications in various studies. In this chapter, patient- and procedure-related risk factors are discussed separately.

Patient-Related Risk Factors

The most important patient-related risk factors are the presence of chronic lung diseases, like Chronic Obstructive Pulmonary Disease (COPD) and asthma, as well as smoking history and the patient's overall state of health. Age and obesity are relatively minor factors; and the precise risks associated with malnutrition and recent viral infections are unknown.

TABLE 27.2: Risk factors for postoperative pulmonary complications*

Patient-Related Risk Factors	*Procedure-Related Risk Factors*
Age >60 years	Surgical site
Smoking	Type of anesthesia
General state of health (ASA class >2)	Duration of surgery (>3 hours)
Nutritional status	Type of incision
Obesity	Emergency/elective surgery
COPD/Asthma/OSA	Immobilization
Abnormal chest radiograph	Inadequate pain control
Antecedent respiratory tract infection	

*Modified from reference 20

1. *Smoking*: Smoking is a risk factor for postoperative pulmonary complications, as has been demonstrated repeatedly since the first report in 1944.[23] Smoking increases risk even among those without chronic lung disease.[24] The available data are mixed, but suggest a modest increase in risk for postoperative pulmonary complications among current smokers, and when the patient is older or has smoked longer. The ill effects of smoking are mainly related to the high level of carboxyhemoglobin in smokers, which usually ranges from 3% to 15%. Carboxyhemoglobin reduces the amount of hemoglobin available to bind with oxygen and shift the oxygen-hemoglobin saturation curve to the left, which facilitates the loading of oxygen onto hemoglobin, but impairs unloading at the tissues. Nicotine can cause systemic vasoconstriction and increase both the heart rate and the systemic blood pressure. A statistically significant reduction in complications occurs only when patients discontinue smoking for at least eight weeks prior to the surgery.[25]
2. *Chronic lung disease*: Among studies reporting multivariable analyses, chronic obstructive pulmonary disease is the most commonly identified risk factor for postoperative pulmonary complications. While one may consider patients with restrictive lung diseases with severe limitations to have an increased risk for postoperative pulmonary complications, the literature did not support an estimate of the magnitude of this risk in this group.[21]

   Chronic obstructive pulmonary disease: COPD is the single most important patient-related risk factor for the development of postoperative pulmonary complications. The relative risk of pulmonary complications attributable to COPD is three to four folds.[22] Physicians should aggressively treat patients with COPD who, before surgery, do not have optimal reduction of symptoms and airflow obstruction on physical examination and who do not have optimal exercise capacity. Elective surgery should be deferred if acute exacerbation is present. The treatment and preparation of patients who have COPD before elective surgery are the same as those in nonoperative settings.

   The increased incidence of postoperative pulmonary complications in patients with COPD is due, in part, to an increase in the CC, favoring the development of the areas of low ventilation-to-perfusion ratios and atelectasis. In addition, in patients who continue to smoke, impaired ciliary function and chronic tracheobronchitis may be contributing factors. Although not precisely quantified in the literature, the risk for postoperative respiratory complications appears to increase significantly (greater than 50%) when the FEV_1 is below 65% of predicted. The risk is also increased in patients who are hypercapnic. However, patients with an FEV_1 as low as 450 ml have tolerated surgery safely. Therefore, the potential benefits of the operative procedure must be weighed against the operative risk in every individual patient.

   Asthma: Patients with acute bronchospasm are probably at increased risk for perioperative complications, since several maneuvers associated with anesthesia may aggravate bronchospasm.[26] However, the same is not true for patients with stable asthma.[21,22] Before surgery, patients should be free of wheezing, with a peak flow greater than 80% of the predicted or personal best value. If necessary, the patient should receive oral corticosteroids to achieve this goal. A short course of perioperative corticosteroids does not increase the incidence of infection.

   Obstructive sleep apnea (OSA): OSA increases the risk for airway management difficulties in the immediate postoperative period. In one case-control study, nonsignificant trends were seen toward the higher rates of reintubation, hypercapnia and hypoxemia for patients with OSA.[27] Pulmonary hypertension is particularly associated with a significant perioperative risk. As cardiovascular dysfunction in OSA patients can be modified by treatment, it is important to identify patients not known to have OSA and have them treated to improve their perioperative outcomes, as well as to improve their general health.

   Restrictive lung diseases: While some experience has been reported with patients undergoing thoracic and corrective orthopedic surgery, very little data exist with regard to abdominal and extremity surgery. Postoperative respiratory complications after corrective surgery in patients with kyphoscoliosis, have been reported in up to 20% of these patients, with pleural space-related processes (e.g. pneumothorax, pleural effusion, bronchopleural fistula and empyema) among the most common. Video-Assisted Thoracoscopic (VAT) approaches have emerged as good alternatives to open thoracotomy in such patients.
3. *Age*: Previous reviews have suggested that age is not a predictor of postoperative pulmonary complications and they are more strongly related to coexisting conditions than to chronologic age.[22] However, a recent review found that the risk of pulmonary complications increases with the advancing age.[21]

These findings appear to hold true when lung tissue is resected. There have been many reports detailing the outcomes of lung resection in the elderly. The general concerns raised by the literature are that the operative mortality is greater in the elderly, operative risks for pneumonectomy are relatively high, and complications may be increased. Despite the study trends, the sum of the evidence suggests that surgery should not be withheld on the basis of age alone.[28]

4. *General health status:* Several integrated measures of comorbidity have been evaluated as the potential predictors of postoperative pulmonary complications. The widely used American Society of Anesthesiologists (ASA) classification, which was developed to evaluate the risk of overall perioperative mortality, is strongly predictive of postoperative pulmonary complications.[29] In addition, the Goldman cardiac-risk index, which includes factors from the patient's history, the physical examination, and laboratory data, also predicts pulmonary complications.[30]
5. *Obesity*: Despite the changes that occur in pulmonary mechanics and pulmonary functions in obese individuals, studies evaluating clinically meaningful pulmonary complications after surgery have generally found no increased risk attributable to obesity, even for patients with morbid obesity. Obesity is, however, clearly a risk factor for obstructive sleep apnea syndrome, which may be unmasked or exacerbated because of the use of postoperative analgesics or narcotics.[21]
6. *Others*: The risk of postoperative pulmonary complications in patients with viral upper respiratory infections is unknown. It is reasonable to delay truly elective surgery in patients with upper respiratory infection. Although patients with compromised nutritional status are at higher risk for developing postoperative pulmonary complications, aggressive preoperative nutritional support has not been shown to decrease postsurgical pulmonary morbidity.

Procedure-Related Risk Factors

Procedure-related risk factors are as important as patient-related factors in estimating risk for postoperative pulmonary complications. The surgical site is the most important predictor of pulmonary risk. Risk increases as the incision approaches the diaphragm; therefore, upper abdominal and thoracic surgery carries the greatest risk of postoperative pulmonary complications. Studies using multivariable analyses have found that prolonged surgery duration, ranging from three to four hours, is an independent predictor of postoperative pulmonary complications. The contribution of risk from the type of anesthesia itself has been controversial. Many have reported a lower risk of pulmonary complications among patients receiving spinal or epidural anesthesia than among those receiving general anesthesia, but the results have been inconsistent and the effect small.

Except for the reduced risk of postoperative thromboembolism, there is no clear evidence in the current literature that regional anesthesia results in better intraoperative or postoperative pulmonary function.[31,32] Emergency surgery has been identified as a significant predictor of postoperative pulmonary complications. Abdominal laparoscopic procedures and thoracoscopic lung resection are associated with less postoperative respiratory problems, as compared to open procedures because of reduced patient discomfort, shortened length of hospitalization and faster patient return to full activity. Prolonged bed rest and inactivity following surgery is a major risk factor for deep venous thrombosis and pulmonary embolism.

PREOPERATIVE EVALUATION

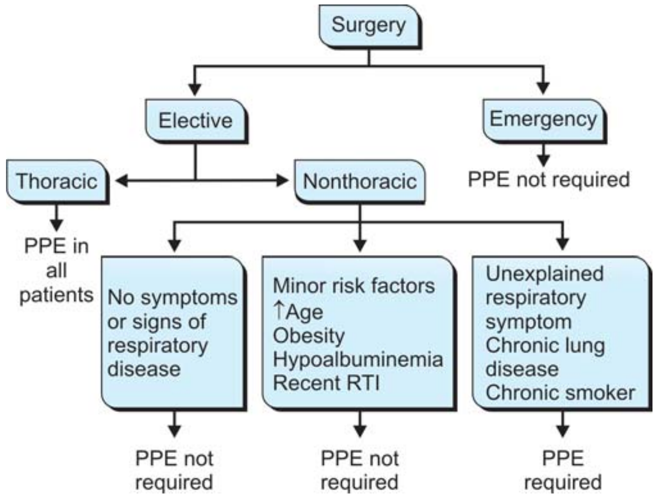
This section of the chapter is intended to provide an evidence-based approach to the preoperative physiologic assessment of a patient undergoing either thoracic or nonthoracic surgery. After discussing the initial evaluation, which is to be done in all the patients, the pulmonary specific evaluation is discussed. The task of the preoperative physiologic assessment is to identify patients who are at increased risk for both perioperative complications and long-term disability from surgical resection of lung tissue using the least invasive tests possible.

A. Initial Evaluation

Initial preoperative pulmonary evaluation is required in almost all elective surgeries. In case of emergency, the surgery should not be delayed for the cause of pulmonary evaluation unless the likelihood of perioperative mortality or postoperative complication is so high that the surgery should not be performed (Fig. 27.1). The principal components of preoperative evaluation of the surgical patient are: (1) the history and physical examination, (2) the chest radiograph, (3) spirometry, and (4) arterial blood-gas analysis.

History and Physical Examination

A careful history taking and physical examination are the most important parts of preoperative pulmonary risk



PPE: Preoperative pulmonary evaluation; RTI: Respiratory tract infection

Fig. 27.1: Suggested approach for preoperative evaluation (See text for details)

assessment. One should seek a history of respiratory symptoms (like chronic cough, dyspnea and chest pain) including symptoms of sleep apnea. History should also include the patient's functional capacity and the degree of the limitation of activity. Smoking history should be taken in detail and all patients should be encouraged to quit smoking. If there is history of recent respiratory tract infection, it is advisable to delay the surgery till it gets cured.

The physical examination may identify the findings suggestive of unrecognized pulmonary disease. Among such findings, decreased breath sounds, dullness to percussion, wheezes, rhonchi, and a prolonged expiratory phase predict an increase in the risk of pulmonary complications. It should include an evaluation for signs of metastatic spread (e.g. lymph node enlargement, hepatomegaly or focal neurologic deficits) and the presence of cardiac failure and pulmonary hypertension.

Chest Radiograph

The current evidence suggests that this test only rarely provides unexpected information that influences preoperative management and clinicians may predict most abnormal preoperative chest radiographs by history and physical examination. Thus, a preoperative chest radiograph is indicated when there are new or unexplained symptoms or signs, when there is a history of underlying lung disease and no recent chest radiograph, or when thoracic surgery is planned.

Spirometry

Spirometry is a simple, inexpensive, standardized, and readily available test, which is used to diagnose the obstructive and restrictive lung diseases. But it does not translate into effective risk prediction for individual patients. There is a consensus that all candidates for lung resection and coronary artery bypass should undergo preoperative spirometry; its value before extrathoracic surgery, however, remains unproven. Moreover, the data do not suggest a prohibitive spirometric threshold below which the risks of surgery are unacceptable. So, preoperative spirometry is reserved for patients undergoing thoracic surgery, or patients having unexplained chest symptoms especially those suggestive of COPD, or history of cigarette smoking.

Arterial Blood Gas (ABG) Analysis

A partial pressure of arterial carbon dioxide ($PaCO_2$) greater than 45 mm Hg is identified as a strong risk factor for pulmonary complications, based on several case series, as it usually indicates chronic respiratory failure.[33,34] Hypercapnia has been a relative contraindication to lung resection.[35] So, it is recommended that the arterial blood gas analysis should be done in the patients of chronic lung disease, or who have a significant pulmonary process and patients undergoing lung resection. The routine use of ABG is not recommended in all patients.

B. Pulmonary-Specific Evaluation

Pulmonary-specific evaluation is required in all patients undergoing lung resection surgeries. The two main aims of pulmonary specific evaluation are to assess the perioperative mortality and morbidity to tolerate the surgical procedure; and, to assess the postoperative pulmonary function to allow reasonable quality of life. A number of physiologic tests exist for this purpose, although, there is no single test that is a "gold standard" in accurately predicting complications. This part of preoperative evaluation is divided into the three stages of tests, which are performed in a sequential manner, that help to risk-stratify the patients prior to the planned surgery.

Stage I

The first stage consists of tests to assess the overall functions of both the lungs.

1. *Spirometry:* Of all the indices assessed by spirometry, FEV_1 is regarded as being the best for predicting the

complications of lung resection in the initial assessment, and it is the one most commonly used for decision making. The FEV_1 helps to predict those at risk for postoperative complications, including death. Little evidence exists to utilize one cutoff absolute value of FEV_1 to permit resection of varying extent. Preoperative values of 2 L for pneumonectomy and 1.5 L for lobectomy have been suggested. The risk of postoperative respiratory complications also increases significantly when the FVC or Maximal Voluntary Ventilation (MVV) is less than 50% predicted.

2. *Diffusion capacity*: Diffusing capacity of the lung for carbon monoxide (DL_{CO}) reflects alveolar membrane integrity and pulmonary capillary blood flow in the patient's lungs. A retrospective study found DL_{CO} as most important predictor of mortality and was the sole predictor of postoperative pulmonary complications.[36] Absolute cut-offs are not clearly established in the literature. However, individuals with a preoperative DL_{CO} less than 60% predicted were found to have more frequent respiratory complications, hospitalizations for respiratory compromise, and worse median dyspnea scores than individuals with preoperative DL_{CO} more than 60% predicted.[37] Predicted Postoperative (PPO) DL_{CO} has been found to be an independent predictor of pulmonary complications, morbidity, and death in other studies.[38,39] A combined value, the Predicted Postoperative Product (PPP), was found to be the best predictor of surgical mortality in one study. The PPP is the product of the PPO FEV_1 and PPO DL_{CO}. A PPP greater than 1650 was found in 75% of those who died and 11% of those who survived surgery.[40]

Stage II

The next stage consists of tests that measure differential lung function and estimate the PPO lung function. There are three techniques to predict the postoperative values—segment method, radionuclide scanning technique and quantitative computed tomography.

1. *Segment method*: The simplest methods to predict postoperative pulmonary function involve calculating the portion of all bronchopulmonary segments that will remain after resection. The postoperative lung function should be approximated by the preoperative value multiplied by this portion. The conventional method is to use 19 total segments as the starting value (10 on the right and 9 on the left).

$$\text{PPO } FEV_1 = \text{Preoperative } FEV_1 \times (1 - x/19)$$

where x is the number of lung segments to be removed.

The other method is to use the number of subsegments, corrected for those that were obstructed preoperatively. A regression equation relating the predicted and measured lung function was developed from this method (measured = 0.85 predicted + 0.286 +/– 0.296, r = 0.821).[41] A predicted postoperative FEV_1 of 800 ml has been used as a cutoff for withholding resectional lung surgery, based on the clinical impression that below 800 ml many patients are disabled and develop carbon dioxide retention.

2. *Quantitative ventilation-perfusion scan*: Ventilation lung scans (using inhaled ^{133}Xe) and perfusion lung scans (using ^{99}Tc macroaggregates) are equally accurate in calculating the PPO FEV_1, although perfusion scanning is more commonly used because it is technically easier to perform. The general principle of this technique is same as for the segment methods.

$$\text{PPO } FEV_1 \text{ postlobectomy} = \text{Preoperative } FEV_1 \times (1 - y/z)$$

where y is the number of functional or unobstructed lung segments to be removed, and z is the total number of functional segments.[17]

$$\text{PPO } FEV_1 \text{ postpneumonectomy} = \text{Preoperative } FEV_1 \times (\text{\% of function of affected lung})$$

Normally, the right lung contributes 55% of lung function, while the left lung contributes 45% of lung function. The PPO and %PPO DL_{CO} after lung resection can be calculated using the same formula. Using this method, the r-value for correlation between predicted and actual postoperative FEV_1 has been as high as 0.88.[42,43] That for DL_{CO} has been as low as 0.68.[43] The anatomic method can also be applied to segmentectomies because lobectomy does not cause a significantly greater loss of function when compared to segmentectomy.[17]

3. *Quantitative computed tomography*: In this technique, the volume of lung with attenuation between –500 and –910 Hounsfield units is used to estimate functional lung volume. By calculating the lung volume in the area to be resected as a portion of total lung volume and using the principles stated above, the predicted postoperative pulmonary function may be estimated. However, this technique is not widely used despite the evidence of it being better than radionuclide quantitative perfusion imaging.[44]

The PPO FEV_1 can also be calculated without performing a split lung function test. According to Juhl and Frost formula,[45,46]

$$\text{PPO FEV}_1 = \text{Preoperative FEV}_1 \times \{1 - (S \times 5.26)/100\}$$

where S is the number of bronchopulmonary segments involved.

Other tests assessing differential lung function include bronchospirometry (the measurement of oxygen uptake in each lung, individually), lateral position testing, and total unilateral pulmonary artery occlusion. These tests are no longer performed in the preoperative evaluation as they are invasive; require specialized equipment, a high level of technical expertise and concerns over the reproducibility of results.[35]

Stage III

The third stage comprises of exercise testing that provide the confirmatory evidence of operability.

Exercise testing: Exercise testing has been used to determine whether individuals with unacceptable lung function by other measures might be able to tolerate resection. Formal testing such as symptom-limited cycle ergometry and simpler tests, including exercise oximetry, stair climbing and shuttle walking, have been studied. Cycle ergometry with incremental workloads, which measures VO_2, VO_2 max, minute ventilation, and carbon dioxide output with concomitant monitoring of ECG, BP, oximetry, while the patient exercises to the maximal end point or to the symptom-limited maximum, is probably the best form of exercise testing.

Exercise testing could be fixed exercise challenge, in which a sustained level of work is performed; and incremental exercise testing, in which the work rate is sequentially increased to a desired end point. Exercise capacity, measured as the VO_2 max during Cardiopulmonary Exercise Testing (CPET), has been shown to be a predictor of postoperative complications, including postoperative and long-term mortality.[47-54] A VO_2 max less than 15 to 20 ml/kg/min is associated with an increased incidence of postoperative complications.

Other simpler tests can be used in situations where a complete CPET is not possible. In one study, a 4% or greater desaturation during exercise oximetry performed better than FEV_1 and DL_{CO} in predicting postoperative pulmonary complications, including death and respiratory failure.[55] Stair-climbing test and six-minute walk tests are other technologically simpler tests that have been used to estimate the risk from lung resection. The significant risk of postoperative pulmonary complications has been demonstrated in patients who are unable to climb two flights (where one flight is the equivalent of 12 steps). Patients who are unable to complete a six-minute walk of more than 500 feet are unacceptable candidates for lung resection. The distance obtained during a shuttle walk test, a type of incremental exercise test, where an individual walks back and forth over a defined distance at an incremental and progressive rate has correlated well with VO_2 max obtained on a treadmill. Walking 25 shuttles (10 m each) approximated a VO_2 max of 10 mL/kg/min.[56]

RECOMMENDED APPROACH

Preoperative pulmonary evaluation for lung resection should be done by a multidisciplinary team. And no patient should be denied surgery on the basis of age alone. Operability for pneumonectomy is determined in the event that this procedure should become necessary, either to remove the tumor completely or because of an intraoperative complication. Patients with post-bronchodilator FEV_1 (PostBD FEV_1) more than 2 L (or more than 80% predicted normal) and more than 1.5 L are suitable for pneumonectomy and lobectomy respectively without further evaluation, unless there is the evidence of interstitial lung disease or undue dyspnea on exertion. In that case the DL_{CO} should be measured. DL_{CO} should also be measured, if the preoperative FEV_1 is less than these values. The patient is cleared for pneumonectomy and lobectomy, if the DL_{CO} is more than 80% and 60 to 80% predicted normal respectively.

If an individual is not clearly operable after initial testing (DL_{CO} less than 60% predicted normal), then PPO lung function should be estimated. If the PPO FEV_1 and PPO DL_{CO} is less than 30% predicted normal or the product of the PPO FEV_1 and PPO DL_{CO} is less than 1650, then there is a very high risk of perioperative death and cardiopulmonary complications. In such cases, surgery should be avoided. The patient can undergo lobectomy and possibly pneumonectomy, if the PPO FEV_1 and PPO DL_{CO} is more than 40% predicted. The patient is considered borderline, if this number is between 30% and 40% of the predicted value. In borderline patient, if confirmatory evidence of operability is required, an exercise test should be performed. If the VO_2 max is less than 15 mL/kg/min with both PPO FEV_1 and PPO DL_{CO} less than 40% predicted, then the individual is at very high risk for perioperative death and cardiopulmonary complications. The patient is cleared for lobectomy and possibly pneumonectomy if the VO_2 max is more than 20 mL/kg/min. The borderline patients are at high risk for surgery and it is recommended that these patients be counseled about nonoperative treatment options for their disease (Fig. 27.2). Individuals with very poor lung

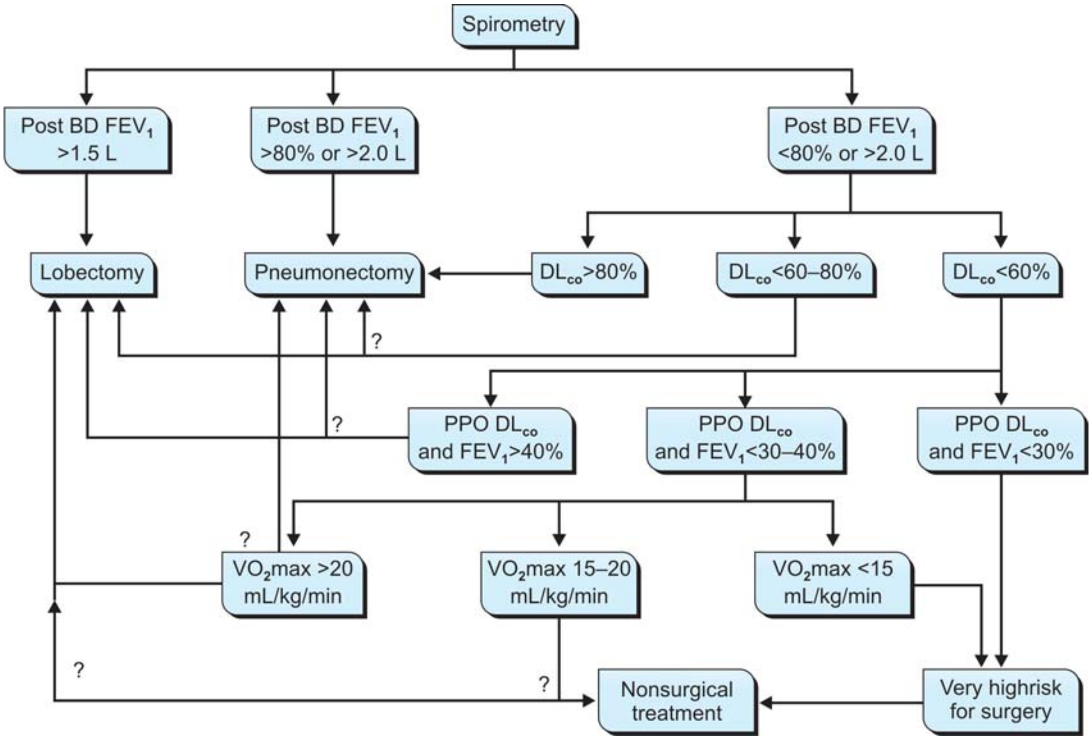

Spirometry
Post BD FEV₁ >1.5 L
Post BD FEV₁ >80% or >2.0 L
Post BD FEV₁ <80% or >2.0 L
Lobectomy
Pneumonectomy
DLco>80%
DLco<60–80%
DLco<60%
?
PPO DLco and FEV₁>40%
PPO DLco and FEV₁<30–40%
PPO DLco and FEV₁<30%
VO₂max >20 mL/kg/min
VO₂max 15–20 mL/kg/min
VO₂max <15 mL/kg/min
Nonsurgical treatment
Very highrisk for surgery

Fig. 27.2: Recommended approach of evaluation for lung resection. See text for details (*Courtesy:* Dr Navneet Singh)

function may be considered for combined Lung Volume Reduction Surgery (LVRS) and lung cancer resection, if the emphysema is heterogeneous and involves primarily the lobe to be resected, provided both the FEV_1 and the DL_{CO} are more than 20% predicted.[17,28,57]

OPTIMIZING THE CHANCE OF A SUCCESSFUL OUTCOME

Preoperative and intraoperative strategies to reduce the risk of pulmonary complications follow logically from the established risk factors. There has been little rigorous research on how one might increase the chance of a successful outcome in the lung resection candidate. Areas that have been considered include smoking cessation, pulmonary rehabilitation, and the immediate postoperative care regimen includes the use of bronchodilators, corticosteroids and antibiotics (Table 27.3).

Current and former smoking has been shown to be a risk factor for postoperative pulmonary complications, and an optimal period of abstinence prior to surgery is

TABLE 27.3: Risk reduction strategies*

Preoperative

Smoking cessation (ideally, a minimum of 8 weeks prior to surgery)
Optimize treatment of COPD/asthma/OSA
Antibiotics for respiratory tract infection
Pulmonary rehabilitation
Weight reduction for severely obese individuals
Lung expansion maneuvers

Intraoperative

Limit duration of surgery to <3 hours
Regional anesthesia
Minimal invasive or laparoscopic surgery

Postoperative

Early patient mobilization and ambulation
Lung expansion maneuvers (incentive spirometry, deep-breathing exercises)
Adequate analgesia (epidural/ intercostal nerve blocks)
Thromboprophylaxis

*Modified from reference 22

associated with fewer pulmonary complications, better wound healing, and shorter length of stay in the ICU.[58] Accordingly, the preoperative evaluation of smokers should include enrolling them in smoking cessation programs or, at a minimum, provide a time when a serious discussion can occur regarding smoking. At least 12 to 24 hours of preoperative abstinence should be sought to achieve possible cardiovascular benefits and optimally six to eight weeks of preoperative abstinence to decrease the incidence of postoperative respiratory complications. Pulmonary rehabilitation programs have been shown to improve outcomes and decrease the postoperative pulmonary complications in different studies, whether used before or after the surgery.[59,60] There is no direct evidence to support an additional role for bronchodilators and antibiotics in the lung resection candidate beyond what would be considered the standard use for COPD or asthma.

Intraoperative strategies involve collaboration with anesthesia and surgery colleagues. These strategies include selecting a lower risk or briefer (less than 3 hours) procedure for high-risk patients with few opportunities for risk reduction, recommending laparoscopic rather than open surgeries when possible, using spinal or epidural anesthesia in the lieu of general anesthesia, and avoiding pancuronium.[20]

Lung-expansion maneuvers lower the risk of atelectasis by increasing lung volume. Deep breathing exercises, incentive spirometry and intermittent positive pressure breathing have been studied most extensively. However, there is no evidence to support a significant difference between any of the three modalities.[61] Preoperative education in lung expansion maneuvers reduces pulmonary complications to a greater degree than instruction that begins after surgery.[62] The advantage of postoperative Continuous Positive Airway Pressure (CPAP) and Bilevel Positive Airway Pressure (BiPAP) is that, it is not dependent on the patient's effort.[63] It is costly, however, and requires more intensive involvement by hospital personnel than other methods. Because less costly lung-expansion maneuvers are available, physicians should not use CPAP or BiPAP for the primary prevention of complications.

Conventionally, parenteral narcotics have been used for postoperative analgesia. However, concerns over adverse respiratory effects may lead to inadequate dosing and inadequate pain relief. Alternative approaches like patient-controlled analgesia, epidural analgesia and intercostals nerve blocks have been used to overcome this issue. These pain control strategies reduce splinting and promote the ability to take deep breaths after thoracic, aortic and upper abdominal surgeries. While pain control is improved when compared with systemic opioids, studies of their ability to reduce postoperative pulmonary complications have shown conflicting results.

Prophylaxis for thromboembolism constitutes a key management issue in all patients. Finally, careful monitoring for postoperative complications constitutes a key element in all surgical patients. Other perioperative interventions like total parenteral nutrition, pulmonary artery catheterization,[21] chest physiotherapy in the absence of excessive secretions or sputum production, and routine application of positive end-expiratory pressure in mechanically ventilated patients have been shown to be ineffective.

CONCLUSION

The goal of preoperative evaluation of the patient being considered for surgery is to identify everyone who has an acceptable chance of tolerating that procedure, while guiding those found to have the greatest likelihood of major complications about the options that exist. The evaluation of candidates for thoracic surgery differs substantially from the evaluation before general surgery. By using the above described tests and recommendations, the best option for cure to many patients can be provided.

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28

Arterial Blood Gases and Acid Base Balance

Vinaya S Karkhanis, Jyotsna M Joshi

INTRODUCTION

Arterial Blood Gas (ABG) analysis is the sampling of blood from an artery for the determination of Oxygen (O_2), Carbon Dioxide (CO_2) and acid content. ABG represents the "ultimate" test[1] in clinical practice in the evaluation of severity and causes of:

- Lung gas exchange abnormalities using Arterial Oxygen Tension (PaO_2) and Arterial Carbon Dioxide Tension ($PaCO_2$)
- Acid-base disturbances using pH, $PaCO_2$ and Serum Bicarbonate (HCO_3).

PHYSIOLOGY OF GAS EXCHANGE

The primary function of the respiratory system is to provide oxygen to the cells at a rate adequate to satisfy their metabolic needs by the uptake of O_2 and discharge of CO_2. Inhaled oxygen enters the lungs and reaches the alveoli. Oxygen passes quickly through this air-blood barrier into the blood in the capillaries while carbon dioxide passes from the blood into the alveoli and is then exhaled (Fig. 28.1). Three processes essential for this exchange are ventilation, diffusion and perfusion. Abnormalities of any of these functions result in inadequate gas exchange indicated by low PaO_2 with or without elevated $PaCO_2$.[2,3]

Gas diffuses from alveoli to the blood in the pulmonary capillaries or vice versa across the thin alveolar-capillary membrane made up of the pulmonary epithelium, the capillary endothelium and their fused basement membranes. The diffusing capacity of the lung for a given gas is directly proportionate to the surface area of the alveolar-capillary membrane and inversely proportionate to its thickness.

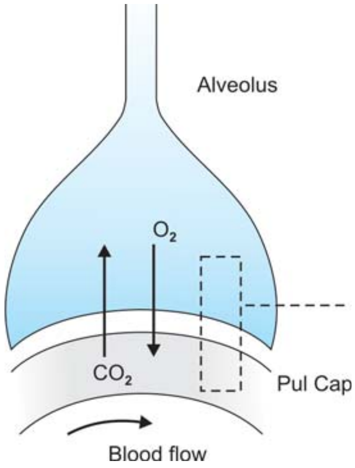


Fig. 28.1: Alveolar gas exchange unit

O_2 diffusion depends on the following:[4]

- Alveolar ventilation/capillary perfusion ratio, which establishes the partial pressure gradient of O_2 between alveolus and plasma
- Physical characteristics of the alveolar-capillary interface
- Capillary blood volume available for gas exchange
- Hemoglobin concentration
- Reaction rate between O_2 and hemoglobin.

Ventilation-Perfusion Relationship[5]

Ventilation and perfusion are normally matched in the lungs so that gas exchange (ventilation) nearly matches pulmonary arterial blood flow (perfusion). The concentration of Oxygen (PO_2) in any lung unit is measured by the relation of ventilation to blood flow and presented as Ventilation/Perfusion Ratio ($\dot{V}/\dot{Q}$). Ventilation-perfusion mismatch results in abnormal gas exchange. Shunt and dead space are terms used to describe extreme conditions where either blood flow or ventilation does not meet the other in the lung as it should for gas exchange to take place.

Diffusion and $\dot{V}/\dot{Q}$ abnormalities result in alveolar (A)-arterial (a) PO_2 difference. PAO_2 can be calculated using the equation:

$PAO_2 = FIO_2\ (Patm - PH_2O) - (PaCO_2/R)$

At sea level, $FIO_2 = .21$, $PH_2O = 47$, P breath = 760, $PaCO_2$ measured by lab analysis, R = 0.8

$PAO_2 = (150 - PaCO_2/0.8)$

$P\ (A\text{-}a)\ O_2 = (150 - PaCO_2/0.8) - PaO_2$

PaO_2 is measured by lab analysis.

Normal P (A-a) O_2 gradient = 10, increasing by 4–6 per decade over 50.

Alterations in Gas Exchange

The mechanisms of abnormal gas exchange and their characteristic features are as follows:

1. Reduced fraction of inspired O_2-Fi O_2 (e.g. high altitudes)
   - Low PaO_2 that improves by O_2 administration
   - PAO_2-PaO_2 is normal
   - $PaCO_2$ is normal.
2. Hypoventilation
   (Reduced ventilatory drive, e.g. obesity hypoventilation syndrome) or reduced effective alveolar ventilation, e.g. end stage lung disease)
   - Low PaO_2 that improves by O_2 administration
   - PAO_2-PaO_2 is normal in central hypoventilation and increased in alveolar hypoventilation
   - Increase in $PaCO_2$.
3. Diffusion defect [e.g. Interstitial Lung Diseases (ILDs)]
   - Low PaO_2 that improves by O_2 administration
   - PAO_2-PaO_2 increased
   - $PaCO_2$ is normal.
4. Ventilation-perfusion ($\dot{V}/\dot{Q}$) imbalance (e.g. emphysema)
   - Low PaO_2 that improves by O_2 administration
   - PAO_2-PaO_2 is increased
   - $PaCO_2$ normal.
5. Shunt effect [e.g. Adult Respiratory Distress Syndrome (ARDS)]
   - Low PaO_2 that does not improve after O_2 administration (refractory hypoxaemia)
   - PAO_2-PaO_2 is increased
   - $PaCO_2$ is normal.

PHYSIOLOGY OF ACID BASE BALANCE

Acids and Bases

An acid is defined as any compound, which forms hydrogen ions in solution. For this reason, acids are sometimes referred to as "proton donors." A base is a compound that combines with hydrogen ions in solution. Therefore, bases can be referred to as "proton acceptors." Both acids and bases are related to the concentration of hydrogen ions present. Acids increase the concentration of hydrogen ions, while bases decrease the concentration of hydrogen ions. The acidity or basicity of something therefore, can be measured by its hydrogen ion concentration. In 1909, the Danish biochemist SP Sorensen[6] invented the pH scale for measuring acidity. The body's balance between acidity and alkalinity is referred to as acid-base balance and is indicated on the pH scale.

pH

The pH, which is an abbreviation for "pouvoir hydrogene" or "power of hydrogen," is a measuring unit of acidity and alkalinity of a solution. The pH is calculated by the Sorensen formula as the negative logarithm of the hydrogen ion concentration, i.e.

$pH = -\log10[H^+]$ where $[H^+]$ is the hydrogen ion concentration.

At rest, the normal blood pH of a human being is slightly alkaline, with a pH around 7.4 (7.35–7.45) on the pH scale. Anything above that value is considered alkaline; anything below is described as acidic. Both, in their extremes (below 6.8 or above 7.8) are not compatible with life.

The Henderson-Hasselbalch equation[7] describes the correlation of metabolic and respiratory regulations, which maintain pH.

$pH = 6.1 = \log HCO_3/0.3 \times PaCO_2 = pK+$ kidney/lung where, pK is the negative logarithm of the dissociation constant.

Kassirer and Bliech[8] have rearranged the Henderson equation that relates H^+ (instead of pH) to PCO_2 and HCO_3 and have derived an expression, which has great clinical utility.

$H^+ = 24 \times PCO_2 / HCO_3$ nmol/L

Where, 24 = the numerical value of the solubility coefficient of carbon dioxide and the dissociation constant of carbonic acid.

$PaCO_2$ = arterial blood partial pressure in mm Hg

HCO_3^- = arterial blood bicarbonate concentration in mmol/L

H^+ = arterial blood H^+ ion concentration in nmol/L

Normally, $H^+ = 24 \times 40/24 = 40$ nmol/L which is equivalent to normal pH of 7.4.

The Hydrogen Ion

The hydrogen ion consists of a single positively charged particle (the proton). The metabolic processes within the body add a daily load of H^+ ions to the body. Small amounts are formed from the oxidation of amino acids and the anaerobic metabolism of glucose to lactic and pyruvic acid. For more, acid is produced as a result of CO_2 release from oxidative (aerobic) metabolism. Although, CO_2 does not contain hydrogen ions, it rapidly reacts with water to form carbonic acid (H_2CO_3), which further dissociates into hydrogen and bicarbonate ions (HCO_3-). This reaction is shown below:

$$CO_2 + H_2O <=H_2CO_3 => HCO_3- + H^+$$

This reaction occurs throughout the body and in certain circumstances is speeded up by the enzyme carbonic anhydrase.

Acid Base Balance

As already discussed, acid base balance is indicated by pH, which alters with change in H^+ ion concentration in the body. The hydrogen ion is highly reactive and will combine with bases or negatively charged ions at very low concentrations. These H^+ ions if not properly deal with; the body would produce a disastrous rise in H^+ ion concentration and a catastrophic fall in the pH. Proteins contain many negatively charged and basic groups within their structure. Thus, a change in pH will alter the ionization of a protein, which may in turn affect its functioning. At more extreme hydrogen ion concentrations, a protein's structure may be completely disrupted (the protein is then said to be denatured). Although, most enzymes function optimally around physiological pH, any disturbances in pH may result in abnormal respiratory and cardiac function, derangements in blood clotting and drug metabolism. The body thus, needs to maintain the pH within a normal range in spite of variation in dietary intake of acid and alkali and endogenous acid production. Three systems are involved for this maintenance: Blood and tissue buffering, excretion of CO_2 by the lungs, and the renal regulation of excretion and regeneration of HCO_3 with excretion of H^+.

TABLE 28.1: Buffer mechanisms for acid base balance

Buffers	*Mechanism*	*Time*
Extracellular fluid	Bicarbonates	Immediate
Intracellular fluid	Phosphates, HCO_3^-	2-4 hours
Lungs	Increased rate of breathing to decrease CO_2	Minutes to hours
Kidneys	H^+ ion excretion and HCO_3^- reabsorption and generation	Hours to days

Buffers[9] *(Table 28.1)*

Buffers are substances, which react with an acid or base and thereby, minimize changes in pH. In the body fluids, there are several buffer systems. In blood, main buffers are the hemoglobin, bicarbonate system and plasma proteins. Within the cells, the buffers include bicarbonates, phosphates and proteins. The bicarbonate buffer system is of primary importance in regulating acid base balance.

Bicarbonates (Fig. 28.2A): The bicarbonate carbonic acid reaction is important in regulating acid base balance. It constitutes a weak buffer system, which can be used as a measure of all acid base reactions in the body. Its efficiency is improved since CO_2 is removed by the lungs and HCO_3^- regenerated by the kidney.

The CO_2 produced by tissue metabolism diffuses into plasma and red blood cells. The enzyme carbonic anhydrase within the red blood cells catalyses the formation of carbonic acid.

$$H_2O + CO_2 = H_2CO_3-$$

The carbonic acid within the red blood cells is dissociated as:

$$H_2CO_3 <=> H^+ + HCO_3-$$

The bicarbonate within red blood cells diffuses out into the plasma, while the H^+ ions are mopped up by the hemoglobin. The loss of HCO_3^- ion from the cell is compensated by the entry of an chloride ions from the plasma. When the blood reaches the lungs, the chloride ion shift is reversed and bicarbonate ions enter the red blood cells in capillary. The bicarbonate within red blood cells breaks down into water and CO_2.

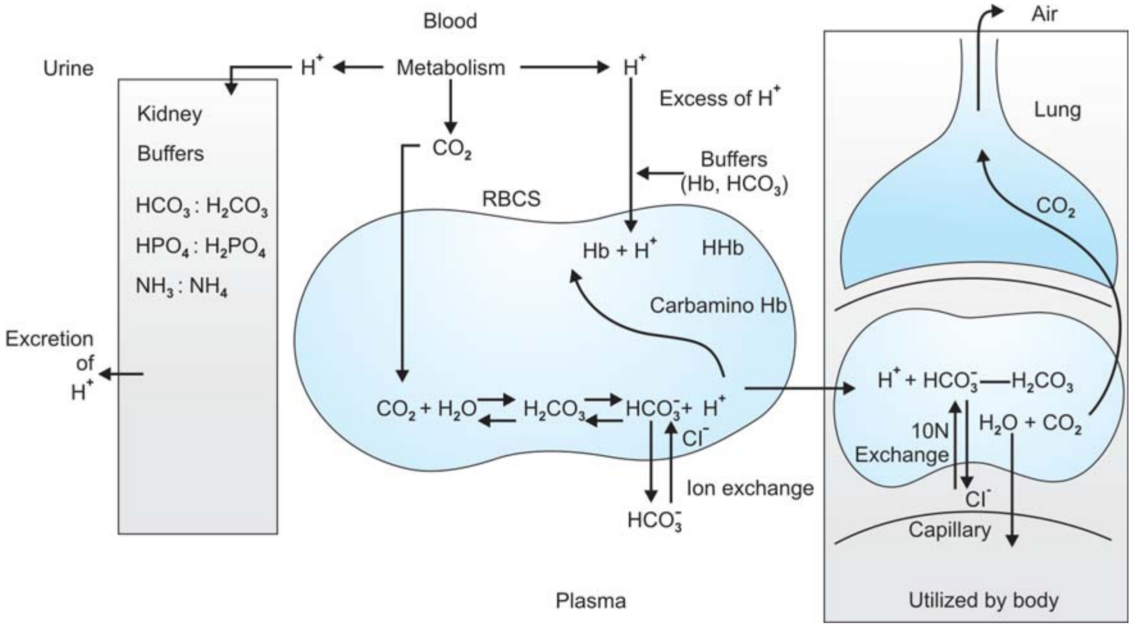


Fig. 28.2A: Acid base balance: Blood and tissue buffering and CO_2 elimination

In acid base balance the bicarbonate carbonic acid reaction is as follows when, H$^+$ enters tissue fluids:

$$H^+ + HCO_3\text{-} \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$$

Hemoglobin (Fig. 28.2A): The hemoglobin buffer is an important one, as it is involved in handling the largest daily acid load of the body. It is not only important in the carriage of oxygen to the tissues, but also in the transport of CO_2 and in buffering hydrogen ions. Hemoglobin binds both with CO_2 and H$^+$ and acts as a powerful buffer. Deoxygenated hemoglobin has the strongest affinity for both CO_2 and H$^+$; thus, its buffering effect is strongest in the tissues. Little CO_2 is produced in red cells, which either combines directly with hemoglobin reversibly to form carbaminohemoglobin or combines with water to form carbonic acid. In the lungs the CO_2 is released and passes down its concentration gradient into the alveoli.

Proteins: Other buffers, such as plasma proteins, phosphates and histidine act in a similar way to bicarbonates; however, these are present in smaller concentrations in intracellular and extracellular fluid. Many proteins notably albumin, contain weak acidic and basic groups within their structure. Therefore, plasma and other proteins form important buffering systems. Intracellular proteins limit pH changes within cells, whilst the protein matrix of bone can buffer large amounts of hydrogen ions in patients with chronic acidosis.

Respiratory Regulation (Fig. 28.2A)

It is clear when considering the Henderson equation that variations in PCO_2 alter the pH. The effect is rapid and influences both the intracellular fluid and extracellular fluid. Arterial PCO_2 varies inversely with alveolar ventilation and directly with carbon dioxide production. By excreting volatile acids, lung regulates $PaCO_2$. Normally, CO_2 production and excretion are balanced, which maintains CO_2 at 40 mm Hg. When rate of CO_2 production increases, it stimulates $PaCO_2$ sensitive chemoreceptors at central medulla with resultant rise in the rate and depth of breathing. This hyperventilation will maintain $PaCO_2$ at normal range. Respiratory regulation acts rapidly and has double buffering power as compared to chemical buffers.

Renal Regulation[10]

Maintenance of pH of the blood within its normal range is done by the renal regulation of excretion of H$^+$ ions with urine buffers and also by retaining and excreting HCO_3^- ions depending on the utilization of HCO_3- during the titration process of buffering in extracellular fluid. As the blood pH decreases, the kidneys will compensate by retaining HCO_3- and as the pH rises, the kidneys excrete HCO_3- through the urine. Although, the kidneys provide an excellent means of regulating acid-base balance, the system may take from hours to days to correct the imbalance. The kidney generates bicarbonate

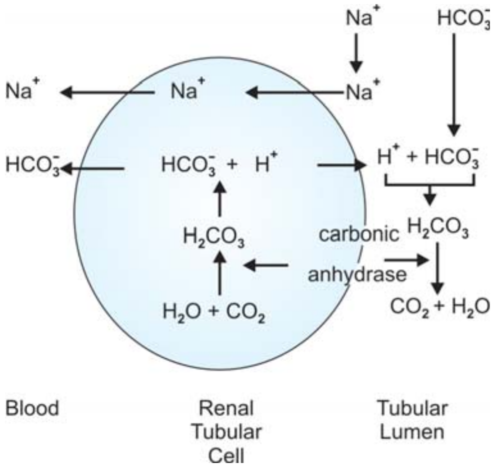


Fig. 28.2B: Acid base balance: Regulation of excretion and reabsorption of HCO_3^- by kidneys

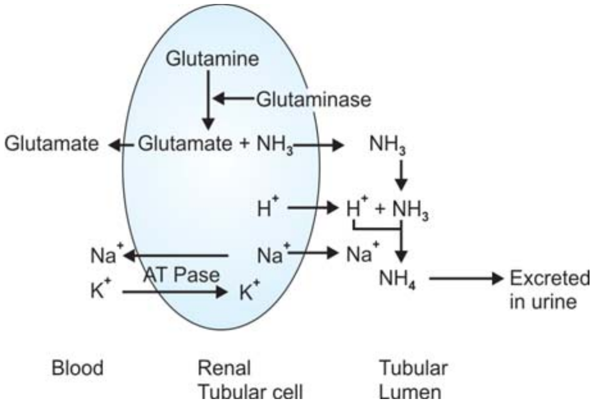


Fig. 28.2C: Acid base balance: Regulation of excretion of H^+ ions with formation of NH_4

through nonbicarbonate buffer systems, such as phosphates and proteins and by metabolizing glutamine. The renal handling of electrolytes also influences acid base balance.

Regulating Excretion and Reabsorption of Bicarbonates (Fig. 28.2B)

Bicarbonate is filtered by the glomerulus. The quantity of bicarbonate in the filtrate is dependent on the plasma bicarbonate and the glomerular filtration rate. Reabsorption of bicarbonate happens in the proximal renal tubules at a rate which is dependent on the PCO_2. The higher the PCO_2, the greater the degree of bicarbonate reabsorption; the lower the PCO_2, the lesser the degree of reabsorption of bicarbonate and the greater its excretion. This enables respiratory acidosis to be compensated through the retention of bicarbonate (metabolic alkalosis), and respiratory alkalosis to be compensated by an increased excretion of bicarbonate (metabolic acidosis). This can be explained as follows:

Filtered HCO_3- combines with secreted H^+ ions to form carbonic acid, which dissociates to form CO_2 and H_2O in the renal tubules. This CO_2 crosses into the tubular cell and combines with H_2O to form carbonic acid, which dissociates to form HCO_3- and H^+ ions. Bicarbonates passes back into the blood and H^+ back into the tubular fluid in exchange for sodium.

Regulating excretion of hydrogen ion: Hydrogen ions are actively secreted in the proximal and distal tubules by the means of various buffers such as phosphates and ammonia. Kidneys by using phosphate buffers (HPO_4-) remove H^+ ions while conserve bicarbonates. Hydrogen ions are secreted in exchange for sodium ions. Under the influence of carbonic anhydrase in tubular cells,

$$H^+ + HCO_3\text{-} = H_2CO_3$$
$$H_2CO_3 \rightarrow HCO_3\text{-} + H^+$$

Bicarbonate ions are reabsorbed. The H^+ ion excreted into the tubular infiltrate is mopped up by a buffer, which is excreted via the urine.

Formation of ammonia (Fig. 28.2C): The major site for ammonia (NH_3) production is in the proximal convoluted tubule epithelium although it can be formed in tubular epithelia throughout the nephron.[13] Ammonia is formed in the tubular cells by the conversion of glutamine to glutamate. The NH_3 diffuses into the renal tubular lumen where it binds H^+ ion to form a nondiffusible ammonium ion (NH_4^+), which is subsequently excreted.[14] Ammonia combines with chloride and excreted via the urine, the reaction being controlled by the enzyme glutaminase. Excretion of ammonia allows the excretion of a significantly large quantity of H^+ ions via the kidney.

Reabsorption of sodium (Fig. 28.2D): The active reabsorption of sodium from the filtrate into tubule cells causes a potential gradient across the cell membrane. The positively charged H^+ion within the tubule cells thus passes across the membrane into the filtrate, and is buffered within the filtrate by a phosphate buffer.

$$H^+ + NaHPO_4 \rightarrow NaH_2PO_4$$

Sodium reabsorption and hydrogen ion excretion are interlinked. Sodium reabsorption is controlled by the action of aldosterone on ion exchange proteins in the distal tubule. These ion exchange proteins exchange sodium for hydrogen or potassium ions.

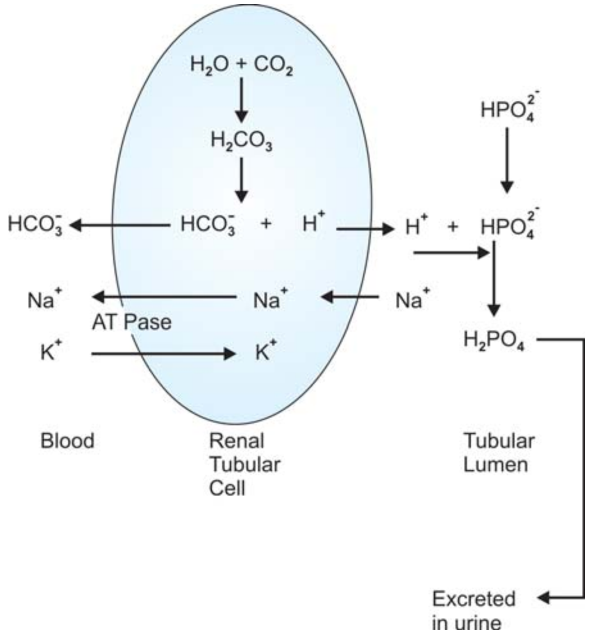


Fig. 28.2D: Acid base balance: Regulation of excretion of H^+ with phosphate buffers and electrolytes

Alterations in Hydrogen Ion Homeostasis

Disturbance of the body's acid-base balance results in the plasma containing either too many hydrogen ions (acidemia) or too few hydrogen ions (alkalemia). In other words, the pH is too low in acidemia (less than 7.35) whilst in alkalemia the pH is too high (more than 7.45). These disturbances may be due to respiratory causes (i.e. changes in $PaCO_2$) or non-respiratory or metabolic causes (i.e. changes in HCO_3^-). When the cause of the acid base disturbance has been discovered, the words acidosis or alkalosis may be used in conjunction with the physiological cause of the disturbance (i.e. respiratory acidosis, metabolic alkalosis, etc.).

ARTERIAL BLOOD GAS ANALYSIS

Applications

Blood gas analysis is indicated in any situation where assessment of arterial blood and tissue oxygenation, alveolar ventilation, gas exchange across the lungs or acid base status is required, for example:

- To document respiratory failure and to assess its severity
- To monitor patients on ventilators and to assist in weaning
- To assess acid base imbalance in cases with critical illness
- To assist in the diagnosis of conditions, e.g. ILD by exercise desaturation and increase alveolar arterial gradient and Obesity Hypoventilation Syndrome (OHS) by daytime hypercapnia
- To assess response to therapeutic intervention like supplemental oxygen administration and mechanical ventilation
- As a preoperative assessment in high-risk patients who require general anesthesia for major surgery.

Arterial Blood Sampling[11,12]

Arterial blood collection is the preanalytical stage, the stage where the greatest variance is likely to occur. It is critical to understand and control these variances. Examples of potential areas for error include the type of syringe, anticoagulant, storage. Blood for arterial blood gas analysis is drawn by direct arterial puncture. When frequent monitoring of ABG is required blood sample may also be obtained via an indwelling arterial cannula. The commonest artery used is the radial followed by the dorsalis pedis; rarely the brachial and the femoral vessels. With the change of ventilatory parameters or the FiO_2 at least five minutes (at least 30 minutes in cases of obstructive lung disease) should be allowed to obtain a steady state.

Checking Patency of Radial Artery

If the radial artery is to be used, the collaterality of blood flow to the hand must be checked by the Allen's test. Allen's test was devised for confirming the presence of radial arterial occlusion. First, the suspected radial artery is occluded at the wrist for three minutes and the hand color is compared with that of the other hand. If there is no change in color, the hand has sufficient collateral circulation through the ulnar artery. The ulnar artery is occluded next for three minutes. A positive Allen's test indicated by change in the color of the hand denotes the presence of radial artery occlusion and contraindicates radial artery puncture.

Drawing an Arterial Blood Sample

Direct arterial puncture is usually done with a 21 gauge or smaller needle. The wrist is kept immobilized and if necessary extended with a support just below the dorsum of the wrist. Under aseptic precautions and with (out) local anesthesia, the heparinized syringe with needle is introduced at an angle of 45° to the horizontal (Fig. 28.3). Heparin salt is the only anticoagulant acceptable for the measurement as it has little effect on the analytes measured.

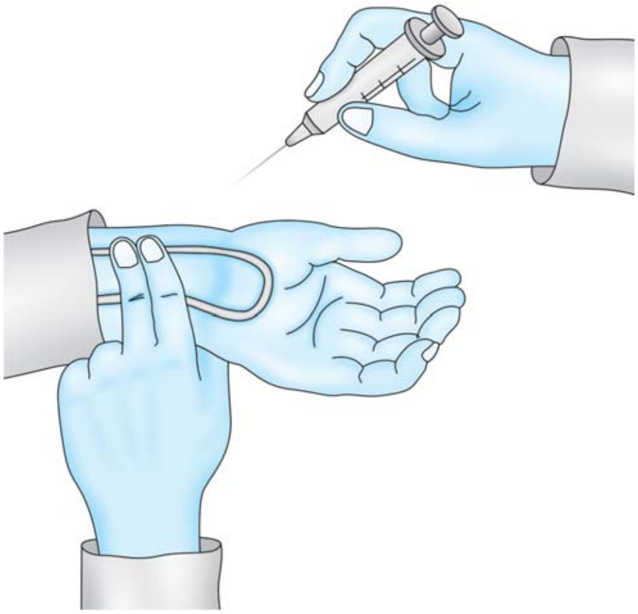


Fig. 28.3: Arterial puncture technique

The blood can then be aspirated in two ways. One is to penetrate the needle till it hits the bone and then withdrawing the needle while maintaining suction in the syringe till one sees bright red blood coming freely into the syringe. The other way is to penetrate the tissues while maintaining suction so that the artery is not pierced through and through. Traditionally, the blood volumes required are 2.7 to 3.0 mL. After drawing a sample, firm pressure must be applied at the site of arterial puncture for at least two minutes.

Transporting the Blood Sample for Analysis

It is acceptable to leave a sample at room temperature if the analysis will occur in 10 to 15 minutes. Blood is living tissue in which oxygen continues to be consumed and carbon dioxide continues to be produced, even after the blood is drawn into a syringe. Very high leukocyte values, as seen in leukemia patients, can cause a significant drop in the PO_2 over a short period. Hence, arterial blood samples must be placed in ice slurry or analyzed immediately. Elevated potassium levels have been observed in healthy individuals, even when the specimen was iced only for a few minutes. When potassium is measured, the specimen should be analyzed in 10 to 15 minutes and not iced. The following should also be considered in specimen preservation and transport:

- Removal of air contamination
- Capping the specimen

Failure to process sample properly is a common source of preanalytic error.

Arterial Blood Gas Equipment

The modern day equipment is a three-electrode system blood gas analyzer that measures three fundamental variables—PaO_2, $PaCO_2$ and pH. All other parameters, such as plasma HCO_3 are computed by software using standard formulae.

Using Venous Blood Gas (VBG) instead of ABG[13]

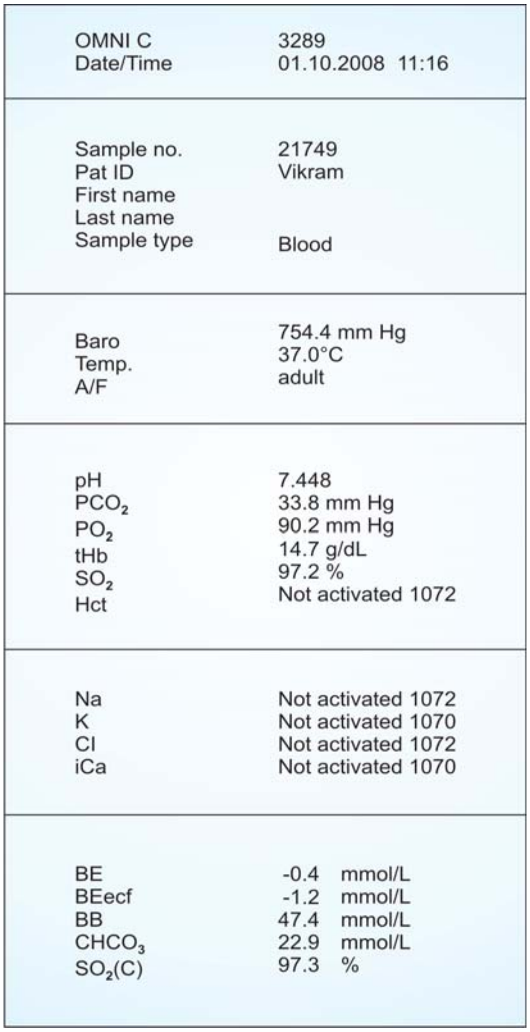
Various studies suggest that a venous sample is relatively accurate for acid-base assessment. The most obvious advantage to obtaining a VBG instead of an ABG is decreased pain for the patient. Also, a VBG sample can be drawn using the same Intravenous (IV) line that is used to draw blood for other lab tests, thus, necessitating only one puncture. This translates into decreased costs, labor and risk of needle stick injury to the health care provider. Furthermore, complications such as arterial laceration, hematoma and thrombosis rarely occur with venous blood sampling. Therefore, venous blood sample and venous blood gas analysis for pH, bicarbonate and PCO_2 is acceptable as a substitute for ABG analysis (Table 28.2). A venous sample may collected in a heparinized syringe and transported in the same way as an arterial sample for assessing the acid base status in the initial evaluation of patients particularly those presenting to the emergency department.

Serum Electrolyte Measurement

An electrolyte abnormality is often the first laboratory sign of an acid-base disorder. In any patient with a blood gas or acid-base abnormality serum electrolytes sodium, chloride and bicarbonate should always be measured by drawing a separate sample routinely. Since potassium is often deranged in acid-base disorders, hence it should also be measure additionally.

TABLE 28.2: Comparison of Arterial Blood Analysis (ABG) and Venous Blood Gas (VBG) values in healthy volunteers

	Arterial	*Venous*
pH	7.38–7.42	7.35–7.38
PCO_2	38–42 mm Hg	44–48 mm Hg
PO_2	90–100 mm Hg	40 mm Hg
HCO_3	24 mmols/L	21–22 mmols/L



```
OMNI C          3289
Date/Time       01.10.2008  11:16

Sample no.      21749
Pat ID          Vikram
First name
Last name
Sample type     Blood

                754.4 mm Hg
Baro            37.0°C
Temp.           adult
A/F

pH              7.448
PCO2            33.8 mm Hg
PO2             90.2 mm Hg
tHb             14.7 g/dL
SO2             97.2 %
Hct             Not activated 1072

Na              Not activated 1072
K               Not activated 1070
Cl              Not activated 1072
iCa             Not activated 1070

BE               -0.4   mmol/L
BEecf            -1.2   mmol/L
BB              47.4    mmol/L
CHCO3           22.9    mmol/L
SO2(C)          97.3    %
```

Fig. 28.4: A typical automated ABG report

ARTERIAL BLOOD GAS INTERPRETATION

A typical ABG report is shown in the (Fig. 28.4). Despite several parameters available in the ABG report, the following are sufficient for interpretation:

pH: Arterial blood pH, normal 7.35–7.45

P_aCO_2 (PCO_2): Arterial CO_2 pressure, mm Hg, normal 35–45 mm Hg

P_aO_2 (PO_2): Arterial O_2 pressure, mm Hg, normal 95–100 mm Hg

HCO_3^-: Serum bicarbonate concentration, mEq/liter, normal 22–26 mmols/L

These parameters are written as:

7.40/40/98/24
PH/$PaCO_2$/PaO_2/HCO_3

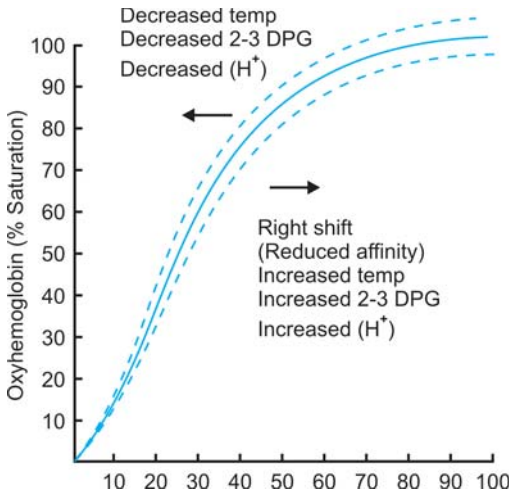


Fig. 28.5: Oxyhemoglobin dissociation curve

Using the above parameters ABG is analyzed for:

- Gas exchange
- Acid base status.

Gas Exchange

Oxygenation

Oxygenation is measured by the partial pressure of oxygen in arterial blood, P_aO_2 mm Hg, often written more simply as PO_2. Normal value of PO_2 is 95–100 mm Hg. Reduced PaO_2 indicates hypoxia/hypoxemia. Hypoxia refers to reduced oxygen pressure in the alveolus, while hypoxemia refers to low arterial oxygen pressure.

Oxygen saturation SaO_2/SpO_2: The basis for using O_2 saturation (SO_2) is the relationship of SO_2 to PaO_2 shown by the O_2 dissociation curve (Fig. 28.5). This curve shows that maximum saturation, greater than 90% is achieved at PaO_2 of 60 mm Hg, beyond, which increases in O_2 saturation is marginal. Thus, if the measured SO_2 is 90% the PaO_2 can be assumed to be 60 mm Hg.

Pulse oximetry[14]: Monitoring of O_2 saturation with Small Portable Pulse Oximeters (SpO_2) is a simple and effective way of monitoring O_2. Pulse oximetry using pulse oximeters measures the oxygen saturation of the blood. Oxygen saturation is calculated by shining light through tissue and measuring the light absorption on the other side of the tissue at two specific wavelengths. The site most commonly used is the fingertip, although the earlobe is also used. The light source consists of two light emitting diodes that emit light at known wavelengths, generally 660 nm and 940 nm. These wavelengths are used because oxyhemoglobin and reduced hemoglobin have different absorption spectra at these particular wavelengths.

Abnormal Gas Exchange

Hypoxemia: The partial pressure of O_2 in the arterial blood in normal individuals is 80 mm Hg or greater. When the value of O_2 on Arterial Blood Gas (ABG) analysis is less than 80 mm Hg the term hypoxemia is used (hypoxia is the term for reduced O_2 in the tissues). The following can serve as useful guidelines for assessing the degree of hypoxia:

- Mild hypoxemia: PaO_2 of 60–80 mm Hg. At this level, arterial blood is 90% saturated
- Moderate hypoxemia: PaO_2^- of 40–60 mm Hg. These values will be reflected in clinical signs, including tachycardia, hypertension and perhaps the appearance of cool extremities
- Severe hypoxemia: PaO_2 lower than 40 mm Hg. At these level serious arrhythmias, brain damage or death may ensue.

Alveolar-arterial oxygen gradient: Calculation of alveolar arterial O_2 gradient P (A-a) O_2, the difference between alveolar O_2 (PAO_2) and arterial O_2 (PaO_2), in presence of hypoxemia is useful in determining the cause of hypoxemia. The formula for alveolar O_2 (PAO_2) is 150-Pa CO_2/RQ, where, Respiratory Quotient (RQ) is .8 when breathing room air and 1 when on 100% O_2. The alveolar arterial gradient is normally up to 21 in young adults and subsequently increases by four to six for every decade of life. Increase P (A-a) O_2 indicates lung parenchymal disease.

Exercise hypoxemia: Exercise consists of a six-minute walk at a moderate pace on a flat surface performed under the supervision of a respiratory therapist. Patients are encouraged to walk at their own pace for six minutes, alternatively until target heart rate (200-age in years) is reached or until limited by shortness of breath or fatigue. Clinically significant desaturation is considered to be any SO_2 decrease of 4% or more to a nadir of 88% or less during exercise regardless of the baseline SO_2. Exercise hypoxemia/desaturation using a finger pulse oximeter -SpO_2 is a practical alternative to using ABG-SO_2. Demonstration of exercise hypoxemia/desaturation is useful for the diagnosis of ILD and other disorders and for prescribing oxygen therapy.

Oxygenation index: The P/F ratio, i.e. ratio of partial pressure of alveolar O_2 and fraction of inspired O_2 (PaO_2/FiO_2) is called the oxygenation index, an index on greater than 300 is considered normal. It is used to determine a diagnosis of ARDS. In the absence of cardiac or other major system involvement, an index less than 300 indicates, Acute Lung Injury (ALI) and an index of less than 200 indicates ARDS. Recently the S/F ratios, i.e. ratio of O_2 saturation (SO_2) and FiO_2 have been found to correlate with P/F ratios.[15] Since, SO_2 can be measured noninvasively with portable pulse oximeters use of S/F ratio to measure oxygenation is a simple and easy alternate to performing ABG. S/F ratios 315 and 235 correlate with P/F ratio of 300 and 200 for ALI and ARDS.

Hypercapnea: $PaCO_2$ is directly proportional to CO_2 production and indirectly proportional to alveolar ventilation, i.e. $PaCO_2$ = CO_2 production/alveolar ventilation. Increase in $PaCO_2$ level in blood is due to hypoventilation, which is due to central nervous system depression, neuromuscular or chest wall diseases, upper airway obstruction and due advanced lung diseases with reduced effective alveolar ventilation. In the case of OHS demonstration of daytime hypercapnea helps to distinguish the disorder from, Obstructive Sleep Apnea (OSA) syndrome. Hypercapnea is measured by the pressure of carbon dioxide in arterial blood as $PaCO_2$ mm Hg, often written more simply as PCO_2. Normal $PaCO_2$ is 35–45 mm Hg. An algorithm for the interpretation of O_2 and CO_2 (gas exchange) is shown in Flow chart 28.1.

Acid Base Status

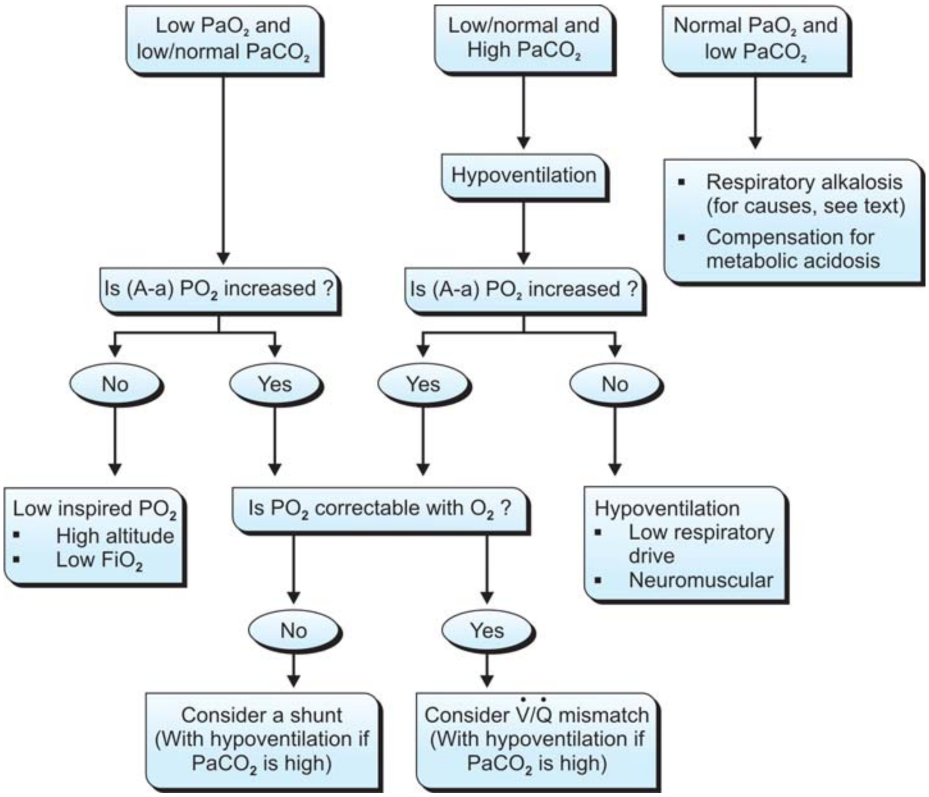
Acidemia and alkalemia refer to alterations in the blood pH. Both respiratory and metabolic disorders can contribute to alterations in pH and are referred to as a respiratory acidosis or respiratory alkalosis and a metabolic acidosis or metabolic alkalosis. A single disorder may account for the observed acidemia or alkalemia, but often more than one disorder occurs concurrently. These are referred as mixed or complex acid base disorders. Acid base balance is assessed using the “three acid base variables”—pH, $PaCO_2$ and HCO_3 (Table 28.3).

While pH and $PaCO_2$ are directly measured during ABG analysis, HCO_3 levels are calculated using the Henderson-Hasselbalch equation. HCO_3 levels on serum chemistry are directly measured and are therefore more

TABLE 28.3: pH, PCO_2 and HCO_3 in primary acid base abnormality

Acidosis	*Alkalosis*
pH < 7.35	pH > 7.35
HCO_3 < 22 mmols/L (Metabolic)	HCO_3 > 26 mmols/L (Metabolic)
PCO_2 > 45 mm Hg (Respiratory)	PCO_2 < 35 mm Hg (Respiratory)

Flow chart 28.1: Algorithm for blood gas analysis: O_2 and CO_2


Low PaO₂ and low/normal PaCO₂
Low/normal and High PaCO₂
Normal PaO₂ and low PaCO₂
Hypoventilation
Respiratory alkalosis (for causes, see text)
Compensation for metabolic acidosis
Is (A-a) PO₂ increased ?
Is (A-a) PO₂ increased ?
No
Yes
Yes
No
Low inspired PO₂
High altitude
Low FiO₂
Is PO₂ correctable with O₂ ?
Hypoventilation
Low respiratory drive
Neuromuscular
No
Yes
Consider a shunt (With hypoventilation if PaCO₂ is high)
Consider V̇/Q̇ mismatch (With hypoventilation if PaCO₂ is high)

accurate. Therefore, routine serum electrolytes must always be performed to measure bicarbonate. Serum electrolytes also provide the levels of sodium and chloride, which are necessary for the calculation of anion gap.

Normal pH ranges from 7.35–7.45, less than 7.35 suggests acidosis and greater than 7.45 alkalosis. A disorder in which the primary abnormality is a change in the $PaCO_2$ is referred to as a respiratory disorder. Normal $PaCO_2$ ranges from 35–45 mm Hg. Reduced $PaCO_2$ less than 35 mm Hg is seen in respiratory alkalosis due to CO_2 washout related to hyperventilation. Elevated $PaCO_2$ greater than 45 mm Hg is seen in respiratory acidosis due to CO_2 retention associated with hypoventilation. A disorder in which the primary abnormality is a change in HCO_3 concentration in the blood is referred to as a metabolic disorder. Normal HCO_3 ranges from 22–26 mmols/L. Elevated HCO_3 greater than 26 mmols/L is seen in metabolic alkalosis and reduced HCO_3 less than 22 mmols/L is seen in metabolic acidosis. Thus, there are four types of acid base abnormalities respiratory alkalosis and acidosis and metabolic alkalosis and acidosis.

Metabolic acidosis can be clinically classified as:

- Metabolic acidosis with normal anion gap
- Metabolic acidosis with increased anion gap.

Anion Gap (AG) [16,17] (Fig. 28.6)

The term anion gap represents the concentration of all the unmeasured anions in the plasma. The AG calculation is the sum of routinely measured cations minus routinely measured anions: $(Na^+ + K^+) - (Cl^- + HCO_3^-)$. However, because K^+ is a small value numerically, it is usually omitted from the AG equation. Thus, the anion gap is calculated by subtracting the serum concentrations of chloride and bicarbonate (anions) from the concentrations of sodium. The normal anion gap is 12 + 2 (mean + SD) mmols per liter.

$$\text{Anion gap (AG)} = (Na)-(Cl+HCO_3) = 12$$

Metabolic acidosis with normal AG occurs due to the loss of HCO_3, compensated by increase in chlorides. Increase in AG occurs due to the decreased excretion of fixed acids, addition of lactate or ketones or ingestion of certain toxins.

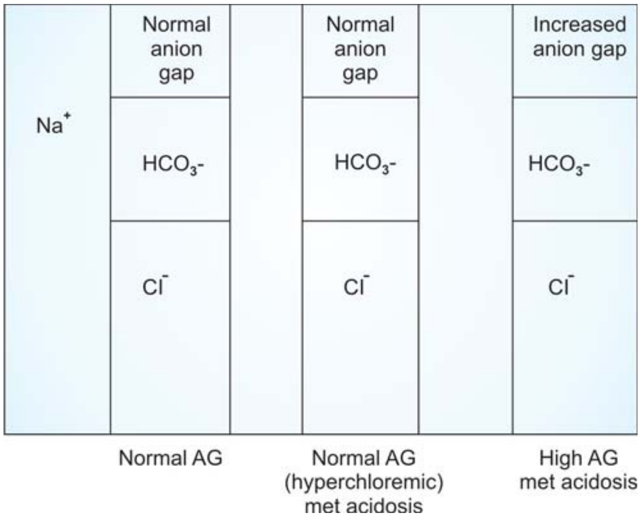

Na⁺
Normal anion gap
HCO₃-
Cl⁻
Normal anion gap
HCO₃-
Cl⁻
Increased anion gap
HCO₃-
Cl⁻
Normal AG
Normal AG (hyperchloremic) met acidosis
High AG met acidosis

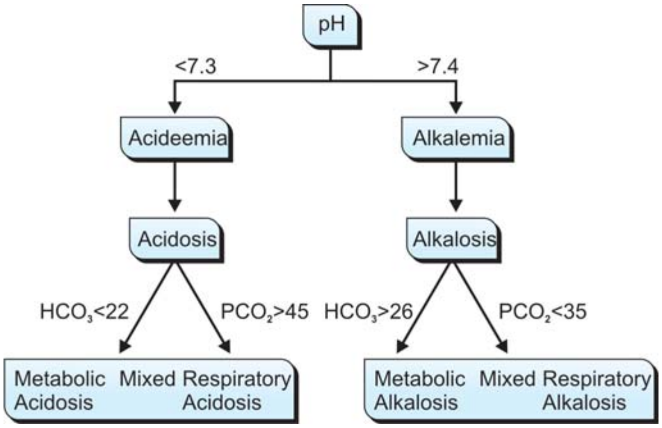
Fig. 28.6: Figure shows normal, metabolic acidosis with normal anionic gap due to increase in Cl^- and increased anion gap metabolic acidosis where no Cl^- compensation occurs. Excess anion gap (AG) = total AG – normal AG =12 mmols/L, and AG– 12 + HCO_3 = 22–26 mmols/L.

Types of Primary Acid Base Abnormality[18]

Primary Acid Base Disorders (Flow chart 28.2)

Primary acid-base disturbances are defined as metabolic or respiratory based on clinical context and whether the primary change in pH is due to an alteration in serum HCO_3 or in PCO_2. If the pH is lower than 7.35, then lowered bicarbonate (metabolic acidosis) or elevated PCO_2 (respiratory acidosis) would be primary abnormalities. If the pH is higher than 7.45, then elevated bicarbonate (metabolic alkalosis) or a lowered PCO_2 (respiratory alkalosis) would be primary.

Flow chart 28.2: Simple algorithm for blood gas analysis: Acid base status


pH
<7.3
>7.4
Acideemia
Alkalemia
Acidosis
Alkalosis
HCO₃<22
PCO₂>45
HCO₃>26
PCO₂<35
Metabolic Acidosis
Mixed
Respiratory Acidosis
Metabolic Alkalosis
Mixed
Respiratory Alkalosis

Metabolic alkalosis: pH > 7.45, $PaCO_2$ 35–45 mm Hg, serum HCO_3 >26 mmols/L

Volume contraction (vomiting, over diuresis, ascites), hypokalemia, alkali ingestion (bicarbonate), excess corticoids.

Metabolic acidosis: pH < 7.35, $PaCO_2$ 35–45 mm Hg, serum HCO_3 < 22 mmols/L

High Anionic Gap Metabolic Acidosis (HAGMA)

$$(Na)\text{-} (Cl+HCO_3) > 12$$

Uremia, ketoacidosis, lactic acidosis, ethyl/methyl alcohol poisoning.

Normal Anionic Gap Metabolic Acidosis (NAGMA) or hyperchloremic metabolic acidosis.

$$(Na)\text{-} (Cl+HCO_3) = 12$$

Diarrhea, Renal Tubular Acidosis (RTA), carbonic anhydrase inhibitor

Respiratory alkalosis pH > 7.45, PCO_2 < 35 mm Hg, serum HCO_3 <=24 mmols/L

Hyperventilation due to anxiety, pregnancy, drugs (salicylates, progesterone), ILDs, catastrophic CNS event

Respiratory acidosis pH < 7.35, PCO_2 > 45 mm Hg, serum HCO_3 22–26 mmols/L

Central nervous system depression, pleural disease, lung disease, musculoskeletal disorders.

Compensated Acid Base Disorders (Table 28.4)

When an acidosis or alkalosis develops acutely pH changes occur, thus, showing uncompensated disorder. If the disturbance persists for some time compensatory buffering mechanisms help restore the pH to normal values. However, in this process significant changes in $PaCO_2$ and HCO_3 occur opposite to the primary abnormality. As a result of the compensatory mechanism the pH approaches, but does not completely return to normal. This principle allows us to use the direction of pH change to identify the primary disorder even when compensation is present. The pH, PCO_2, and bicarbonate values could be the same in two patients with different abnormalities. Clinical correlation would readily differentiate between the two. As is the case for other diagnostic tests, acid-base abnormalities must not be interpreted without clinical correlation.

Mixed Acid Base Disorder

Mixed acid-base disorders can be identified by determining the expected compensatory response to a given change in the primary abnormality and assuming that any value that falls outside this range represents an

TABLE 28.4: Formulae for compensation in acid base disturbances

Disorder	*Primary changes*	*Response and limits*	*Expected compensation*
Metabolic Acidosis	↓HCO_3	↓PCO_2 (PCO_2 usually 10)	$PCO_3 = (HCO_3 \times 1.5) + 8 \pm 2$ pH = 7. (15 + HCO_3) (12)
Metabolic Alkalosis	↑HCO_3	↓PCO_2 (PCO_2 usually <55)	$PCO_2 = (HCO_3 \times 0.9) + 8 \pm 2$ pH = 7. (15 + HCO_3)
Respiratory Acidosis	↑PCO_2	↑HCO_3 (HCO_3 < 30[acute]) (HCO_3 < 45[chronic])	For every 10 mmols ↑ in PCO_2 HCO_3 ↑ by 2 in acute and by 3-4 in chronic disorder
Respiratory Alkalosis	↓PCO_2	↓HCO_3 (HCO_3 < 18) [acute]) (HCO_3 < 12 [chronic])	For every 10 mmols ↓ in PCO_2 HCO_3 ↓ by 2 in acute and by 5 in chronic disorder

*If values more than expected for compensatory mechanism consider mixed acid base disorder.

additional primary disorder. A maximum of three disorders can be present at a given time, as respiratory alkalosis caused by hyperventilation and respiratory acidosis caused by hypoventilation cannot occur simultaneously. Mathematical equations[19] (Fig. 28.3) and nomograms[20] are available for identifying mixed disorders. Unfortunately, mathematical equations, different for acute and chronic disorders, can be difficult to memorize and nomograms, though simple to use do not help understand the physiology behind the abnormality detected.[21] Additionally nomograms may not be readily available to the clinician. A simpler alternative, which will identify most clinically important disorders, is to calculate the delta gap.

Delta Gap[22]

The coexistence of two metabolic acid-base disorders may be apparent by calculating the delta gap. The difference between the patient's anion gap and the normal anion gap is termed the delta gap or the delta-delta. For every unit rise in the anion gap, the HCO_3 should lower by one (by buffering). Thus, if the delta gap is added to the measured HCO_3, the result should be in the normal range for HCO_3, i.e. 22–26 mmols/L. Elevation greater than 26 mmols/L indicates the additional presence of a metabolic alkalosis and reduction less than 22 mmols/L indicates additional non AG metabolic acidosis. Thus,

$$\text{Delta gap} = \text{anion gap} - 12$$
$$\text{and, delta gap} + HCO_3 = 22\text{–}26 \text{ mmols/L}$$

The physiologic principle behind this is i) that the body does not generate a large anion gap as a compensatory mechanism even for a chronic alkalosis. Therefore, a substantial increase in unmeasured anions indicates a primary disorder, a metabolic acidosis, regardless of the pH or the bicarbonate concentration and ii) each mmol decrease in bicarbonate is accompanied by a mmol increase in the anion gap, the sum of the new (excess) anion gap and the remaining (measured) bicarbonate value should be equal to a normal bicarbonate concentration.

INTERPRETATION OF ARTERIAL BLOOD GAS

Use the following six easy steps to interpret an ABG report.[23,24] However, the "golden rule" of ABG interpretation is: "Always look at the patient first."

1. Look at the PaO_2 (<80 mm Hg) and O_2 saturation (<90%) for hypoxemia
2. Look at the pH (7.35–7.45): Low acidosis, high alkalosis
3. Look at the $PaCO_2$ (<35 mm Hg- > 45 mm Hg) and HCO_3 (<22 mmols/L ->26 mmols/L)
   HCO_3 is abnormal and the abnormality *(acidosis / alkalosis)* matches pH it is primary metabolic abnormality
   CO_2 is abnormal and the abnormality *(acidosis / alkalosis)* matches pH it is primary respiratory abnormality
4. Are the CO_2 or HCO_3 of opposite type? If so, there is compensation
5. Is there an anion gap? (Na - Cl - bicarbonate > 12). If no, analysis is done
6. If yes, AG metabolic acidosis is present.
   Next, calculate delta (Δ) gap, i.e. (anion gap – 12)
   Add measured bicarbonate to the delta gap
   (Measured AG – 12) + HCO_3

If it is greater than 26, there is a metabolic alkalosis as well.

If it is less than 22, there is a non-anion gap metabolic acidosis, too.

PITFALLS IN ARTERIAL BLOOD GAS INTERPRETATION

The following are common errors in performing and interpreting ABG:

- Not drawing the electrolytes and ABG at the same time
- Using the HCO_3 on the ABG, which is a calculated value (must use the HCO_3 from electrolytes)
- Failing to make sure the ABG correlates with patients clinical situation.

EXAMPLES

ABG Report 1

Diagnosis: 33 years old man with diabetic ketoacidosis

ABG = 7.0/14/90/4

Electrolytes: Na = 128, Cl = 90, HCO_3 = 4, Glucose = 800

Interpretation:
O_2= normal
pH(7.0) = acidosis
PCO_2(14)= alkalosis
HCO_3 (4) = acidosis .... primary abnormality, type metabolic

Compensation: PCO_2 is opposite (alkalotic)
Anion Gap (128 – 90 + 4= 34) = AG acidosis
Δ gap= AG –12= 34 – 12 = 22+HCO_3 (+ 4) = 26, no additional metabolic problem

Final interpretation: AG metabolic acidosis with compensatory respiratory alkalosis, compensation is partial.

ABG Report 2

Diagnosis: 23 years old man with asthma on high dose steroid therapy
ABG = 7.48/44/75/32

Electrolytes: Na = 134, Cl = 90, HCO_3 =32

Interpretation:
O_2: Normal
pH (7.48) = alkalotic
PCO_2 (44) = normal
HCO_3 (32) = alkalosis .... primary abnormality, type metabolic

Compensation: None
AG (134) – (90+32) = 12 =normal

Final interpretation: Metabolic alkalosis

ABG Report 3

Diagnosis: 50 years old woman with interstitial lung disease
ABG = 7.46/24/55/16

Electrolytes: Na = 130, Cl = 106, HCO_3 =15

Interpretation:
O_2: Hypoxemia
pH (7.46) = alkalosis
PCO_2 (24) = alkalosis .... primary abnormality, type (chronic) respiratory
HCO_3 (16) = acidosis

Compensation: HCO_3 (acidotic) opposite
AG (136) – (110+15)= 11 normal
Final Interpretation: Respiratory alkalosis with compensatory metabolic acidosis, complete compensation.

ABG Report 4

Diagnosis: 60 years old man with chronic obstructive pulmonary disease
ABG = 7.36/54/55/28

Electrolytes: Na = 140, Cl = 100, HCO_3 =28

Interpretation:
O_2: Hypoxemia
pH (7.36) = Normal
PCO_2 (54) = acidosis ...... primary abnormality, type (chronic) respiratory
HCO_3 (28) = alkalosis

Compensation: Metabolic HCO_3 alkalotic
AG (140 – 100 +28) = 12, normal

Final interpretation: Respiratory acidosis with compensatory metabolic alkalosis, complete compensation.

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29

Nuclear Imaging in Pulmonary Medicine

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INTRODUCTION

Nuclear medicine is an exciting frontier field of medical practice where the minute quantities of unsealed radioisotopes are used for understanding the human body, both in healthy, as well as the diseased individuals. The procedures, which employ open radionuclide sources have become an important tool in medical sciences for diagnosis, therapy and clinical research. Most diagnostic radionuclides emit gamma rays while radionuclides emitting beta particles are used in therapeutic applications. Radiopharmaceuticals after administration to the patient emit gamma rays that are detected externally by sophisticated instruments such as the gamma camera or the Positron Emission Tomography (PET) scanners. This process is unlike a diagnostic X-ray where external radiation is passed through the body to form an image. Planar studies provide a two-dimensional image whereas tomography provides three-dimensional images. The two most widely used emission tomographic studies are Single Photon Emission Computed Tomography (SPECT) and PET. Nuclear Medicine also plays a pivotal role in the diagnosis and the management of various pulmonary disorders. The various nuclear medicine procedures in pulmonology include ventilation scan, perfusion scan and positron emission tomography. (This chapter is an outline of the current applications of nuclear medicine in the routine clinical practice. For more details, the reader may refer to specific nuclear medicine books or periodicals).

PULMONARY ANATOMY AND PHYSIOLOGY

A proper interpretation of Ventilation/Perfusion ($\dot{V}/\dot{Q}$) lung scans requires the proper understanding of the pulmonary vascular segmental anatomy and physiology. The respiratory system consists of airways and two lungs. The airways are divided 23 times from the trachea to the alveoli. The first 16 of these divisions up to the terminal bronchioles are involved in the transportation of gases. The remaining seven divisions, which include the respiratory bronchioles and alveoli, are involved in the gas exchange. There are approximately 350 million alveoli, each enmeshed by a capillary web, arising from precapillary arterioles having a diameter of 10–30 microns. The lower zones of lungs are better ventilated and perfused normally. However, the rate of increase in ventilation from the apex to the base is relatively less compared to the increase in the blood flow. In the recumbent position, this hydrostatic gradient decreases and is reoriented to an anteroposterior plane. Effect of posture on regional pulmonary blood flow in rats has also been demonstrated recently using Ga-68-microspheres PET.[1] Increased perfusion to the upper lobes in an upright patient is suggestive of Congestive Heart Failure (CHF), increased left atrial pressure or alpha-1-antitrypsin deficiency.

INVESTIGATIONS

Ventilation Imaging

Ventilation in an erect patient is greater at the lung base than at the apex. In supine position, there is relatively a uniform distribution of ventilation. Ventilation scan is primarily used in addition to perfusion scan and the chest X-ray for the diagnosis of pulmonary embolism. Only ventilation scan is used for studying the transfer of gases across the capillaries. Ventilation studies may be

TABLE 29.1: Characteristics of agents used for ventilation

Agent	*Category*	*Usual dose (MBq)*	*Gamma emission*	*Half life*	*Drawbacks*
Tc99m DTPA	Aerosol	20-30	140 keV	6 hours	Deposition in central airways
Technegas	Aerosol	20-30	140 keV	6 hours	Expensive, availability
Xe133	Gas	555-740	81 keV	5.24 days	Only posterior and single breath hold views are possible
Xe127	Gas	370-740	172, 203, 375 keV	36.4 days	Only posterior and single breath hold views are possible
Kr81m	Gas	40-400	190 keV	13 sec	Expensive

performed using any of the following agents[2-6] (Table 29.1):

Tc99m-DTPA Aerosols

The most commonly used ventilation agent in India is Tc99m-Diethylenetriaminepentaacetic Acid (Tc99m-DTPA) aerosol. Technetium that is produced from a Mo99-Tc99m generator system is the main workhorse in nuclear medicine. This decays with gamma energy of 140 keV and half life of six hours. About 25–30 mCi of Tc99m-DTPA is injected into a shielded aerosol system. Aerosols of Tc99m-DTPA are generated by running oxygen through the aerosol system at a rate of 8 liters/minute. Patient is made to breathe via a face mask for two to three minutes with his nose clipped. The expired air is captured in a disposable plastic bag to avoid contamination. Particles produced are generally of 0.5–0.8 microns in diameter, which are delivered to the alveoli like gases during inhalation. Particles larger than one micron deposit in the tracheobronchial tree due to inertial impaction and gravitational sedimentation. After sometime, aerosolized Tc99m-DTPA crosses the alveolar-capillary membrane and enters the bloodstream where it is filtered by the kidneys and excreted. In normal subjects, the pulmonary clearance of Tc99m-DTPA has a half-time of over 60 minutes (1–1.5 hours).[2] Unlike gases, multiple projections can be obtained due to the persistence of activity in the lungs. In patients with obstructive airway disease, excessive tracer in the proximal bronchial tree is often seen due to turbulent airflow. The critical organ is the urinary bladder. The usual radiation exposure to the lungs is about 100 rads.[2] A normal lung ventilation image performed with Tc99m-DTPA aerosols is shown in Figure 29.1.

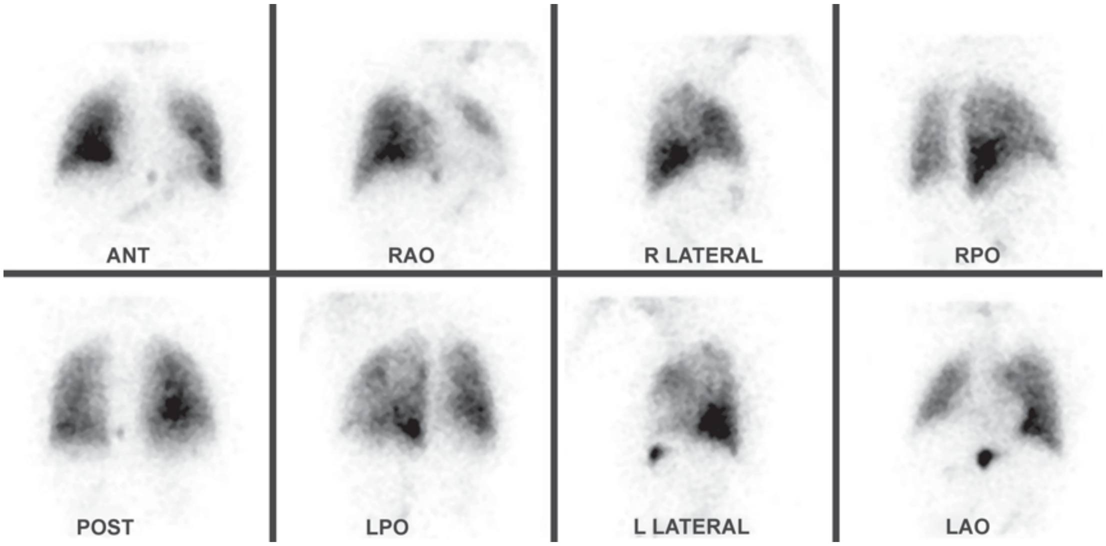


Fig. 29.1: Normal ventilation study of the lungs performed with Tc99m-DTPA aerosols. Uniform distribution of tracer activity is noted throughout both lungs

Tc-99m Technegas

Technegas and pertechnegas are being used in Australia and some centers in Europe. In this method, Tc99m gas is passed over heated carbon particles at a high temperature of 2000–2500°C in the presence of 100% argon gas. Fine particles of technegas are generated, which provide a uniform distribution over the entire lung field. This property of technegas is particularly useful in patients with COPD.

Xenon-133

It is a fission product of U-235 having a physical half-life of 5.24 days and a low energy gamma emission (81 keV).[3,4] The usual dose for inhalation is 15–25 mCi, but it can be administered intravenously in saline. It requires a separate exhaust ventilation system to avoid contamination of the laboratory. Often, only the posterior view is possible. Typical ventilation scan using Xe-133 consists of three phases:

i. *Single breath (wash in)*: The patient takes a single deep inspiration and holds it for as long as possible. This imparts information about regional ventilation and can detect 50 to 60% of ventilation defects associated with obstructive airway disease.
ii. *Equilibrium*: During this phase, the patient performs normal tidal respirations for three to five minutes while rebreathing a mixture of Xenon-133 and oxygen. In this view, overall lung volume is demonstrated as tracer equilibrates between all aerated portions of the lungs. It is the least sensitive to detect obstructive airway abnormalities. However, adequate duration of rebreathing ensures diagnostic quality washout phase.
iii. *Washout*: Inhalation of Xenon-133 is discontinued and the patient breaths room air or oxygen while exhaling the xenon into a charcoal trap. Normally, Xenon-133 clears from the lungs within two or three minutes. Retention of tracer activity beyond three minutes is noticed in obstructive airway disease. The washout phase of the exam can detect about 90% of abnormalities associated with obstructive airway disease. Xenon is overall more sensitive than aerosolized Tc99m-DTPA for detecting obstructive lung disease.

Xenon 127

Xe-127 has also been used for lung ventilation studies.[5] It is cyclotron produced radionuclide with a physical half-life of 36.4 days. It has three gamma emissions: 172 keV (25%), 203 keV (68%) and 375 keV (18%).

Krypton-81m

It is produced from a Rubidium-81/Krypton-81m generator system. Krypton-81m decays with a gamma emission of 190 keV and a physical half-life of only 13 seconds. This provides an exact comparison of ventilation and perfusion as the ventilation images can be acquired immediately after each perfusion view without moving the patient.[6]

Perfusion Imaging

Lung perfusion scan is typically performed by injecting Tc99m-Macroaggregated Albumin (Tc99m-MAA) intravenously. The particle size is generally between 10–90 microns. These particles are trapped in the pulmonary precapillary arterioles. On an average, this dose contains 5,00,000 particles, which obstruct nearly 0.1% of the precapillary arterioles.[7] The number of particles need to reduce to about 1,00,000 in patients with pulmonary arterial hypertension (acute right heart failure may occur due to limited pulmonary vascular reserve) and in those with known right to left shunts (may produce symptoms due to lodging of particles in the cerebral/coronary circulations). In neonates, the number of particles should be reduced in the range of 10,000–50,000. The biological half-life of MAA in the lungs is about six to eight hours. The particles get degraded into smaller particles by enzymatic hydrolysis and are phagocytized by Reticuloendothelial (RE) cells.[2] Thus the occlusion of arterioles is only temporary. The critical organ, i.e. the lung receives a dose of about 1 radian (1 cGy) from a typical 5 mCi dose[2]. The kidneys and bladder receive moderate exposure largely from the excretion of degraded albumin. Figure 29.2 represents a normal lung perfusion images performed with Tc99m-MAA.

Ventilation/Perfusion ($\dot{V}/\dot{Q}$) Imaging

Acquisition and Interpretation

Imaging is performed using a large field of view camera coupled with a parallel hole, high-resolution collimator. The scan protocol includes multiple static images in eight standard views (anterior, posterior, right lateral, left lateral, right anterior oblique, left anterior oblique, right posterior oblique and left posterior oblique) with the patient lying in supine position. Each perfusion image is acquired for 5,00,000–7,50,000 counts. SPECT imaging is performed wherever deemed necessary. The ventilation images are acquired for 1,00,000 counts or five minutes. It may be performed before or after the perfusion study. In a normal scan, all the views show uniform tracer distribution without any defect. Sometimes, one sees a few artifacts on $\dot{V}/\dot{Q}$ images.

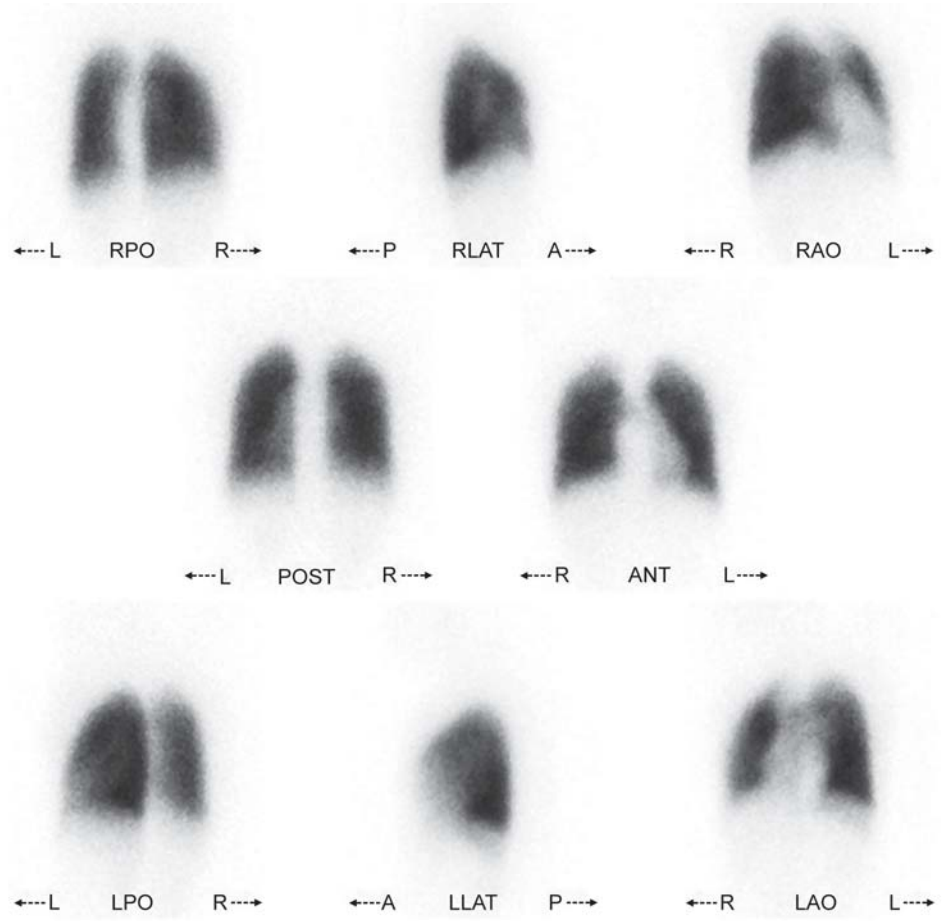


Fig. 29.2: Normal perfusion study of the lungs performed with Tc99m- macroaggregated albumin (Tc99m-MAA). Uniform distribution of tracer activity is noted throughout both lungs

i. *Artifacts on $\dot{V}/\dot{Q}$ images:*
   - Hot Spots, which occur due to the injection of blood clots inadvertently formed in the syringe. Therefore the syringe containing Tc99m MAA should be vigorously shaken before injection. Moreover, at the time of injection, blood should not be withdrawn in the syringe.
   - Attenuation defects due to effusions: When the patient is scanned in the supine position, effusions may collect posteriorly/superiorly and mimic a defect.
   - Liver uptake: Xenon is fat soluble (somewhat soluble in blood) and may get deposited in the liver, especially in case of fatty liver.

ii. *Common causes of $\dot{V}/\dot{Q}$ mismatch:*
   - Pulmonary embolism: Impaired perfusion with normal ventilation. Fat emboli typically produce a mottled appearance due to the presence of many small fat emboli.
   - Pneumonia/pleural effusion/atelectasis: Usually, there is more ventilation abnormality with normal or minimally reduced perfusion.
   - Tumor/hilar lymphadenopathy: Bronchi are more resistant to extrinsic compression than are the pulmonary arteries because of their rigid cartilaginous rings.
   - Radiation treatment/vasculitis: Can reduce regional lung perfusion. Radiation treatment results in the obliteration of the microvasculature. Perfusion defects from radiation are usually geometric and follow the treatment port. They are typically nonsegmental. Ventilation may also be reduced in the irradiated area, but it is usually less affected than perfusion.
   - Pulmonary artery atresia or hypoplasia.
   - Segmental or branch pulmonary artery stenosis.
   - Fibrosing mediastinitis: Can lead to central vascular obstruction.

- AVM: Short circuit delivery of the particulate tracer to the regional pulmonary precapillary arterioles.
- CHF: Multiple nonsegmental perfusion defects can be seen.

iii. Causes of unilateral decreased perfusion:[8-10]

$\dot{V}/\dot{Q}$ scans can also show unilateral decreased perfusion in some conditions, which has been described below:

- Pulmonary agenesis: Absent ventilation, while X-ray chest may show a small, opaque hemithorax.
- Hypoplastic lung (pulmonary artery atresia): Usually ventilation to a small lung with no evidence of perfusion. On X-ray chest, the involved lung is usually small, hyperlucent and contains few normal pulmonary markings.
- Swyer-James syndrome: Characterized by bronchial destruction. It produces a more severe impairment of ventilation than of perfusion in the affected lung. Perfusion typically is decreased and inhomogeneous, but may be severely reduced and nearly unapparent.
- Tumor/mediastinal mass: A central mass can compress or occlude the pulmonary artery resulting in "absent" perfusion. Endobronchial obstruction can produce hypoxic vasoconstriction.
- Massive pleural effusion
- Pneumothorax
- Pulmonary embolism: Unilateral decreased perfusion can be secondary to Pulmonary Embolism (PE). Chronic PE has been shown to be the cause of unilateral hypoperfusion.
- Aortic dissection: Unilateral absent perfusion in the right lung due to direct compression of the right pulmonary artery by the intramural hemorrhage within the adjacent ascending aorta.
- Fibrosing mediastinitis: Vessels are occluded by progressive fibrosis prior to occlusion of the bronchi.
- Shunt procedures for congenital heart disease.
- Lung transplantation with nonperfusion of the native (diseased) lung.

Applications of Ventilation/Perfusion Scan

Ventilation and perfusion scans are applied in combination with chest X-ray for the diagnosis of pulmonary embolism, to evaluate integrity of the pulmonary alveolar membrane, quantification of lung perfusion prior to a planned pulmonary resection to determine the residual functional lung mass. Various pulmonary disorders in which lung perfusion scan is utilized are discussed below:

Pulmonary Embolism

Pulmonary embolism, a potentially fatal condition, is a frequently overlooked diagnosis, which can be associated with significant mortality if left untreated. More than 80% of deaths from PE occur in the first 30 minutes and 90% within the first two to three hours of the event.[10] It is commonly seen in bed ridden hospitalized patients. The common conditions predisposing to this entity are: Postoperative states especially following operations on the abdomen and pelvis; trauma, including fractures particularly of the lower extremities; neoplasms; prior history of thromboembolic disease; venous stasis; vascular spasm; intimal injury; hypercoagulability states and immobilization. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 92% of the patients with pulmonary embolism had at least one of these above-mentioned risk factors.[11]

No single or combination of clinical findings is either specific or sensitive enough to diagnose or exclude PE. Most commonly, the emboli arise from the veins of lower extremity or the pelvis. Patients are usually present with acute onset breathlessness, pleuritic chest pain and rarely with hemoptysis. ECG findings may or may not be characteristic of PE. Diagnosis is straight forward in a patient with predisposing clinical problems and typical manifestations. When the clinical features are atypical, a high index of suspicion is required to diagnose pulmonary embolism. A chest X-ray at the time of presentation is often normal. Classic signs described in a chest X ray for PE are Hampton's hump (wedge shaped opacity above the diaphragm) and Westermark's sign (focal oligemia). Computed Tomography Pulmonary Angiography (CTPA) is being more frequently used nowadays at the emergency rooms for rapid diagnosis of PE. CTPA has a high negative predictive value. The ready availability of CT has resulted in the modality largely supplanting $\dot{V}/\dot{Q}$ scanning, but CTPA is less accurate in detecting sub segmental thrombi. There is an additional risk of excessive radiation exposure.[12,13] Breast irradiation from a $\dot{V}/\dot{Q}$ scan is approximately 0.2–80.9 mGy, which is less than 5% of the radiation dose to the breast resulting from CTA.[14] It has been determined that approximately 1 of the 300 women in the reproductive age group, who undergo CTPA, has a risk of developing carcinoma breast.[12] CTPA in addition, cannot be used in patients with previously known allergy to iodinated contrast agents and in patients with compromised renal function. Though presently under utilized, $\dot{V}/\dot{Q}$ scan offers the advantages of lower radiation exposure.

$\dot{V}/\dot{Q}$ scans: $\dot{V}/\dot{Q}$ scanning had been the mainstay for screening symptomatic patients for the presence of PE.

A Normal $\dot{V}/\dot{Q}$ scan essentially excludes the possibility of recent significant pulmonary embolus. Ventilation-perfusion mismatch (an area of normal ventilation corresponding to a segmental wedge-shaped area of decreased or absent perfusion) is the hallmark of a pulmonary embolism on $\dot{V}/\dot{Q}$ scanning.[13-22] $\dot{V}/\dot{Q}$ lung scan acquired within four to six hours of a large (lobar) embolism may show a matched defect due to vascular insult inducing reflex bronchoconstriction. In cases with high clinical concern for PE, SPECT images may help to better define the defect. The false-positive rate of high probability scans is only about 10%. In general, emboli are more frequent in the lower lobes due to the greater blood flow. Emboli are also frequently multiple (in 90%) and bilateral (in 85% of cases). Thus, unilateral decreased/absent perfusion to one lung is uncommonly the result of pulmonary embolism. Injection of Tc-99m MAA into the veins of the feet may help to reveal a DVT. Venous obstruction or collateral flow can be seen. Images recorded several minutes after the injection may also show hot spots where the Tc-99m MAA is adherent to thrombus in the vein.

Interpretation criteria: Traditionally, the $\dot{V}/\dot{Q}$ scans are interpreted using the PIOPED criteria, though original interpretation was based on Biello's criteria. In PIOPED criteria,[11, 15, 16] planar perfusion scan is compared with planar ventilation scan and interpreted along with a recent chest X-ray (<12 hours old). The perfusion defects are classified as small (<25% of a segment), medium (25% to 75%) and large (>75%) defects. Two or more large mismatched perfusion defects with a normal chest X-ray indicate the high probability of PE. One to three moderate-sized mismatched perfusion defects are considered as intermediate probability. Less than three small-sized mismatched perfusion defects are considered to be low probability. Modifications to PIOPED criteria were suggested on the bases of retrospective PIOPED data review. Gottschalk suggested that a high probability study should be interpreted as PE present and that normal and very low probability exams be interpreted as PE absent for a more conclusive interpretation. All other exams should be interpreted as PE uncertain. The modified PIOPED was based using this type of scheme.

PIOPED II study compared CTPA and $\dot{V}/\dot{Q}$ scan with pulmonary angiography as the gold standard.[17-20] PIOPED II concluded the superiority of CTPA against $\dot{V}/\dot{Q}$ scan. The main drawback of $\dot{V}/\dot{Q}$ scan as per this study was large number of indeterminate studies. The complicated probabilistic approach and results of PIOPED II study led to the decline in use of $\dot{V}/\dot{Q}$ scan. However, it is to be remembered that in PIOPED II, CTPA an inherently tomographic technique of was compared with technically inferior planar $\dot{V}/\dot{Q}$ scans. Alternatively the PISAPED (Prospective Investigative Study of Pulmonary Embolism Diagnosis) study proposed a simpler way of reading the lung perfusion scans. It proposed that a wedge-shaped perfusion defect of any size irrespective of the chest X-ray findings should be considered as indicative of PTE.[21] This approach led to the decline in the number of indeterminate scans. PISAPED criteria did not require ventilation scan. Recently $\dot{V}/\dot{Q}$ SPECT has been found to be as accurate as CTPA for diagnosis of PE.[22] Early reports of perfusion only SPECT/CT for diagnosis of PE on hybrid gamma cameras had appeared promising. $\dot{V}/\dot{Q}$ scan is also the investigation of choice in the women of reproductive age group in patients with renal failure and in patients with allergy to intravenous contrast agents.[23] Figure 29.3 is a

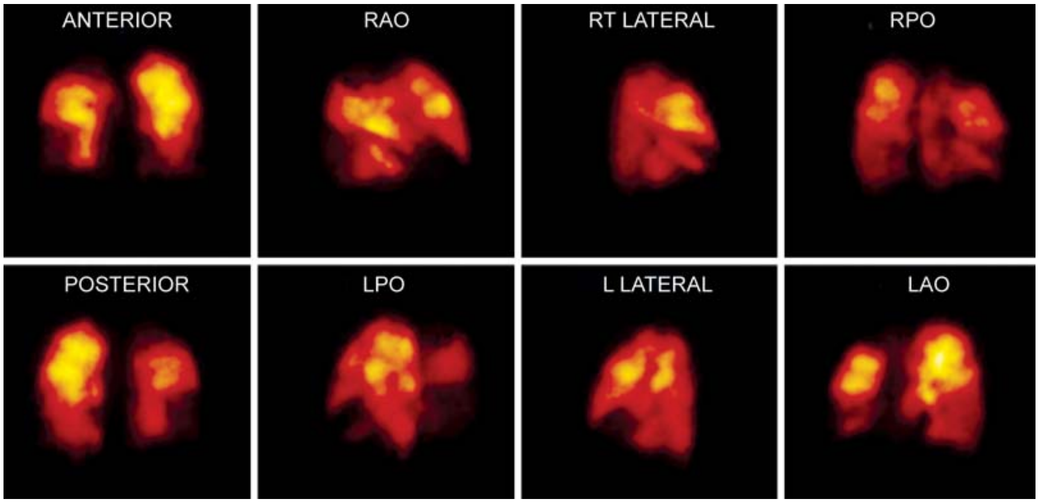


Fig. 29.3: Lung perfusion study with Tc99m-MAA (macroaggregated albumin) showing multiple large segmental perfusion defects in bilateral lungs, indicating high probability for pulmonary embolism

representative image of pulmonary embolism showing multiple perfusion defects.

In patients with prior pulmonary embolism having persistent ventilation-perfusion abnormalities, false-positive interpretation may be made. Pulmonary emboli resolve because of natural thrombolytic processes. A residual perfusion defect can be found in 9% to 30% of patients and incomplete resolution, more common in patients with an underlying cardiopulmonary disease.

Fat Embolism

Classically, a heterogeneous perfusion pattern (multiple small to moderate perfusion defects scattered throughout both lungs) is observed. Segmental perfusion defects are rarely present. However, in the majority of cases due to small-sized emboli, $\dot{V}/\dot{Q}$ scan may be normal. Unfortunately, the lung scan is not very useful in diagnosing fat emboli, but can be used to exclude thromboemboli as the cause of the patient's hypoxia in these patients.

Pulmonary Infarction

Pulmonary infarction may occur as a complication of PE. The perfusion defect is usually larger than the chest X-ray consolidation.

Pulmonary Hypertension

In secondary pulmonary hypertension, perfusion is typically heterogeneous, with small peripheral defects on $\dot{V}/\dot{Q}$ scintigraphy. However, the scan may also be normal. In primary pulmonary hypertension, the presence of reverse mismatch (diminished ventilation, normal perfusion) representing failure of hypoxic vasoconstriction has been described.[24] If extensive, this finding is of great physiologic importance as blood shunted through poorly ventilated lung tissue can be a major cause of hypoxia. In patients with primary pulmonary hypertension, HRCT demonstrates characteristic mosaic attenuation patterns. Areas of reverse mismatch on the $\dot{V}/\dot{Q}$ scan have been shown to correlate with the areas of increased attenuation on HRCT.[25]

Hepatopulmonary Syndrome

Tc99m-MAA imaging demonstrates heterogeneous pulmonary perfusion and the presence of right to left shunting (Fig. 29.4) with activity outside the lungs in the brain, liver and spleen. Scintigraphy can also be used to quantify the shunt, but it cannot distinguish between intracardiac and intrapulmonary shunting (best diagnosed by echocardiography with saline microbubble injection).

Hemoptysis

Labeled RBCs can also be used in cases of hemoptysis to localize the site of pulmonary hemorrhage. About 50% of patients may show positive scan and bleeding rates as low as 50 ml/day may be detected.

Emphysema

Multiple ventilation defects on the single breath view and abnormal retention on the washout study is visualized on Xenon-133 study in patients with emphysema. The late equilibrium images are typically normal as the gas slowly distributes via collateral airways into the abnormal regions. Due to the turbulent air flow, extensive central deposition of the tracer in the large airways may be seen on aerosol ventilation images. Asthmatic patient also demonstrate similar findings on ventilation images (Fig. 29.5). Xenon-133 has also been used to evaluate ventilation before and after lung volume reduction surgery in patients with pulmonary emphysema.[26] Regional ventilation can also be studied using Tc99m-DTAP aerosols.[27] Perfusion scan may be normal or near normal in early or mild COPD. With the progression of lung parenchymal destruction, matched nonsegmental ventilation-perfusion defects may be seen. Perfusion defects may also result from bullae themselves or by their compression of adjacent lung tissue. Reduced or absent perfusion in the upper lung zones is seen in the apical bullae.

Preoperative Evaluation of Regional Pulmonary Function

It is important to determine the risk of postoperative pulmonary insufficiency in patients with lung cancer. A forced expiratory volume in 1 second (FEV_1) > 2L or greater than 60% of the predicted value and FEV_1 > 1.5 or over 40% of predicted values are essential for pneumonectomy and lobectomy, respectively.[28] Lung scintigraphy provides a fairly accurate determination of the patient's ability to undergo surgery. The American College of Chest Physicians recommends that quantitative perfusion scintigraphy should be used in patients with borderline lung function to predict postoperative lung function.[29] Split function of each lung is determined from the geometric mean of counts obtained from both the anterior and the posterior lung perfusion images (Fig. 29.6). The postoperative FEV_1 can be calculated by

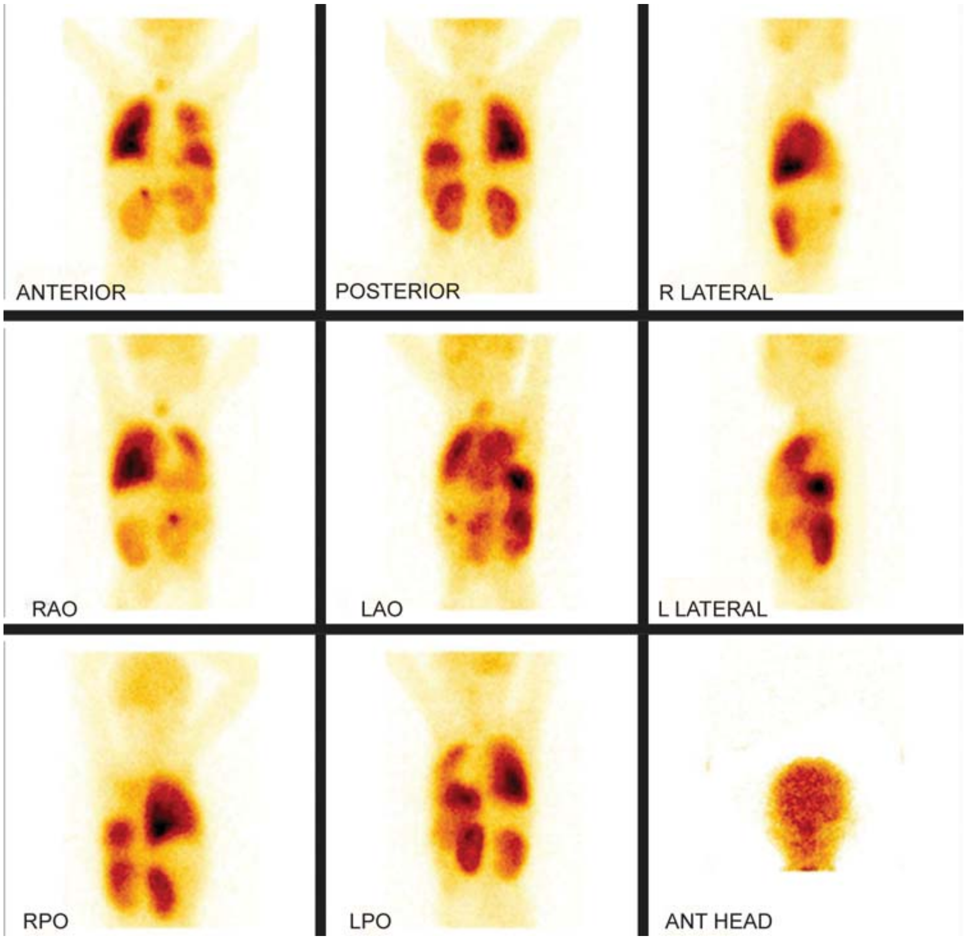

ANTERIOR
POSTERIOR
R LATERAL
RAO
LAO
L LATERAL
RPO
LPO
ANT HEAD

Fig. 29.4: Lungs, kidneys and brain acquired after intravenous injection of Tc99m-macroaggregated albumin (Tc99m-MAA) showing tracer activity in the lungs and in the systemic circulation suggesting right to left shunting

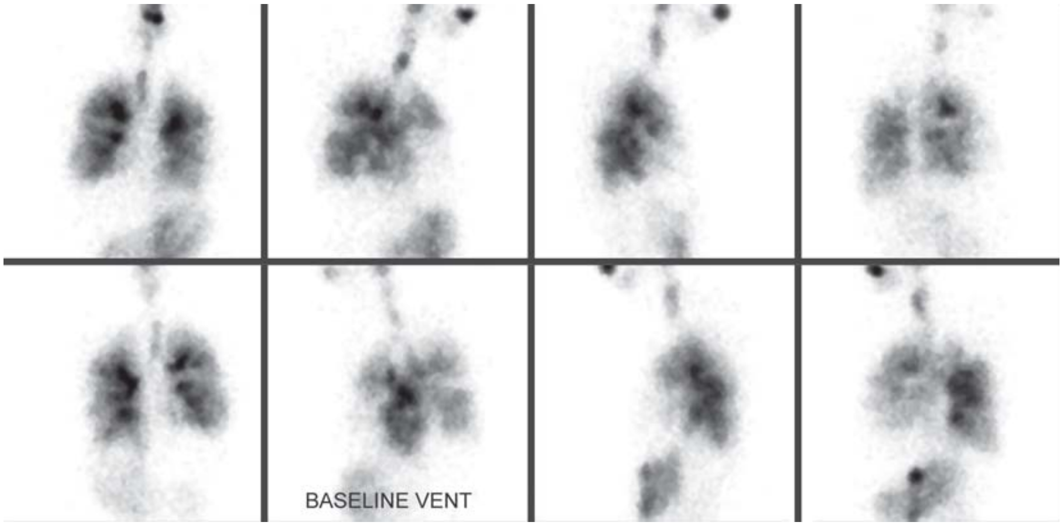
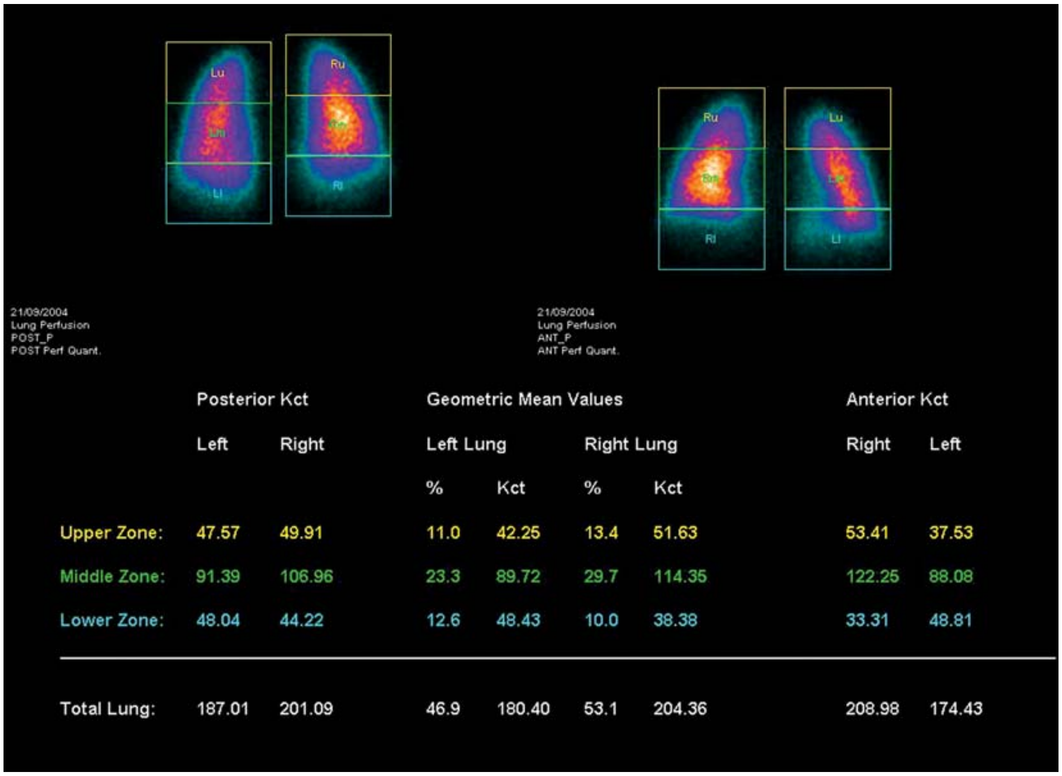

BASELINE VENT

Fig. 29.5: Lung ventilation study, in a patient with bronchial asthma, performed with Tc99m-DTPA aerosol showing central deposition of tracer suggesting obstructive airway disease



21/09/2004
Lung Perfusion
POST_P
POST Perf Quant.

21/09/2004
Lung Perfusion
ANT_P
ANT Perf Quant.

	Posterior Kct		Geometric Mean Values				Anterior Kct	
	Left	Right	Left Lung		Right Lung		Right	Left
			%	Kct	%	Kct		
Upper Zone:	47.57	49.91	11.0	42.25	13.4	51.63	53.41	37.53
Middle Zone:	91.39	106.96	23.3	89.72	29.7	114.35	122.25	88.08
Lower Zone:	48.04	44.22	12.6	48.43	10.0	38.38	33.31	48.81
Total Lung:	187.01	201.09	46.9	180.40	53.1	204.36	208.98	174.43

Fig. 29.6: Tc99m-MAA lung perfusion study with semi-quantitative perfusion analysis. Lungs are divided into three zones and their relative function calculated. The example shows normal function of all the three zones of either lungs

multiplying the global preoperative FEV_1 by the split function of the remaining lung. Ventilation scintigraphy may be a better predictor of postoperative function, but central airway tracer deposition can potentially limit the results.

Inflammatory Lung Diseases

Lung epithelial permeability can be evaluated by studying the clearance of inhaled Tc-99m DTPA aerosol from the lungs.[30-32] Clearance of the tracer is mainly dependent on the epithelial permeability and is only minimally flow dependent. Conditions disrupting the alveolar-capillary membrane, such as the Acute Respiratory Distress Syndrome (ARDS), hyaline membrane disease, sarcoidosis, idiopathic pulmonary fibrosis, systemic sclerosis or inhalational lung injury show rapid clearance of Tc99m-DTPA. Biexponential clearance is always abnormal and indicative of greater lung injury than mono-exponential clearance. In neonates, biexponential clearance curves are observed shortly after birth and become monoexponential after several days, possibly due to the maturation of the surfactant system. Normal Tc-99m DTPA clearance from the lungs is generally between 50 and 80 minutes (T½ approximately 60 minutes).[30] A normal clearance rules out inflammation in the lung from any cause.

Rapid clearance is also observed in active smokers. This is a generalized process throughout the lungs and is proportional to blood carboxyhemoglobin levels. The increased clearance rate is not influenced by the patient's overall smoking history, but rather by their immediate use. Clearance rates can return to normal within three to seven days after the cessation of smoking. Ventilated patients on Positive End Expiratory Pressure (PEEP) or high levels of O_2 (50%) also show more rapid alveolar clearance. Particle deposition in the airways will tend to slow the clearance rates. Patients with primary alveolar proteinosis or congestive heart failure with pulmonary edema also have reduced clearance rates. It is important to exclude extrapulmonary sites of activity (stomach, airways) from the region of interest when determining clearance rates.

Thrombus Imaging

Thrombus imaging may be performed by using either of the following tracers.[33-35]

- Tc-99m-apcitide (AcuTect)
- In-111 platelets
- Tc-99m Antiplatelet antibodies
- Radiolabeled fibrinogen
- Antifibrin antibodies
  - Antifibrin (T2G1s) antibodies F(ab)'2
  - Antifibrin DD-3B6/22 Fab'

Positron Emission Tomography

Positron Emission Tomography (PET) has virtually created a revolution in oncology imaging. F-18 FDG (2-fluoro-2-deoxy-D-glucose) is the most commonly studied PET agent used for the evaluation of malignant tumors. FDG competes with glucose for facilitated transport into tumor cells and also competes with glucose for phosphorylation by hexokinase. Unlike glucose, however, the phosphorylated form is not further metabolized and it gets trapped within the cell. Tumor cells show increased cellular uptake of FDG due to the increased number of surface glucose transport proteins (increased Glut-1 glucose transporter expression) and a higher rate of glycolysis in comparison to non-neoplastic cells. FDG uptake is related to the degree of cell differentiation and increased FDG uptake is generally associated with greater degrees of dedifferentiation. The highly sensitive functional information from PET scan is acquired now in combination with diagnostic quality CT scan for anatomical localization and interpretation.

Lung cancer is the leading cause of cancer death across the world, in part because the disease is usually diagnosed so late. F-18 FDG PET scan finds use in almost all the stages of lung cancer. PET/CT is more accurate with fewer equivocal findings and higher specificity than CT alone for char-acterizing pulmonary nodules. It is useful in the evaluation of a solitary pulmonary nodule measuring more than 8 mm.[36] In a patient with low clinical probability of malignancy, a negative PET scan has a high negative predictive value. The sensitivity of PET/CT for lung cancer is greater than 90%, therefore low to intermediate risk nodules that are metabolically inactive can be followed-up radiographically to ensure stability or resolution. Due to the FDG uptake in benign disorders, as well a positive PET scan in a clinically low-malignancy probability lesion, the patient has to be followed-up with biopsy. In a patient with a high preclinical probability of malignancy, direct biopsy has been found to be useful.

Both Non-Small Cell Carcinoma (NSCLC, squamous cell carcinoma and adenocarcinoma) and Small Cell Carcinoma (SCLC) are FDG avid. However, well-differentiated adenocarcinoma, carcinoid tumor and Bronchoalveolar (BAC) carcinoma show variable FDG uptake and may yield false-negative interpretation. PET is more sensitive than CT for staging of NSCLC, as well as for differentiating lung malignancy from benign lung findings such as postobstructive atelectasis.[37-39] PET scan has a higher diagnostic accuracy for the detection of metastasis in the mediastinal lymph nodes and the presence of distant metastasis (bone, adrenal glands, liver, etc). For stage I and II lung cancers, PET does not replace mediastinoscopy and biopsy. The false negative rate is still higher with PET scan compared with mediastinoscopy. PET is useful in differentiating stage III a (resectable disease) from Stage III b (unresectable disease). Published data indicates that PET/CT provides additional information in almost 40% of patients, with increased accuracy for T stage, as well as the N stage.[40] It is reported that PET/CT detected distant metastases in 92% of patients and was more accurate than CT alone. FDG-PET/CT has become an integral component of NSCLC staging because it improves the detection of nodal and distant metastases and frequently alters patient management (Figs 29.7 and 29.8). Magnetic Resonance Imaging (MRI) is the investigation of choice to detect cerebral metastasis though they may also be seen in a FDG-PET study. Since the FDG uptake is by the background normal brain, it is a less sensitive investigation for the detection of cerebral metastasis. Detection of recurrent disease is another situation in which PET/CT is useful. Recurrence if detected at a time when the disease volume is less, offers a chance for curative resection.

Differentiation of primary tumor (FDG avid) from atelectatic lung (less/non FDG avid) is an issue of concern in planning external beam radiotherapy for NSCLC. Often it is difficult to diagnose chest wall invasion in a case of NSCLC on CT scan. Use of radiation therapy for the curative treatment of lung cancer is limited by the radiosensitivity of surrounding normal structures. This

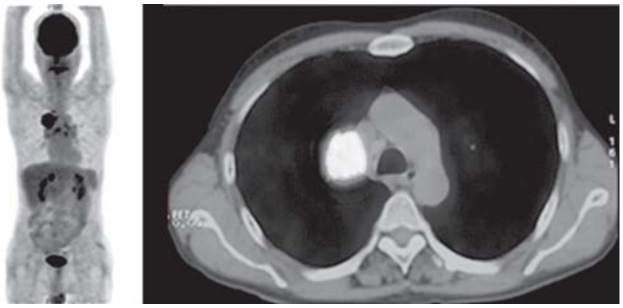


Fig. 29.7: Whole body F-18 FDG PET/CT image (MIP and Transaxial) in a patient with lung cancer showing the hypermetabolic lung tumor with no nodal or distant metastasis thereby enabling curative resection

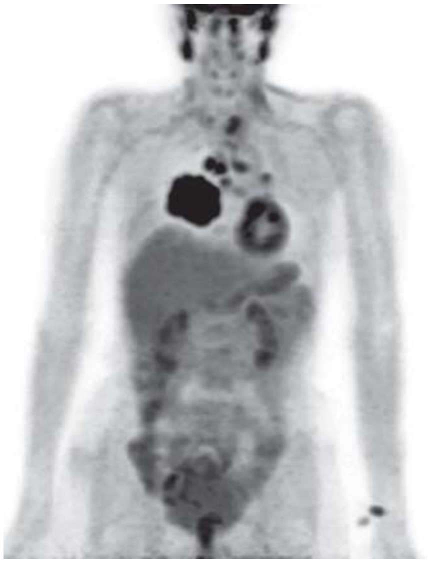


Fig. 29.8: Maximum Intensity Projection (MIP) image of F18-FDG PET/CT showing primary tumor in the right lung with multiple ipsilateral and contralateral mediastinal lymph nodal metastases. The contralateral mediastinal lymph nodes were missed on CT scan because they were sub-centimeter in size. Inclusion of PET prevented a futile thoracotomy

differentiation is easily possible on PET scan. Incorporation of FDG PET images into radiation therapy treatment planning resulted in a 15% to 60% increase or decrease in treated volumes.[41] In 30% to 60% of patients treated with definitive radiotherapy, PET simulation enhanced precision in coverage of the GTV.[42] PET/CT simulation for radiation therapy treatment planning requires the patient to be aligned using the same setup that will be utilized during radiation therapy. 4-D CT respiratory gating can also be utilized. 4-D radiotherapy using PET scan is the optimum method of delivering precisely targeted dose, avoiding normal tissues in the chest.

The assessment of response to therapy with conventional anatomical imaging modalities has inherent limitations. To assess response, for example by using the RECIST 1.1 criteria, a reduction in tumor volume/diameter is required. These changes are often difficult to appreciate on a CT scan and take longer time to become perceptible. Metabolic imaging with FDG PET/CT helps in an early assessment of response to therapy.[43, 44] PET scan is performed after 6–8 weeks of completion of chemotherapy and between 8–12 weeks after the completion of radiotherapy. As per the proposals of recent PERCIST criteria, the total disappearance of FDG avid disease is the complete metabolic response; a reduction of more than 30% in SUL (standardized uptake value) is considered as partial metabolic response; reduction of less than 30% in SUL is stable disease and appearance of new FDG avid lesions or increase in more than 30% is considered as a progressive disease.[45]

Most patients with SCLC have advanced metastatic disease at presentation. There are only a few studies on the role of PET scan in SCLC. These have shown some benefit in the terms of better staging of the patients and in the assessment of response to therapy.

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30

Role of Cytology in Lung Lesions

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CYTOLOGICAL TECHNIQUES IN RESPIRATORY CYTOLOGY

Over the past two decades, there have been dramatic developments in the understanding of pulmonary disease, in the techniques available to identify, define, quantify and evaluate clinical signs and symptoms, radiographic and pulmonary pathology. Technological developments in recent years have rapidly increased the use of less invasive diagnostic techniques in medicine. This trend has influenced the practice of pathology by increasing the use of cytologic material for definitive diagnosis.

The major types of cytologic preparations that are used for the diagnosis of respiratory pathology in laboratories are:

1. Sputum
2. Bronchial washings and aspirates
3. Bronchial brushing
4. Bronchoalveloar Lavage (BAL)
5. Fine-Needle Aspiration Cytology (FNAC):
    - Transthoracic Fine-Needle Aspirations (TTNAs)
    - Transbronchial Fine-Needle Aspirations
6. Pulmonary microvascular cytology
7. Pleural aspirations
8. Imprint cytology of
    - Bronchial biopsy obtained by forceps on bronchoscopy
    - Lung biopsy obtained by transthoracic needle biopsy
    - Mediastinoscopic biopsy

Sputum

Although largely replaced by Fine-Needle Aspiration (FNA) and bronchoscopy, cytological examination of sputum for exfoliated malignant cells still is considered a valuable initial diagnostic test in patients presenting with a lung mass. Exfoliation of cancer cells in sputum from secondary tumors in the lung, is a rare phenomenon in current-day practice, with metastatic colonic adenocarcinoma seen most commonly. Sputum is a specialized product of the respiratory tract, which is the result of an interaction between the mucociliary apparatus and immune system against animate and inanimate invaders from the environment.[1]

A: Sputum may be obtained *spontaneously* or may be *induced*.

1. Spontaneous: Early morning deep cough sputum is taken.
2. Induced: Indicated when patient cannot produce spontaneous deep cough sputum.
   Inhalation of a solution stimulates mucous production. Usual solution used is 15% NaCl + 20% propylene glycol. Heated to 37^o C inhaled for 20 minutes.
3. Postbronchoscopy sputum

B: Sputum can be sent to the laboratory in a *fresh state*, in a *prefixed state*, in *saccomanno fixative* or in Cyto Lyt^R solution.

C: Number of samples: The optimum number of specimens to diagnose cancer is three, and to exclude cancer is five. By using five specimens, the detection rate (sensitivity) can be as high as 90 to 95%.[2,3]

D: Satisfactory specimen:

- For a sputum sample to be considered satisfactory, the sample should have:
  - Alveolar macrophages (dust cells)
  - Respiratory cells in induced sputum and sputum raised following bronchoscopy or other invasive procedures.

E: Impact of specimen collection on the morphology of diagnostic cancer cells: Cancer cells that are expectorated by coughing, originate from tumor close to the lumen of bronchi and from necrotic tumor cells which are discohesive. The diagnostic criteria like nuclear pyknosis in epidermoid carcinoma and nucleolar prominence in adenocarcinoma are actually artifacts due to degenerative changes. These changes can be appreciated in sputum and bronchial wash aspirates rather than bronchial brushing and FNACs. These artifacts are specific and constant enough for typing the tumor as squamous cell and adenocarcinoma respectively.

Bronchoscopy

Gustav Killian[4] in 19th Century developed the rigid bronchoscope to directly visualize the mucosal surface of bronchi and obtain samples for cellular evaluation.

Indications

- Evaluate lung lesions of unknown etiology which appear on X-rays as density, infiltrate, atelectasis or localized by unexplained hemoptysis.
- Origin of unexplained positive sputum cytology
- Stage lung carcinoma and evaluate response to therapy
- Obtain microbiological material for suspected pulmonary infections
- Diffuse and focal lung disease
- Investigate unexplained paralysis of vocal cord, superior vena cava syndrome, chylothorax or unexplained pleural effusion.

Fiberoptic bronchoscope permits the visualization of the lower respiratory tract and a variety of samples can be obtained by the following measures:

1. Bronchial aspirations and washings
2. Bronchial brushings of the suspected lesion
3. Bronchoalveolar lavage
4. Transbronchial fine needle aspirates
5. Imprint cytology of bronchial forceps biopsy.

Bronchial Aspirate and Bronchial Washings

i. *Bronchial aspirates* are obtained by introducing the bronchosope in the lower respiratory tract and aspirating the secretions by suction apparatus.

ii. *Bronchial washings* from the visualized areas are collected by instilling 3–5 ml of a balanced salt solution through the bronchoscope and reaspirating.

Bronchial Brushings

Cell samples are obtained with small brushes under visual control by fiberoptic bronchoscope or by employing imaging guidance technique.

Brushings should be done prior to biopsy procedure to prevent contamination of the specimen by blood.

Bronchoscopic Findings

It is very important to know the bronchoscopic findings before interpreting the bronchial brush cytology.

Bronchoscopy appearance	*Interpretation*
Pale pink:	Normal
Granulation tissue:	Inflammatory mucosal reaction
Irregularity of mucosa:	Early malignancy
Raised lesion:	Malignancy
Cauliflower like with pale yellow or white colour:	Squamous cell carcinoma
Mulberry:	Adenocarcinoma
Necrotic appearance of mucosa:	Small cell carcinoma
Narrowing of airway:	Extrinsic compression by mediastinal nodes

Forceps biopsy can be done for histopathology. Preceding the biopsy, an imprint cytology or "wash technique" (biopsy is put in normal saline, taken out to be sent for histology, while the saline is sent to the cytology lab) can be used and processed for cytology.

Complications:

- Bronchospasm
- Laryngospasm
- Pneumothorax
- Breaking of brushes and forceps
- Fever.

Bronchoalveolar Lavage (BAL)

Bronchoalveolar lavage is based on the concept that cells and noncellular components on the epithelial surface of the alveoli are representative of the inflammatory and immune systems of the entire lower respiratory tract. It is a relatively noninvasive means of sampling the representative cellular component in the alveolar and bronchiolar air spaces. The technique was initially introduced as a therapeutic procedure to remove accumulated secretions in diseases like alveolar proteinosis, cystic fibrosis and asthma. But over the years, this technique has proved to be of immense value in the diagnosis of the following disorders:[5]

1. Detecting opportunistic infections in immunocompromised individuals.[6]
2. Diagnosis and staging of interstitial lung diseases, such as:[7]
   a. *Specific interstitial lung diseases*
      I. Idiopathic pulmonary fibrosis (IPF)[8]
      II. Pulmonary fibrosis associated with collagen vascular disorders (PF-CV)
      III. Hypersensitive pneumonitis (HSP)
      IV. Extrinsic allergic alveolitis (EAA)
      V. Asbestos related interstitial disease
      VI. Silicosis
      VII. Beryllosis
      VIII. Sarcoidosis
      IX. Lipoid pneumonia[9]
   b. *Rare interstitial lung disease*
      I. Histiocytosis-X
      II. Chronic eosinophilic pneumonia[10]
      III. Alveolar hemorrhage: Hemosiderin-laden macrophages
      IV. Obliterative bronchiolitis
3. Detection of lung cancer[11]
   a. Bronchioloalveolar carcinoma
   b. Lymphangitic carcinomatosis

Technique and Processing

The middle lobe or lingula is lavaged routinely in the absence of any localized lesion. The tip of the bronchoscope is wedged into a subsegmental bronchus at the level of fourth or fifth branching. 0.9% sterile saline is inserted at room temperature and reaspirated in 20–50 ml aliquots. This is repeated five times at each site.

Lavage procedure is considered invalid if:

1. There is a presence of purulent secretions in the airways.
2. Bronchoscope is not maintained in wedge position during lavage.
3. Volume of fluid recovered is less than 40% of the volume infused.

Normal Constituents of BAL[12]

In a nonsmoker:

Alveolar macrophages	$\geq$ 85%
Lymphocytes	10-15%
Neutrophils	$\leq$ 1%
Eosinophils	$\leq$ 1%
Ciliated columnar cells	$\leq$ 2 %
T4 : T8 ratio	0 .9–2.5

In smokers, the cell yield is four times greater, with slightly increased number of neutrophils.

BAL: Cell counts are useful in the diagnosis and prognosis of certain disorders.

1. Cell Counts

The presence of increased nucleated cells is of no diagnostic or prognostic value. The reasons for increase in various types of inflammatory cells is shown in Table 30.1.

2. Diagnosis

- Infective agent
- Malignant cells

3. Diagnosis Aided by Special Stains, Additional Stains or Studies

- Langerhans cell histiocytosis (S100)
- Alveolar proteinosis (PAS)
- Pneumoconiosis
- Berylliosis – Positive lymphocyte transformation test

TABLE 30.1: Increase in inflammatory cells

↑ Lymphocytes	↑ Eosinophils	↑ Neutrophils
Sarcoidosis (active) (T4-T8↑) >1	Eosinophilic pneumonia	Collagen vascular disorders
Berylliosis Hypersensitivity pneumonitis (T4: T8 ↓) <1	Collagen vascular disorders	Idiopathic pulmonary fibrosis
Silicosis	Infection due to helminths, fungi	Bacterial and fungal infections
TB and viral infections	Asthma	Bronchitis
	Allergic broncho-pulmonary aspergillosis	Asbestosis and ARDS

4. Cell Counts in Evaluating Prognosis of the Disease

a. Idiopathic pulmonary fibrosis (IPF):
↑ T lymphocytes—good prognosis
↑ Eosinophils in IPF—poor prognosis
b. Collagen vascular diseases
↑ Neutrophils—presence of interstitial involvement
↑ Lymphocytes—clinically stable collagen vascular disease.
c. HSP—↑ T8 protects against pulmonary fibrosis
d. Sarcoidosis: Ratio T4:T8 normal—stable course of diseases
Ratio T4: T8—↑ deterioration in clinical course
BAL lymphocytes > 35% Poor response to therapy
BAL lymphocytes < 35% Good response to therapy
e. Asbestosis: Presence of asbestos body—indicates exposure
Asbestos body with increased lymphocytes, neutrophils and eosinophils indicates subclinical pulmonary involvement.
f. Berylliosis—similar to Sarcoidosis.

ASPIRATIONS

First report of needle biopsy of the lung was prepared by Leyden in 1883 who used it for the diagnosis of pneumonia. In 1886, Menetrier used it for lung cancer. In 1930, Martin and Ellis used this technique with the thin needle followed by Grover and Bindley in 1939.[13,14] X-ray enhanced television screen was used by Söderström in 1966, followed by Sinner and Nordenström in 1975.[15,16] Since most lung masses are carcinomatous in origin, depending on various factors (age, sex, smoking habit and size), the recommendation of FNA as the first line investigation warranted because of high yield to risk for complication ratio.[17]

A. Transbronchial Needle Aspiration (TBNA)

Transbronchial needle aspiration is a special modification of fine-needle aspiration for those cases in which lung neoplasm has not invaded the mucosa, and is therefore inaccessible by sputum or brushing washings.[18-20] This aspiration is done under bronchoscopic, fluoroscopic and Computed Tomography (CT) guidance and the samples are processed through conventional techniques.

Indications of TBNA

1. Mediastinum–diagnosis and staging of lung carcinoma
2. Hilar lesions
3. Intraluminal lesions which are necrotic (so as to sample non necrotic areas) or submucosal (carcinoids, bronchial gland tumor).
4. Parenchymal coin lesions
5. Pancoast tumor
6. Benign parenchymal lesions like sarcoidosis or other granulomatous conditions.

B. Transthoracic Fine-Needle Aspiration Cytology

In this technique, a fine needle (with external diameter 0.6mm, length 10-20 cms) is passed through the chest wall into the pulmonary mass, usually visualized by fluoroscopy or CT. Air dried and wet fixed smears are made from aspirated material and stained by May-Grünwald Giemsa (MGG) and Papanicolaou (PAP) stains.

If the lesion is very deep and small (≤ 2 cm), then wider bore needle with 0.9–1 mm external diameter should be used. If the lesion is hard and solid (Hamartoma and calcified granulomas), the "screw biopsy" is indicated, where a stylet with screw tip is introduced through the needle into the lesion and fixed, which facilitates penetration of the hard tumor by the needle.

Indications for TTNA: The main indication for TTNA is suspected lung cancer patient with negative results for malignant cells, on five consecutive sputum samples, bronchial brush or wash. Other indications are inoperable lung cancer, solitary pulmonary mass, multiple pulmonary masses, superior sulcus tumor, refusal to undergo exploratory thoracotomy, failure to respond to antitubercular therapy or suspected infectious process.

Contraindications:
- Debilitated uncooperative patients who have uncontrollable cough
- Vascular lesion, pulmonary hypertension, bleeding diathesis or anticoagulant therapy
- Echinococcus cyst.

Complications:
- Pneumothorax 2.6%[21]
- Air embolism
- Hemothorax
- Hemoptysis.

C. Pulmonary Microvascular Cytology

Pulmonary microvascular cytology is the examination of a blood sample drawn through a wedged pulmonary artery catheter to diagnose lymphatic carcinomatosis. The blood must be collected in a heparinized tube. In the laboratory, the specimen is placed on a Ficoll-Hypaque gradient to remove the blood and concentrate diagnostic cells.[22]

D. Pleural Aspirations

A proper cytopreparatory technique for effusions is very important for correct interpretation of the disease process occurring in the pleura. A poorly prepared smear causes diagnostic problems and may result in both false-positive and false-negative diagnosis.

To ensure an optimal cytopreparation, certain prerequisites should be fulfilled:

Immediate submission of unfixed specimen to the cytology lab with the immediate processing of the material is mandatory. The fluid is processed by *wet mount technique* where, one drop of centrifuged sediment is added to one drop of toluidine blue solution (0.5 mg of toluidine blue + 20 ml 95% alcohol, 80 ml distilled water)

This technique is performed for:

- Rapid diagnosis of malignancy
- Judge cellularity: If the specimens are very cellular, they should be stained separately to prevent cross contamination while poorly cellular specimens are processed by cytocentrifugation or filtration techniques.
- Ancillary tests: Additional smears may be prepared for special stains, flow cytometry and electron microscopy.
- Preparation of cell block for histochemical and immunohistochemial evaluation.

IMPRINT CYTOLOGY

Imprint can be made from bronchoscopic biopsies, obtained by forceps or transthoracic needle biopsy or mediastinoscopic biopsy. The smears are wet fixed and can be stained by Rapid H and E or PAP.

The sensitivity (tumor detection) and specificity (tumor typing) of sputum and BAL/ bronchial brushings is approximately 70 to 80%.

The sensitivity when all three (brush, biopsy, imprint) methods are used together may be as high as 97%; the specificity approaches 100%.[23]

ENDOSCOPIC ULTRASONOGRAPHY GUIDED FNA AND ENDOBRONCHIAL ULTRASOUND FNA

Endoscopic Ultrasonography (EUS) is a novel method for staging of the mediastinum in lung cancer patients. The recent development of linear scanners enabled safe and accurate FNA of mediastinal and upper abdominal structures under real-time ultrasound guidance.[24] EUS-FNA may replace CT-guided biopsies and reduce the number of exploratory thoracotomies.[25] Bronchoscopy can fail to establish a diagnosis in up to 30% of patients with suspected lung cancer. Intrapulmonary tumors located near or adjacent to the esophagus can be visualized and biopsied under real-time ultrasound guidance by EUS-FNA.[26] Endoscopic ultrasonography-FNA is a minimally invasive procedure that can be used as an adjunct or alternative to mediastinoscopy.[27] The technique is safe and it greatly reduces the number of surgical interventions.[28-30]

Endobronchial Ultrasound (EBUS) with real-time TBNA offers improved sensitivity and accuracy for staging of the middle mediastinum, and, combined with endoscopic ultrasound, should allow investigation of the majority of the mediastinum.[31-33]

INFLAMMATORY DISEASES OF THE LUNG

Acute Inflammation

Acute inflammation is characterized by the presence of neutrophils, histiocytes, debris, and necrosis in pneumonia, abscess and purulent bronchitis, resulting in tissue destruction.

Chronic Inflammation

Nonspecific

Nonspecific chronic inflammation is common.

Follicular Bronchitis

An abundance of immature lymphocytes can point towards follicular bronchitis. This should be distinguished from non-Hodgkin's lymphoma or small cell carcinoma.

Granulomatous Inflammation

Collections of epithelioid histiocytes along with giant cells indicate granulomatous inflammation (Fig. 30.1). In sputum, epithelioid histiocytes may be shaped like elongated cones that stain pink to orange when degenerated and look like carrots, hence are termed "carrot cells." These should be differentiated from bronchial epithelial cells, especially in bronchial brushings or aspiration cytology.

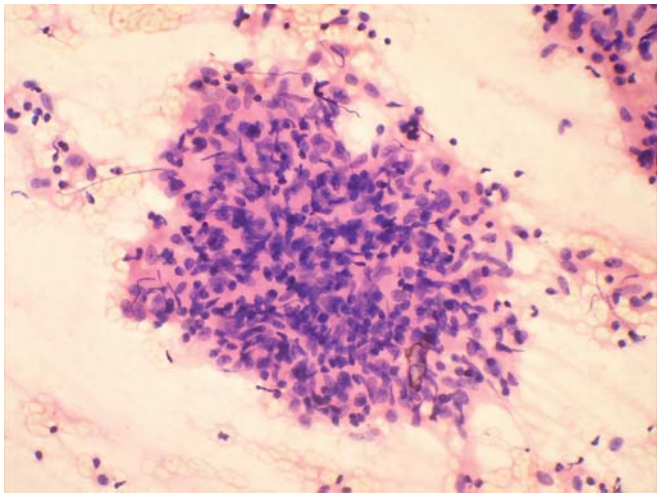

Fig. 30.1: Collection epithelioid cells and lymphocytes forming a granuloma (H and E, 20X)

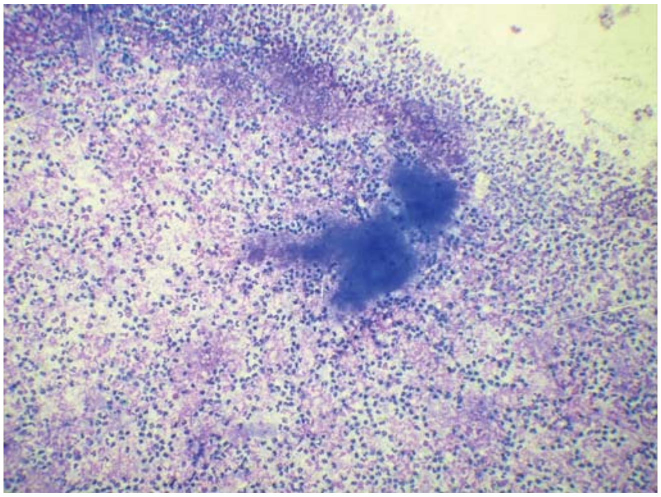

Fig. 30.2: Sheets of degenerated acute inflammatory cells in a necrotic background (MGG, 10X)

Tuberculosis

Epithelioid histiocytes, giant cells (Langhans' type), lymphocytes, and a necrotic caseous background is diagnostic of tuberculosis (Fig. 30.2).[34]

Giant cells are seen in sputum in up to half of cases of pulmonary tuberculosis, however, typical Langhans giant cells are present in only as few as 5% of cases.[35] In tuberculosis, epithelioid histiocytes are found in about 25 to 50% of sputum specimens.[36] In sputum specimens in which either Langhans giant cells or epithelioid histiocytes are seen, almost 60% of the patients have tuberculosis, depending upon the patient population.[37,38] Identification of beaded acid-fast bacilli or a positive culture clinches the definitive diagnosis of tuberculosis. The differential diagnosis of necrotizing granulomas includes fungal infections and Wegener's granulomatosis.[39]

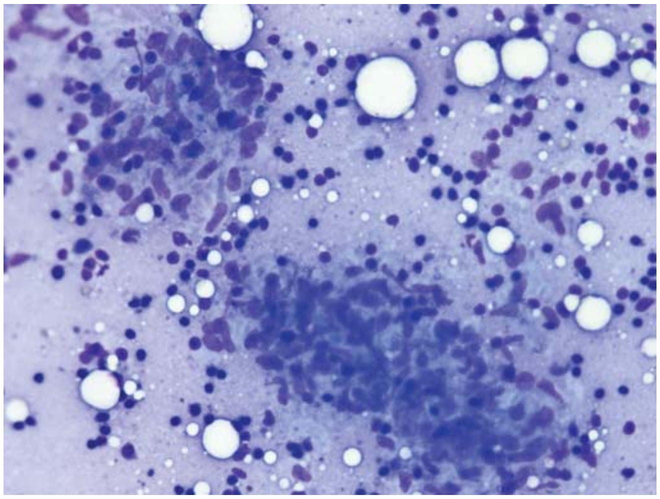

Fig. 30.3: Epithelioid cell collections along with lymphocytes in a case of sarcoidosis (MGG, 40X)

Sarcoidosis

It is a chronic granulomatous disease of unknown etiology. Epithelioid histiocytes or giant cells are seen with absence of caseation necrosis (Fig. 30.3).

Rheumatoid granulomas can also exfoliate epithelioid histiocytes with bizarre shapes. Background may have marked inflammation and necrotic debris.

Specific Infections

Cytologic methods are increasingly being used to diagnose opportunistic infections, especially in immunosuppressed patients.

Viral Pneumonia: Viral infections, such as cytomegalovirus are commonly seen in immunocompromised patients.[40] Viral infection can also cause reactive changes in bronchial cells and it becomes difficult to distinguish the same from bronchioloalveolar carcinoma.

Candida, Bacterial Colonies: First rule out oral contamination, overgrowth.

Miscellaneous Infections: Fungi, pneumocystis, toxoplasma, etc. mostly seen in immunosuppressed patients.[41-43]

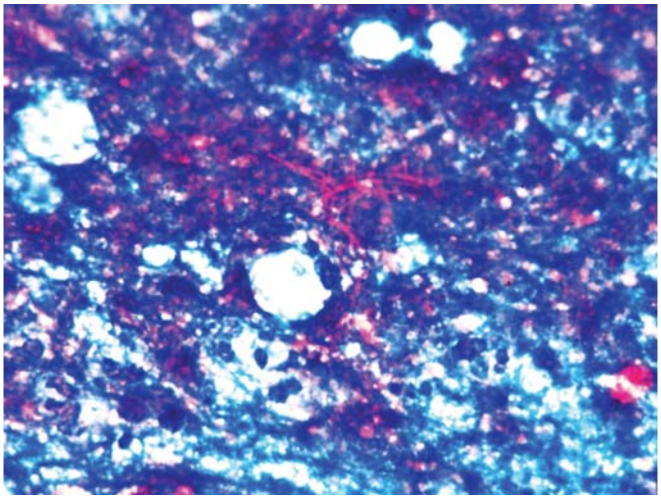

Fig. 30.4: Multiple thin long filamentous branching filamentous structures (Nocardia) in an inflammatory background (Modified Ziehl-Neilsen stain, 100X).

Hemophilus, *Staphylococcus* and *Streptococcus* species, *Klebsiella*, anaerobic, or mixed flora are common and can cause lung abscess.[44,45] Fungi, especially *Mucor* or *Aspergillus*, as well as *Actinomyces* or *Nocardia* (Fig. 30.4),[46,47] can also cause pulmonary abscesses.[48]

Reactive atypia and squamous metaplasia associated with epithelioid granulomas, particularly due to tuberculosis or *Aspergillus* can lead to a false-positive diagnosis of cancer.[49,50] And also, granulomas can coexist with cancer.

When an infectious disease is suspected, the left over sample should be submitted for cultures and special stains.[51] Culture in FNA specimens is a useful adjunct to diagnosis. This method can be used to triage patients with suspected infectious diseases and can aid in managing patients who may have recurrent infections.[52]

Echinococcus—is considered a contraindication to FNAC or biopsy.[53]

In lung FNA specimens, culture and special stains should be restricted to specimens with acute inflammation or necrosis. Gram's stain and fungal culture are insensitive and not cost-effective, and fungi are often identifiable with routine stains.[54]

Cytomegalovirus infection leads to presence of large cells with a nucleus having a large, smooth, amphophilic intranuclear inclusion (Fig. 30.5). The inclusion has a prominent halo, and thin strands of chromatin connect the inclusion with the inner nuclear membrane.[55]

Herpes simplex: Herpes simplex virus pneumonia is a disease of immune compromised individuals. It is characterized by intranuclear inclusions with nuclear enlargement with basophilic ground-glass alterations in the nucleoplasm. Later, the inclusions may coalesce to form single eosinophilic inclusion body surrounded by a halo.

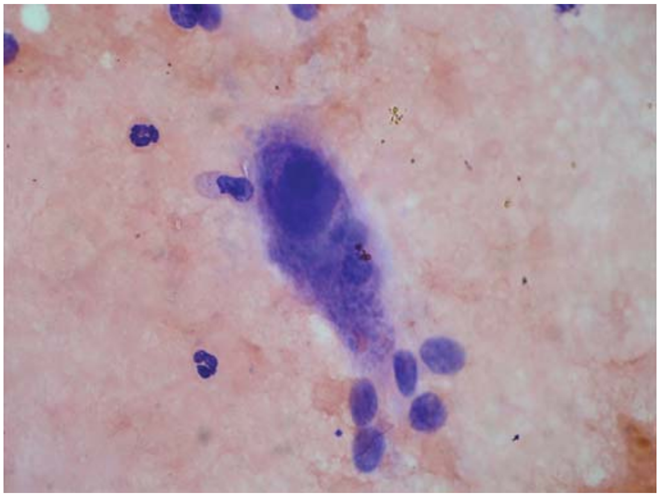

Fig. 30.5: A single cell showing marked nucleomegaly with a basophilic nuclear inclusion in a case of CMV infection (MGG, 100X)

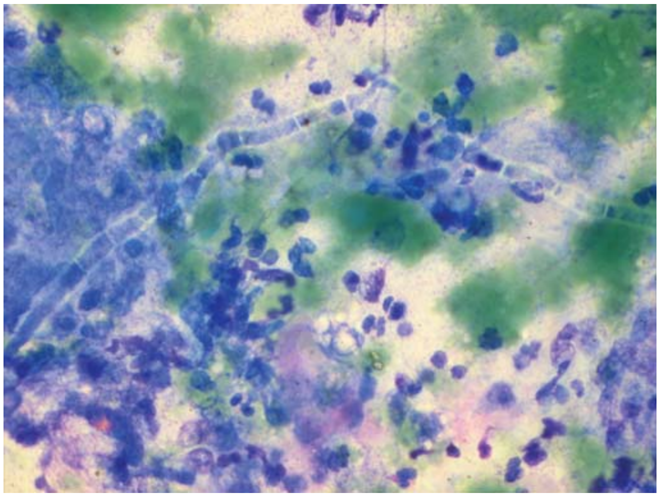

Fig. 30.6: A long septate hyphae with parallel cell walls of the fungus-aspergillus in a necrotic inflammatory background (MGG, 40X)

Aspergillus (fumigatus, niger) is characterized by 45° angle branching of true, septate fungal hyphae of 3 to 6 µm uniform width (Fig. 30.6). Fruiting bodies (conidiophores) are rarely seen.

Coccidioides (immitis) is marked by nonbudding, thick-walled spherules, measuring 20 to 60 µm and round, nonbudding endospores measuring 1 to 5 µm.

Cryptococcus (neoformans) organisms measure 5 to 20 µm and have a very thick, gelatinous capsule which stains

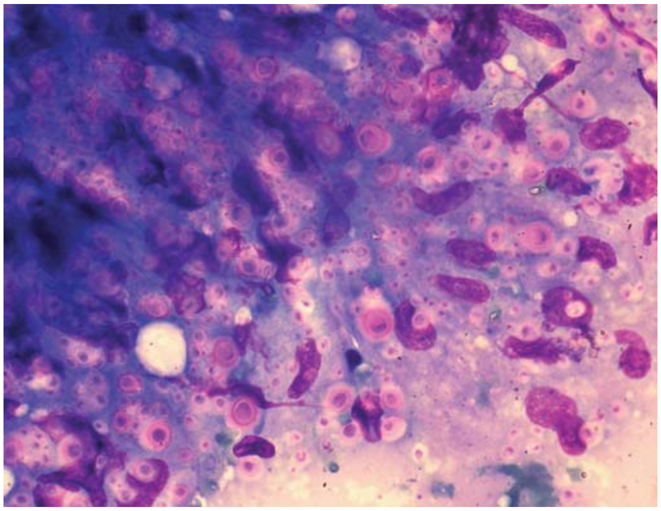

Fig. 30.7: Many extracellular organisms of varying sizes 5 to 15 mm in diameter with evidence of budding in a case of Cryptococcosis (MGG, 100X)

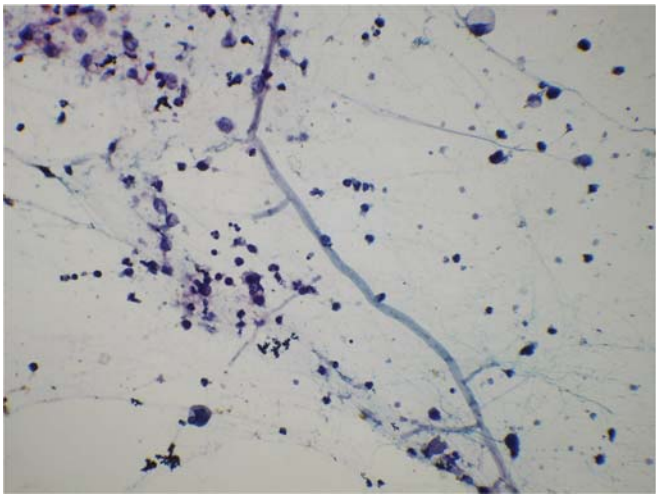

Fig. 30.9: Mucormycosis-Broad (from 5–20 µm), irregular, thin-walled, folding on themselves, ribbon-like, aseptate hyphae that branch at irregular intervals, often at 90° angles (PAP, 40X)

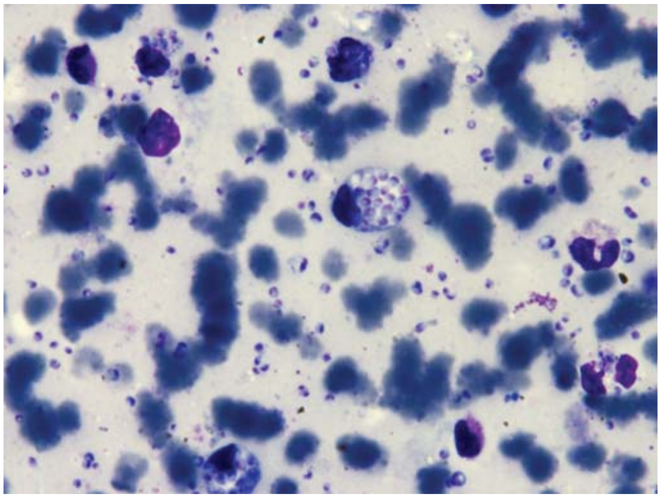

Fig. 30.8: Numerous round to oval, 2–4 µm in diameter, budding yeasts of Histoplasma present both extracellularly as well as intracellularly within histiocytes (MGG, 100X)

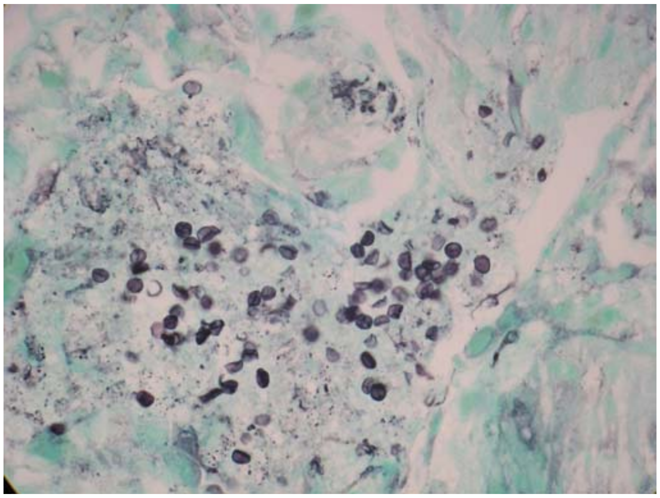

Fig. 30.10: Many cysts, 4 to 8 µm in diameter and spherical to cup shaped in a case of *Pneumocystis jeroveci* (Methenamine Silver stain, 100X)

well with special stains, such as mucicarmine, alcian blue or PAS. Single, teardrop-shaped budding is quite characteristic (Fig. 30.7).

Histoplasma (capsulatum) is a round to oval, budding yeast, measuring 1 to 5 µm which should be identified within cytoplasm of a histiocyte or neutrophil to be diagnostic (Fig. 30.8).

Zygomycetes (*Mucor*, *Rhizopus*, etc.) exhibit broad (from 5–20 µm), irregular, thin-walled, folding on themselves, ribbon-like aseptate hyphae that branch at irregular intervals, often at 90° angles (Fig. 30.9).

Pneumocystis jeroveci is seen more commonly in patients with acquired immunodeficiency syndrome.[56] Organisms are seen in foamy/flocculent alveolar casts (rounded masses of organisms). In GMS, the cell wall of the cyst stains black, often with a central dark dot. Cysts are 4 to 8 µm in diameter and spherical or cup shaped (Fig. 30.10). Trophozoites can be upto 8 per cyst, are about 0.5 to 1.0 µm in diameter. Trophozoites stain in Romanovsky (tiny purple dots).

Echinococcus granulosus (hydatid disease) is considered a contraindication due to possible anaphylaxis. Hydatid

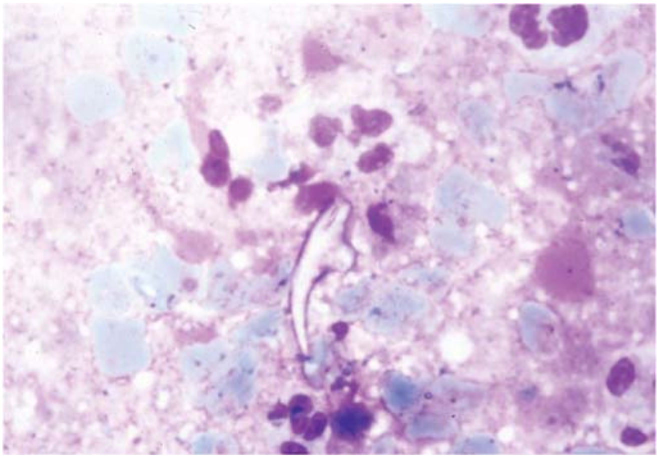

Fig. 30.11: Hooklet of hydatid in a necrotic background (MGG, 100X)

"sand" aspirated from a hydatid cyst shows both scoleces of *Echinococcus* and their hooks (Fig. 30.11).

NEOPLASTIC LESIONS OF THE LUNG

Cytological Classification of Lung Tumors

1. Squamous cell carcinoma
   - Well differentiated
   - Poorly differentiated
2. Small cell carcinoma
   - Oat cell type
   - Intermediate cell type
3. Adenocarcinoma
   - Well differentiated
   - Poorly differentiated
   - Bronchoalveolar
4. Large cell carcinoma
   - Giant cell type
5. Adenosquamous carcinoma
6. Carcinoid tumor
7. Adenoid cystic carcinoma[57]
8. Mucoepidermoid carcinoma
9. Carcinosarcoma
10. Others

However, there is also concept that diagnostic binary categorization of lung carcinoma into small cell carcinoma versus non-small cell carcinoma and evaluation of tumor stage have the only real significant effect on current patient management.

Squamous Cell Carcinoma (SCC)

This is the commonest tumor of the lung, but its incidence is decreasing.[58] It is strongly associated with cigarette smoking. Most SCC arises in the mucosa of the larger bronchi and therefore are generally located in the perihilar or central area.[59]

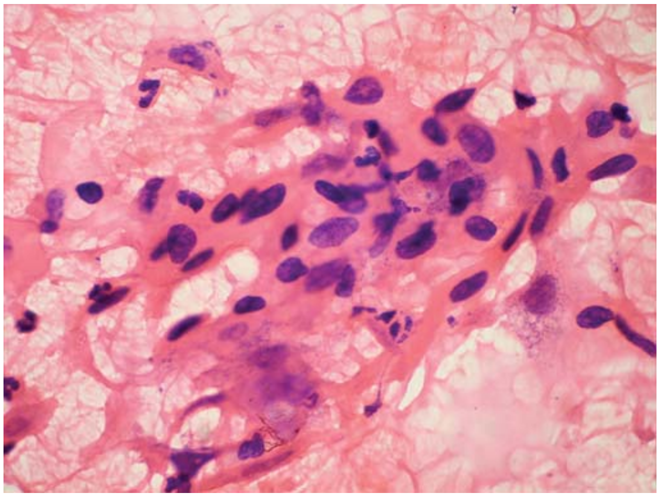

Fig. 30.12: Keratinized highly pleomorphic squamous cells with irregular shapes and staining reactions with many spindle shaped cells (H and E, 40X)

Cytologically, the tumors may be composed of large, pleomorphic to bizarre, poorly cohesive cells to small, uniform and cohesive cells. The nuclei of the cells show hyperchromasia, pyknosis and a coarse chromatin (Fig. 30.12). A typical background may consist of many degenerated cells with blurred outlines and the malignant cells.

The differential diagnosis of Non-keratinising SCC with poorly differentiated adenocarcinoma may be difficult. Very poorly differentiated SCC should also be distinguished from small cell carcinoma. Benign reactive changes due to infectious agents, particularly tuberculosis or fungi, or infarction, can mimic squamous cell carcinoma.

Adenocarcinoma

Adenocarcinoma is the most common primary peripheral lung cancer and occurs more commonly in nonsmokers. Scars in lung cancer have been classically associated with adenocarcinoma. Two basic types of adenocarcinoma are: (1) bronchogenic, the more common type, arising from or mimicking bronchial glands or mucous goblet cells, and (2) Bronchioloalveolar Carcinoma (BAC).[60]

Adenocarcinoma can show a wide range of differentiation, from very well differentiated to anaplastic and finally giant cell carcinoma.

Cytologically: The tumor cells can be singly scattered or tightly clustered. The key diagnostic feature is the

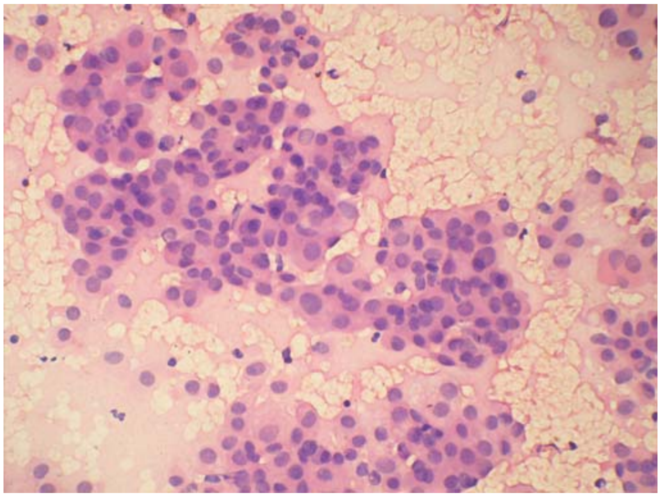

Fig. 30.13: Flat monolayered sheets or cell clusters of regular, small to intermediate sized cells with moderate cytoplasm and fine chromatin (H and E, 40X)

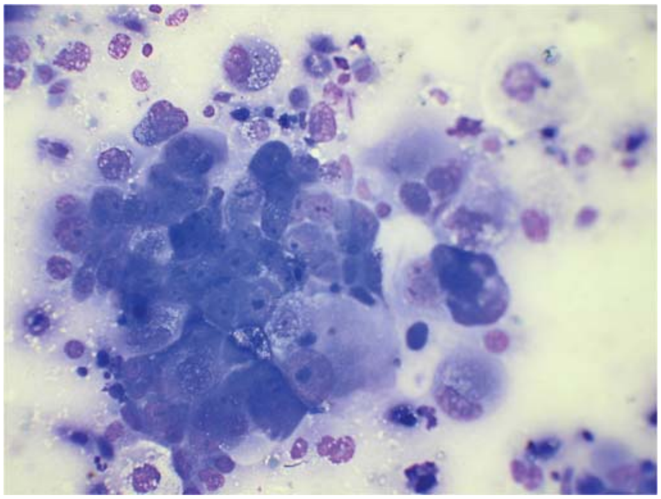

Fig. 30.14: Loosely cohesive cluster of malignant cells with moderate amount of vacuolated cytoplasm, coarse chromatin and prominent nucleoli (MGG, 100X)

formation of glands or papillae, or evidence of mucin production by the malignant cells. The cells are large with classical parameters of malignancy including variable size and shape, coarse chromatin and prominent nucleoli (Figs 30.13 and 30.14). The cytoplasm is pale gray thin and sparsely vacuolated, at times it may be abundant. Two basic subtypes of BAC are mucinous (secretory) and the more common non-mucinous (nonsecretory or serous).[61] Subtyping is based on the quality of the cytoplasm, but there is a significant degree of overlap in the cytological features.[62]

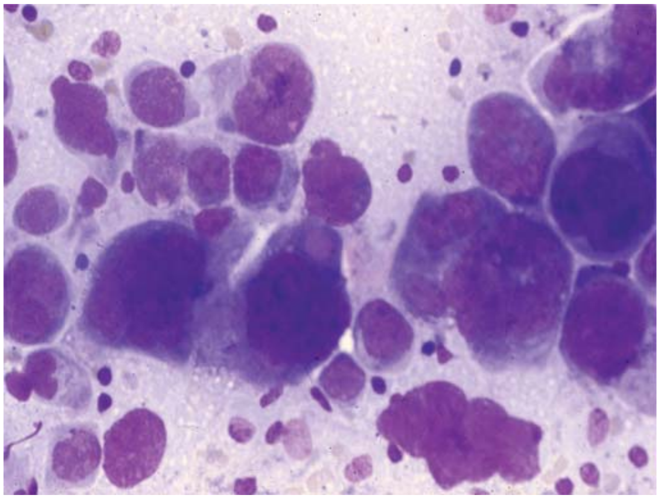

Fig. 30.15: Dispersed population of obviously malignant cells in a case of large cell anaplastic carcinoma (MGG, 100X)

In bronchoalveolar carcinoma, the cells are tall and columnar with anaplastic changes and at times may be confused with metastatic colonic adenocarcinoma.

The differential diagnosis includes large cell undifferentiated carcinoma, metastatic adenocarcinoma and non-keratinizing SCC. Benign reactions due to pneumonia; infarcts; or physical, chemical, or infectious agents can also lead to false-positive results.

Large Cell Undifferentiated Carcinoma

Most of these tumors occur in men and are associated with smoking. These grow rapidly and have poor prognosis. These types of tumors yield irregular groups and dispersed population of obviously malignant cells (Fig. 30.15). The texture of nucleus is finely granular with gray blue cytoplasm. The cells are generally in groups and consist of cell population with large irregular, single nucleus or multinucleation may be seen.

Small Cell Carcinoma

It is thought to arise from primitive cells that have the capacity for Kulchitsky (neuroendocrine) cell differentiation. Small cell carcinoma has the strongest relationship to cigarette smoking and rarely occurs in nonsmokers.[63,64]

Small cell carcinoma is usually centrally located. The tumor characteristically metastasizes extensively to hilar and mediastinal lymph nodes.[65] Fine-needle aspiration cytology is accurate and reliable in the diagnosis of small cell carcinoma.[66,67]

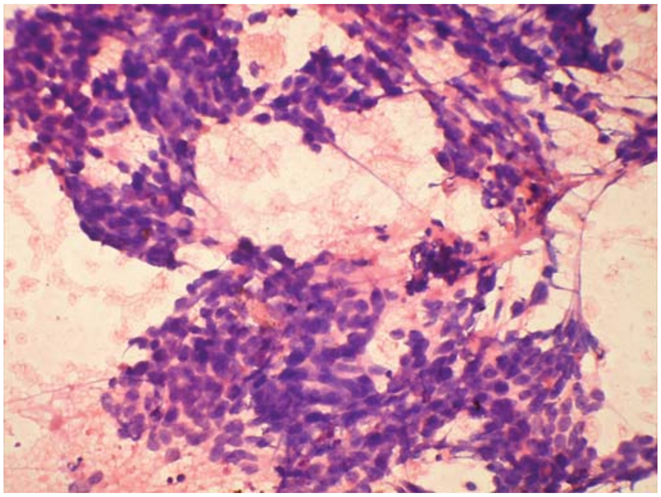

Fig. 30.16: Pleomorphic poorly cohesive cells with little or no cytoplasm and prominent crushing artifact (H and E, 40X)

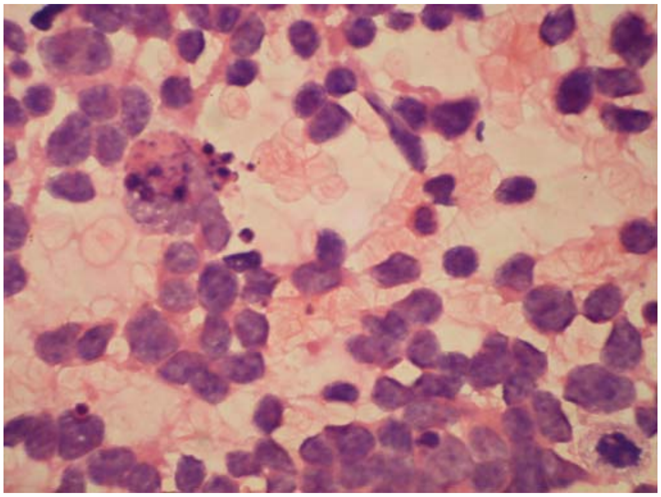

Fig. 30.17: Pleomorphic poorly cohesive cells with absent cytoplasm, nuclear molding, tear drop cells and inconspicuous nucleoli (H and E, 100X)

The aspirated material is abundant and semisolid. The smears are thick and the cells are easily traumatized. The cells have superficial resemblance to lymphocytes but are large round to oval or elongated. They form clusters and have classical tendency towards molding or "Indian file pattern." Crush artifact is quite characteristic of small cell carcinoma in FNA biopsy specimens (Figs 30.16 and 30.17). Small cell carcinoma usually demonstrates features of neuroendocrine origin immunocytochemically, including neuron-specific enolase, neurofilament proteins, synaptophysin, Leu-7, and sometimes chromogranin, and may also be positive for keratin.[68]

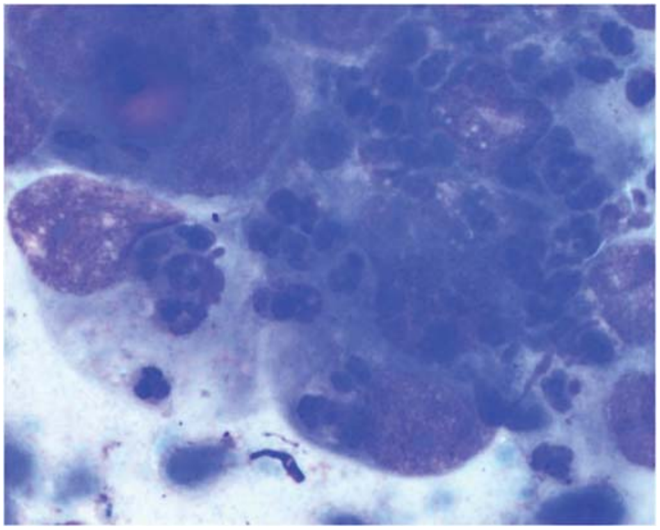

Fig. 30.18: A cluster of obviously malignant cells with marked pleomorphism admixed with polymorphs (MGG, 100X)

The differential diagnosis includes a carcinoid, poorly differentiated squamous and adenocarcinoma, non-Hodgkin's lymphoma or malignant small blue round cell tumors.

Giant Cell Carcinoma

Giant cell carcinoma comprises a heterogeneous group of tumors. Mostly occurs peripherally. This tumor may be a dedifferentiated adenocarcinoma or SCC; a subset of large cell undifferentiated carcinoma; or a specific entity not directly related to other types of lung cancer. Cytologically, smears show the presence of a significant number of multinucleated malignant tumor giant cells with obvious malignant atypia (Fig. 30.18).[69] These tumors are typically associated with neutrophillic infiltration along with prominent neutrophilic phagocytosis by tumor cells (Fig. 30.19).[70]

Neuroendocrine Tumors of the Lung

The following tumors are encountered in this category:

- Typical carcinoid tumor: Central, oncocytic and peripheral types
- Atypical carcinoid tumor
- Large cell neuroendocrine carcinoma
- Small cell carcinoma with neuroendocrine features.

Carcinoids account for about 5% of cases of lung cancer.

Central Carcinoid Tumor

Central carcinoid tumor usually presents with a slow-growing polypoid mass within a major bronchus, can be

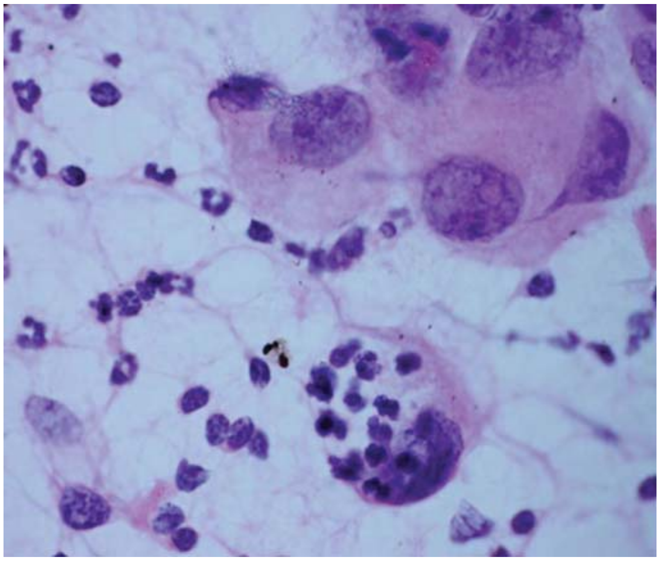

Fig. 30.19: Tumor cells showing neutrophilic phagocytosis in a case of giant cell carcinoma lung (H and E, 100X)

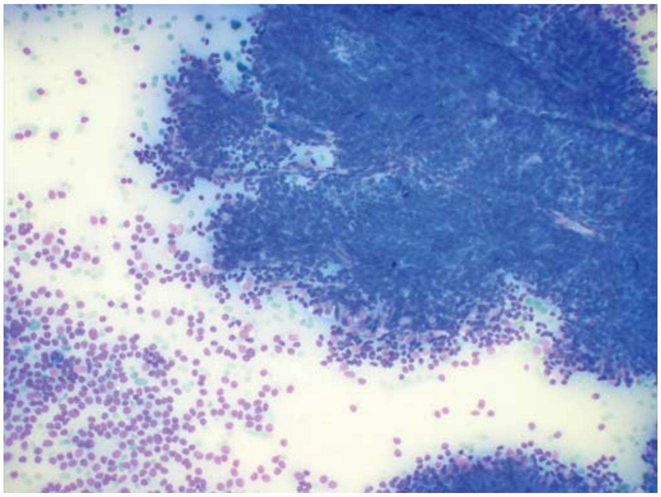

Fig. 30.20: A highly cellular smear showing tumor cells with prominent pericapillary arrangement and dispersed tumor cells (MGG, 10X)

non-hormone producing tumor, and some produce carcinoid syndrome. It is common in young adults and children. Infiltration in the surrounding tissues from the bronchus may occur. Cytologically, it shows a loosely cohesive population of monotonous cells (Fig. 30.20).[71] Rosettes, palisades or small clusters may also be seen. If there is extensive crush artifact, confusion with small cell carcinoma may occur.

Metastases to regional lymph nodes are occasionally reported in about 5% cases. Rarely metastases in bones occur which are of osteoblastic type. Surgery is the treatment of choice and the prognosis is excellent.

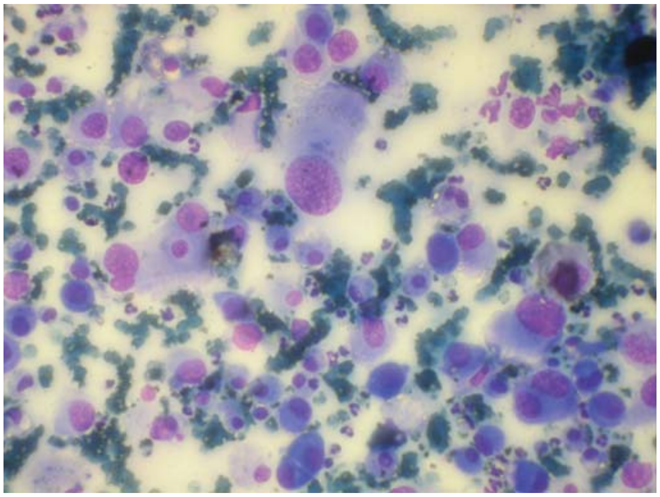

Fig. 30.21: Dispersed population of tumor cells exhibiting sudden anisonucleosis, eccentrically placed nuclei with stippled chromatin and prominent nucleoli (MGG, 40X)

Oncocytic carcinoid is a variant of central carcinoid in which the tumor cells have abundant, granular acidophilic cytoplasm. Electron microscopy shows numerous mitochondria with dense core secretory granules.

Peripheral Carcinoid Tumor

Peripheral carcinoid tumor usually occurs in peripheral lung beneath pleura and is discovered incidentally. Peripheral carcinoids tend to be more aggressive than central carcinoids, especially when the tumor is composed of spindle cells.[72] Pleomorphism and mitosis are present. The prognosis is excellent after surgical removal.

Atypical Carcinoid Tumor

This type of tumor possibly represents a link between typical carcinoid tumor and small cell carcinoma. These have been associated with smoking.[73] Cytologically, the tumor cells are larger than those of either typical carcinoid or small cell carcinoma (Fig. 30.21). Single cells are present with atypical features like increased mitosis, necrosis and nuclear hyperchromasia. Extensive metastasis occurs in lymph nodes. The behavior is aggressive.

Pulmonary Hamartoma

Hamartoma accounts for about 75% of benign lung tumors. It is usually solitary and presents as an asymptomatic clear cut small shadow just beneath the pleura in the lung parenchyma. Radiologically, calcification is seen

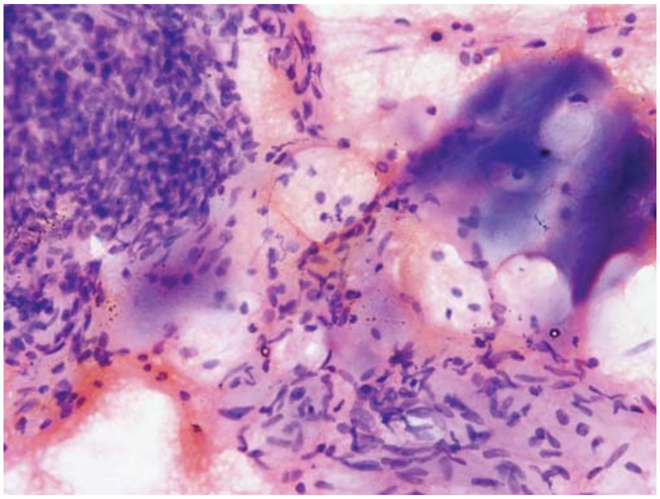

Fig. 30.22: Chondroid and adipose tissue fragments along with bland spindle-shaped cells and scattered benign epithelial cells in pulmonary hamartoma (H and E x40X)

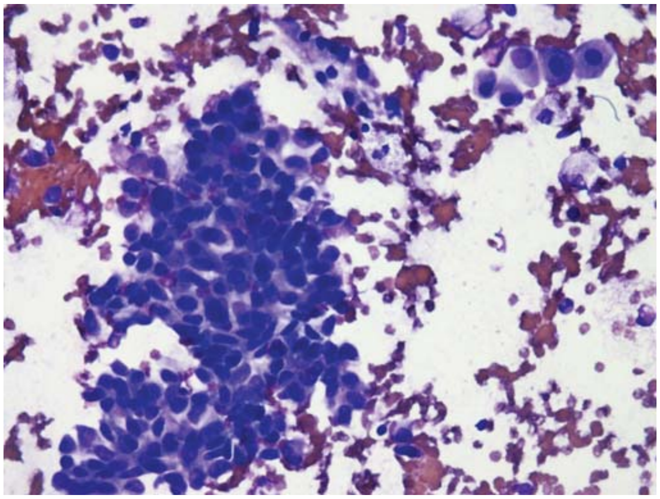

Fig. 30.23: Sheets and single oval to spindle cells in a bloody background with histiocytes in a case of sclerosing hemangioma (MGG, 40X)

which may be of popcorn type. Cytologically, the key diagnostic feature is the presence of cartilaginous or fibromyxoid fragments. Immature cartilage or fibromyxoid matrix, characteristically has wispy, frayed or irregularly feathered outlines (Fig. 30.22). It stains variably, but is usually basophilic in PAP and intensely metachromatic (magenta) in Diff-Quik.[74,75]

Grossly, it is sharply delineated and lobulated. Cut surface shows glistening cartilage with cleft. Microscopy shows cartilage, fat, smooth muscle and the clefts are lined by respiratory epithelium. The cartilage may be calcified or ossified. The lesion is acquired and represents primary overgrowth of mesenchymal tissues with secondary entrapment of bronchial epithelium. The treatment is conservative surgery in the form of wedge resection.

Inflammatory Pseudotumor

Inflammatory pseudotumors are quite rare and include fibroxanthoma (xanthogranuloma) and plasma cell granuloma. These are mostly asymptomatic, slow-growing, well-circumscribed, small peripheral lung masses.[76] Cytological features are nonspecific and may show admixture of plasma cells, lymphocytes, eosinophils, neutrophils, mast cells, histiocytes and myofibroblasts.[77] These cells can be seen in varying proportions. The stroma can be edematous to myxoid to fibrous to hyalinized. Excision is curative.

Sclerosing Hemangioma (Type II Pneumocytoma)

It is a rare, benign tumor of the lung. This occurs frequently in women (4:1). This tumor is usually solitary and located near the pleura with a predilection for the lower lobes. Cytosmears show abundant material in the form of sheets or single cells in a bloody background. Finding in aggregates of cells surrounding small blood vessels or sclerotic cores is characteristic (Fig. 30.23).[78]

Salivary Gland Analog Tumors

These probably arise from submucosal bronchial glands, the pulmonary counterpart of minor salivary glands. Mostly occur in the main bronchi.

Adenoid cystic carcinoma is the most common tumor which usually occurs in a major bronchus. On FNAC, smears show bland, uniform cells with scant cytoplasm.[79] The cells can be present singly or form tight, globular, honeycomb arrangements. The characteristic feature is the presence of mucoid (basement membrane) material, which is seen as rounded, acellular balls or cylinders, sometimes surrounded by tumor cells (Figs 30.24 and 30.25).

This material is transparent and lightly cyanophilic in Papanicolaou, but is brightly metachromatic (magenta) in Diff-Quik.

Mucoepidermoid carcinoma (MEC) of the lung can be high or low grade. On FNAC, the smears may show variable numbers of three cell types: mucus-secreting glandular cells, squamous cells and intermediate cells.

Pulmonary Blastoma

Pulmonary blastoma is also known as peripheral carcinosarcoma of embryonal type, or embryoma and can

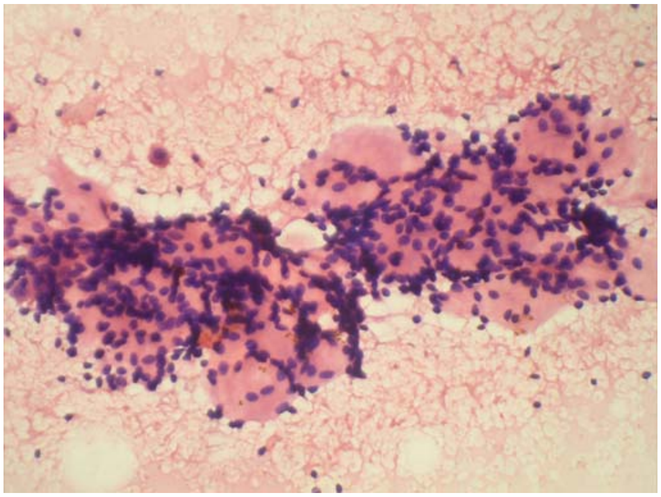

Fig. 30.24: Small uniform cells with hyperchromatic nuclei embedded in hyaline stromal globules in a case of adenoid cystic carcinoma (PAP, 40X)

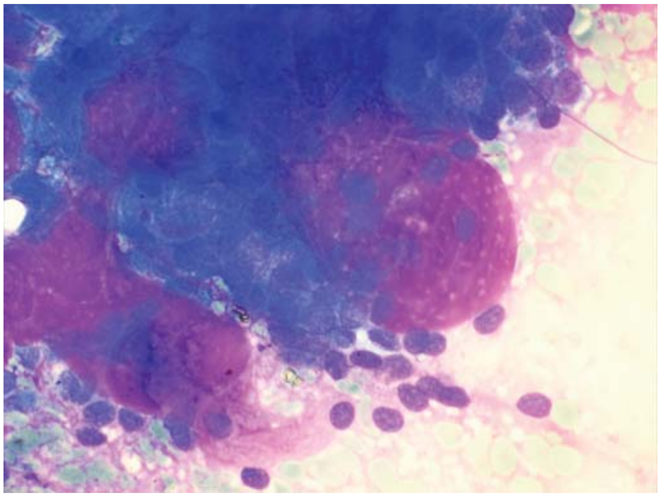

Fig. 30.25: Tumor cells embedded in metachromatically staining hyaline stromal globules (MGG, 100X)

occur at any age. The average age of diagnosis is about 40 years with male to female ratio being 3:1. This is usually located peripherally, but is rarely found intrabronchially. Microscopically, the tumor is reminiscent of fetal lung, the pulmonary counterpart of Wilms' tumor. Fine-needle aspiration cytology shows a biphasic epithelial and spindle cell growth pattern (Fig. 30.26). The cells of the epithelial component are cuboidal to columnar and may be present in sheets, acini or three-dimensional glandular structures. The cytoplasm usually contains glycogen vacuoles, which may give the cells a clear appearance. The nuclei are round to variable depending on the degree of differentiation of the tumor.

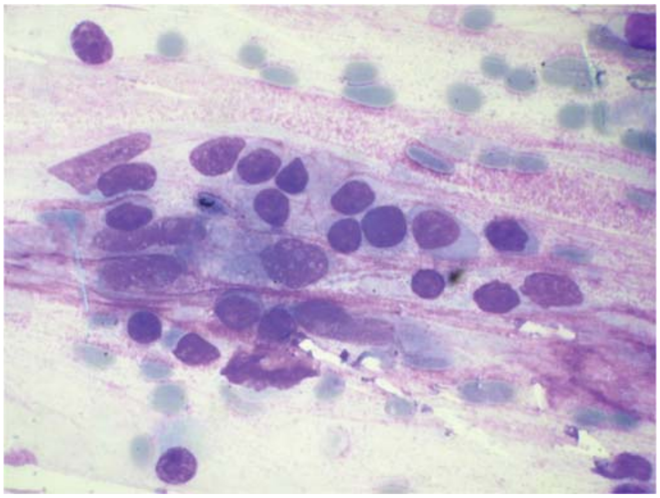

Fig. 30.26: A biphasic epithelial and spindle cell pattern in a case of pulmonary blastoma (MGG, 100X)

The sarcomatous component is usually cellular or myxoid malignant stroma composed of monotonous, small spindle mesenchymal cells (blastemal cells). The nuclei are slightly irregular with fine chromatin and indistinct nucleoli and scant cytoplasm.[80]

The differential diagnosis includes small cell carcinoma, large cell undifferentiated carcinoma or sarcoma, and the features sometimes overlap with those of carcinosarcoma.

Carcinosarcoma

This tumor usually occurs in adults, on average 10 to 20 years later than pulmonary blastomas. Most cases of carcinosarcoma are located centrally and have a worse prognosis. Fine-needle aspiration cytology shows a biphasic pattern of epithelial and spindle elements. The cells tend to be more intermixed and in majority of these tumors, the epithelial component is represented by non-keratinizing squamous cell carcinoma, but can also be adenocarcinoma or undifferentiated carcinoma.[81] The sarcomatous component usually resembles a fibrosarcoma or malignant fibrous histiocytoma. Occasionally, foci of chondrosarcoma, osteosarcoma, rhabdomyosarcoma or angiosarcoma may be seen and osteoclastic giant cells may also be present.[82] The differential diagnosis includes squamous cell carcinoma, non-small cell carcinoma, large cell undifferentiated carcinoma, giant cell carcinoma and pure sarcoma.[83]

Lymphoma

The lymphomas arising in the respiratory tract are rare. The mediastinum is more often involved. The primary lymphoma of this area can be diagnosed by cytological examination or FNAC. The criteria applied are same as described for other organs. The cells in malignant lymphomas are monomorphic, round and sometimes with anaplastic features. Primary Hodgkin's disease is exceedingly rare; however the metastatic lesions are more often seen.

Vascular Tumors: These tumors in lung are extremely rare and include hemangioma, hemangiopericytoma, angiosarcoma, lymphangioma and epithelioid hemangioendothelioma. Epithelioid hemangioendothelioma presents as multiple nodules. Cytologically, the smears may be hemorrhagic and may show loosely cohesive clusters of plump acidophilic endothelial cells. The tumor grows in slow fashion and remains restricted to thoracic cavity. The subtyping of these tumors is difficult in cytology because of compromised aspirated material in majority of cases and considerable cytomorphological overlap.

Primitive Neuroectodermal Tumor (PNET)

The term PNET is used to include a variety of tumors which may include malignant small cell tumor of the thoracopulmonary region (Askin's tumor). The immunocytochemistry and immunophenotyping can be applied to these malignant tumors to categorize them.[84]

Fine-needle aspiration cytology smears show small cells in small clusters or discrete cells. The cells are small monotonous primitive cells with scanty cytoplasm. The nuclei are round to oval with inconspicuous nucleoli. Rosette formation is a common feature (Figs 30.27 and 30.28). These rosettes may be focally present and careful search is required to locate them.

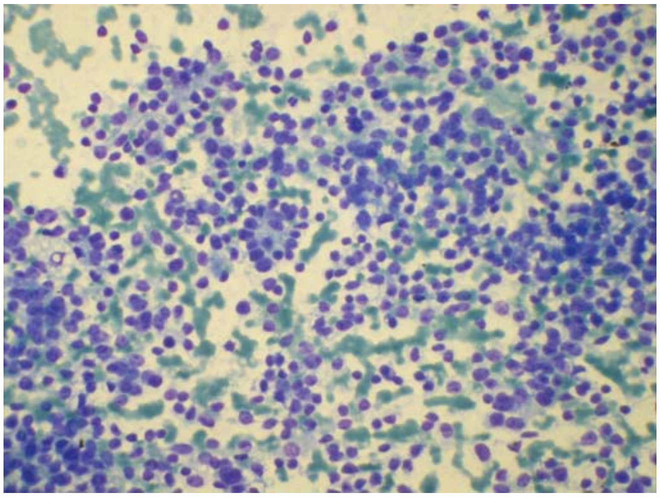

Fig. 30.27: Cellular smear with dispersed population of round cells with coarse chromatin and occasional rosette formation (MGG, 20X)

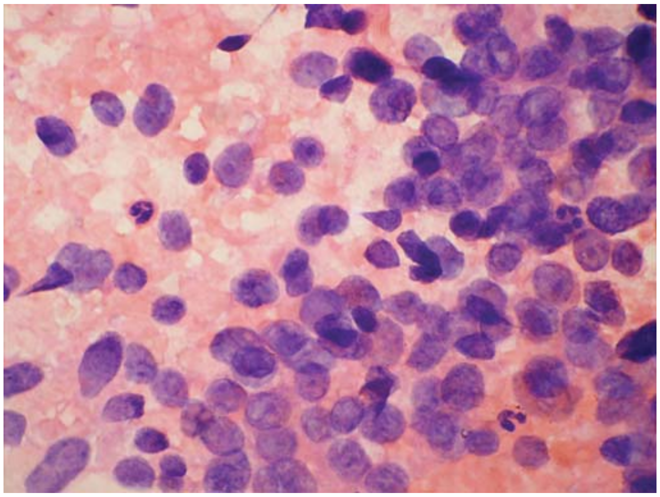

Fig. 30.28: Small round cells with coarse chromatin and occasional conspicuous nucleoli in a case of Askin's tumor (H and E, 100X)

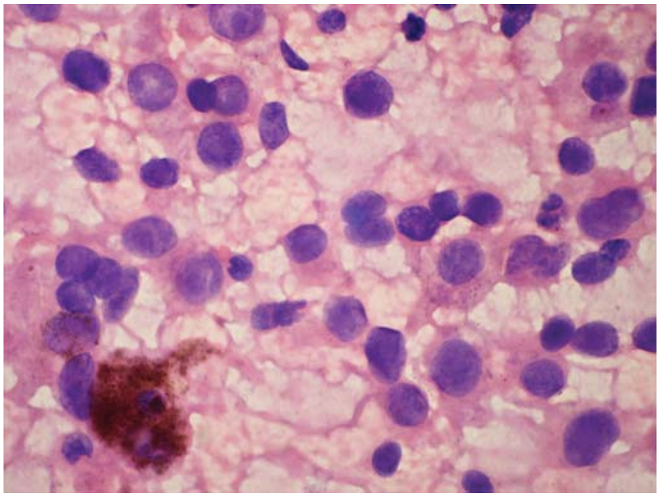

Fig. 30.29: Dispersed population of pleomorphic cells with eosinophilic cytoplasm, eccentric dark nuclei, prominent nucleoli and intracytoplasmic melanin pigment in some cells (H and E, 100X)

Metastasis

Lung metastases develop in upto 50% of all patients dying of cancer. The most common sources of lung metastases are breast, colon, pancreas, stomach, melanoma (Fig. 30.29), kidney (Fig. 30.30), germ cell tumors[85] and sarcomas (Fig. 30.31), however almost any malignant tumor can metastasize to the lung.

Usually the metastases are multiple and described as cannon – ball deposits. Both lung fields are usually involved by well delineated, multiple rapidly growing masses. Sometimes there are military nodules. Rarely it

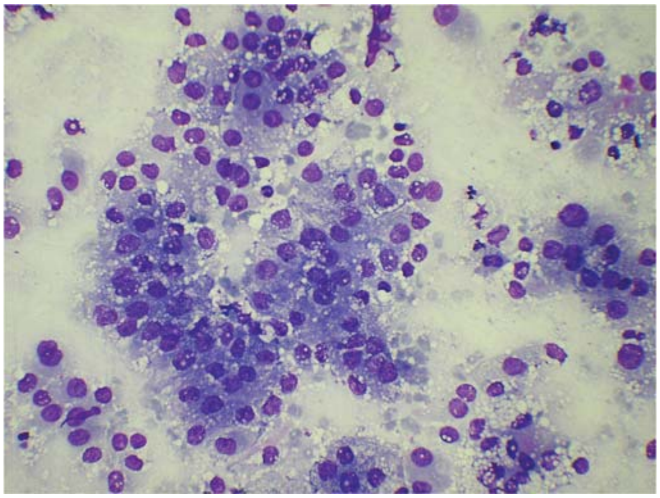

Fig. 30.30: A loosely cohesive cluster of tumor cells with low N:C ratio, abundant vacuolated to clear cytoplasm and conspicuous nucleoli in a case of metastatic renal cell carcinoma (H and E, 100X)

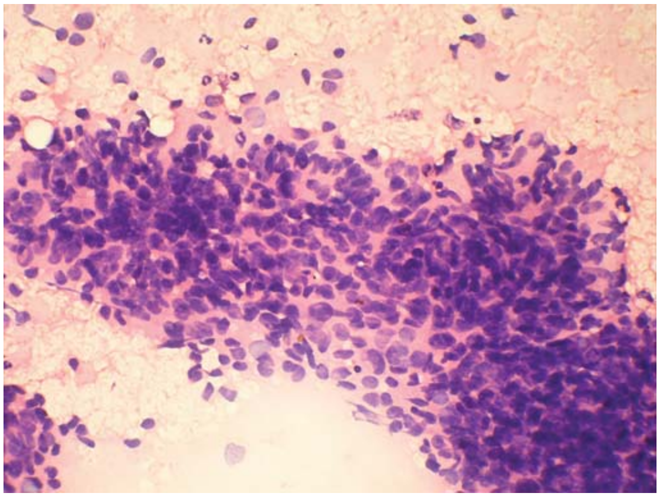

Fig. 30.31: Highly cellular smear with small fascicles of oval to spindle shaped cells with blunt ends in a case of metastatic sarcoma (H and E, 20X)

TABLE 30.2: Immunocytochemistry of primary and metastatic tumors of lung[87]

	TTFI	*CK7*	*CK20*	*PCEA*	*CD15*	*Others*
Lung adenocarcinoma	+	+	-	+	+	
Colon	-	-	+	+	+	
Breast	-	+	-	+	+	ER/PR+
Kidney	-	-	-	-	+	Vim +EMA +
Mesothelioma	-	+	-	-	-	Calretinin + Vim + CK5/CK6 +
Pancreas	-	+	+	+	+	CA 19-9 +
Anaplastic large cell lymphoma	-	-	-	-	-	LCA + CD30 + EMA +
Germ cell tumors						
• Seminoma	-	-	-	-	-	PLAP + CAM 5.2 –
• Non-Seminoma						CAM 5.2 + EMA

may present as solitary nodule and may be mistaken for a primary tumor of lung. There are no reliable cytomorphological features that can distinguish primary from metastatic adenocarcinoma.[86] The cytology of a few metastatic lesions is fairly characteristic, e.g. in malignant melanoma and renal cell carcinoma.

Finally, a clear distinction between Non-Small Cell Lung Cancer (NSCLC), including subgroups and small cell lung cancer, and between primary lung cancer and metastases has therapeutic impact, but the distinction may be difficult at times on smears. In case additional smears are not available, a Cytoscrape (CS) technique can be used on virtually any smear to produce material useful for ancillary methods, including immunohistochemistry.[83,88] The CS technique improves the diagnostic information from FNA in a clinically relevant way. Immunochemistry of primary and metastatic tumors of lung is shown in Table 30.2.

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31

Bronchoscopy

R Narasimhan, AR Gayathri

INTRODUCTION

Endoscopic visualization of the tracheobronchial tree has evolved tremendously from the initial rigid technique originally described by Gustav Killian (Fig. 31.1) in 1867,[1] when an aspirated pork bone was removed from the right main bronchus, to the path breaking invention of the flexible fibreoptic bronchoscope by Professor Ikeda, in the 1960s. Over the subsequent years, newer technologies have been developed and introduced, such as the color video camera by Ikeda and Ono in 1971, bronchoalveolar lavage (BAL) by Reynolds in 1974, video endoscope by Ikeda in 1987, stents by Dumon in 1989 and Endobronchial Ultrasound (EBUS) by Becker in 1999. The bronchoscopic practice is now widespread in India.[2] More interventional procedures are being done for both diagnostic and therapeutic purposes.

Fig. 31.1: Gustav Killian

TYPES OF BRONCHOSCOPY

Rigid Bronchoscopy

The procedure is performed under general anesthesia in the supine position with hyperextended neck, using a rigid bronchoscope (usually a ventilating bronchoscope), visualization is made better with the use of various telescopes and circumferential illumination (Fig. 31.2). Once the preliminary examination is done, the various diagnostic and therapeutic interventions (e.g. stent insertion, laser ablation, dilatation, foreign body removal) can be carried out.[3] The introduction of Charge Coupled Device (CCD) cameras, help in the transmission of images on to the monitors.

Flexible Fiberoptic Bronchoscopy

The flexible fiberoptic bronchoscopy has the advantage over the rigid bronchoscopy technique because it is easy

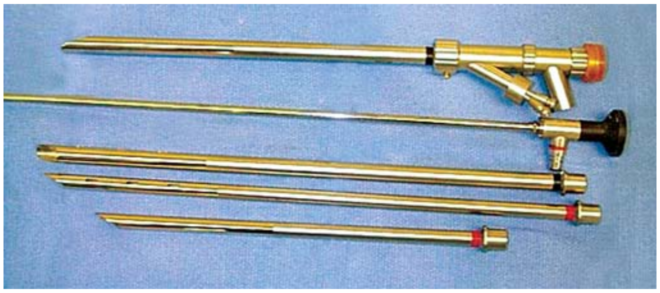

Fig. 31.2: Rigid bronchoscope

TABLE 31.1: Lignocaine content in various formulations

	Each ml of 2% Lidocaine	*Each ml of 4% Lidocaine*	*Xylocaine Viscous*	*Lidocaine Topical Aerosol 15% -Each actuation*
Lidocaine hydrochloride IP	21.3 mg	42.7 mg	21.3 mg	7.5 mg

to manipulate, simple to use, does not require general anesthesia and can be done as an outdoor procedure. Various sizes of bronchoscopes are available, which include the ultrathin bronchoscope (for the visualization of neonatal and smaller airways), pediatric bronchoscopes (2.8 mm outer diameter and 1.2 mm working channel), adult bronchoscopes (outer diameters ranging from 4.9 to 6.0 mm and channel sizes of at least 2.0 mm) and therapeutic bronchoscopes (outer diameter 6.0 mm and working channel of 2.8 mm). The video bronchoscope helps in the better visualization of lesions and data storage.

PATIENT PREPARATION AND ANESTHESIA

General and systemic examination of the patient is mandatory. Any medical condition especially cardiac or pulmonary should be identified and appropriate measures should be taken. There are varying opinions with regard to the use of sedation and premedication, prior to the procedure. In our series of patients undergoing Transbronchial Lung Biopsy (TBLB), there was no administration of either premedication or sedation, the patient comfort and cooperation for the procedure were found to be excellent.[4] Several bronchoscopists favor the use of sedation for routine bronchocopies.[5-7] With more interventional procedures being performed the world over, short-acting benzodiazepines (e.g. midazolam) and fentanyl are commonly used. The performance of an effective bronchoscopy requires the use of appropriate local anesthetics. Either two or four percent lidocaine is used, mainly for the fast onset of action, wide safety margin and the long duration of action. There is a word of caution with regard to the toxicity due to the amount of local anesthetic used, in view of a high systemic absorption of local anesthetic agent from the nasal passages and tracheobronchial tree because of the high vascularity of those regions. It is therefore essential to know the amount of lignocaine of the formulation used (Table 31.1), so as not to exceed the recommended maximum single dose of lidocaine (4.0 mg/kg).

DIAGNOSTIC BRONCHOSCOPY–ACCESSORIES

The working channel of the bronchoscope is designed to allow the use of various diagnostic and therapeutic accessories.

Biopsy Forceps

The alligator and the cupped forceps (Fig. 31.3) are the two principle types of blade design. Alligator forceps have a greater tissue tearing action than its cupped counterpart (Fig. 31.4). However, it is the cupped forceps, which obtains the larger sample size. Despite these facts, neither type of forceps has been shown to have a greater diagnostic accuracy than the other.[5] A forceps with a needle (Fig. 31.5) helps to prevent slippage and allows for the performance of tangential biopsies.

Bronchial Brushes

The bronchial brush consists of a central rigid wire surrounded at the tip by brushes, only 0.001 m of specimen is collected during bronchial brushings. The material has to be immediately transferred on to a slide (for cytology sampling) and either sprayed with a fixative or immersed in a slide container of 95% absolute ethyl alcohol. For microbiological analysis, the brush has to be agitated in 5–10 ml of sterile saline.The yield of the bronchoscopic brushing procedure increases with the proper method, collection and processing of the samples. It has also been found to be a superior technique in comparison to BAL in the diagnosis and morphological typing of lung cancer.[6]

Transbronchial Needles for Aspiration and Biopsy (TBNA)

TBNA is a minimally invasive, nonsurgical technique by which the diagnosis and staging of bronchogenic carcinoma can be done by sampling the mediastinal lymph nodes. In addition, it is useful for accessing peripheral lesions, submucosal and endobronchial lesions, as well as for the sampling of intrathoracic lymph nodes.[7] There are two types of needles available—the cytology needle and the histology needle. Four insertion

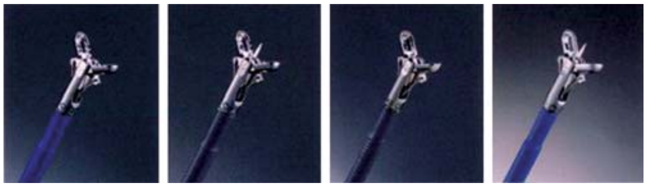

Fig. 31.3: Types of biopsy forceps

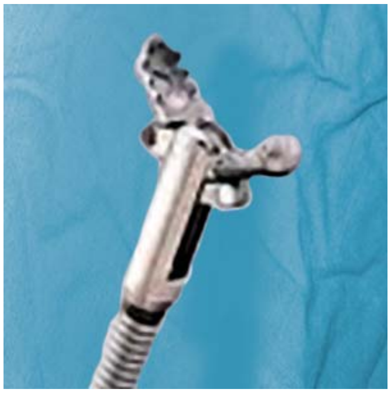

Fig. 31.4: Alligator forceps

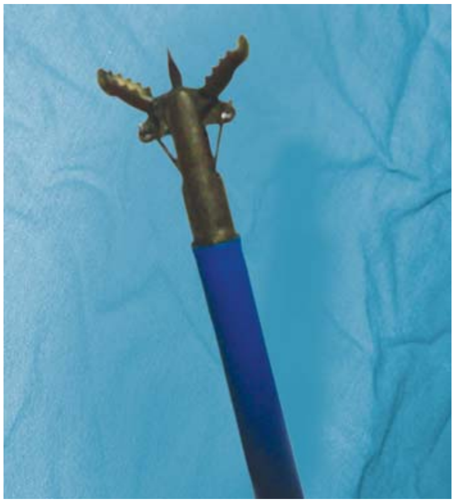

Fig. 31.5: Needle forceps

techniques have been described as follows:[8] (i) the jabbing technique, (ii) the piggyback method, (iii) hub-against-the-wall method, and (iv) the cough method. The major complication of TBNA is the perforation of the working channel of the bronchoscope. This can be avoided by careful attention to technique and needle position.

TABLE 31.2: Indications for diagnostic bronchoscopy

- Bronchogenic Carcinoma
  - Diagnosis
  - Staging
  - Follow-up after treatment
- Other Malignancies
  - Evaluation of esophageal cancer
  - Metastatic carcinoma
- Mediastinal Mass
- Mediastinal Lymph Nodes
- Interstitial Lung Disease
- Chronic Cough
- Wheeze–localized
- Stridor
- Infections
  - Nonresolving pneumonias
  - Immunocompromised host
  - In critical care unit patients
- Lung Collapse
- Vocal Cord Paralysis
- Foreign Body Aspiration
- Chest Trauma
- Pleural Effusion
- Superior Vena Cava Syndrome
- S/P Lung Transplantation
- Fistula
  - Bronchopleural
  - Tracheoesophageal
  - Bronchoesophageal
- Postoperative evaluation following lung surgeries
- Tracheal stenosis and strictures
- Inhalational Injury

Catheters and Balloons

Selective, protected catheters are available to collect uncontaminated specimens from the bronchial tree. The balloons available are either double lumened or low-pressure balloon catheters.

INDICATIONS FOR DIAGNOSTIC BRONCHOSCOPY

Bronchoscopy is one of the most important investigation for the diagnosis of a large number of clinical conditions and their evaluation (Table 31.2).

Assessment of Airway Anatomy

The bronchoscopic assessment of the airways begins with the visualization of the upper airways and with special reference to the vocal cords (Fig. 31.6), their appearance and mobility. The inspection of the lower airways is done

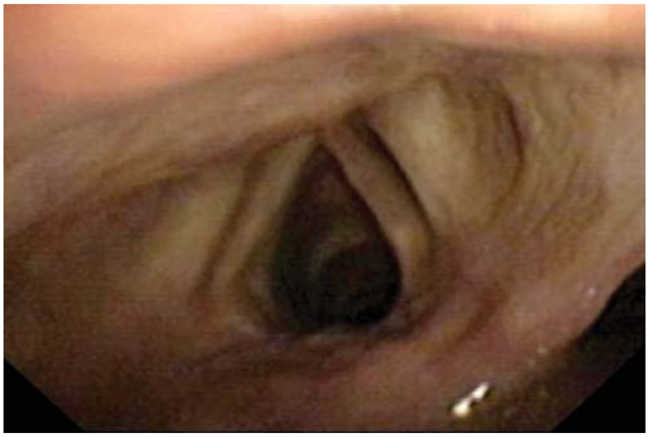

Fig. 31.6: Vocal cords

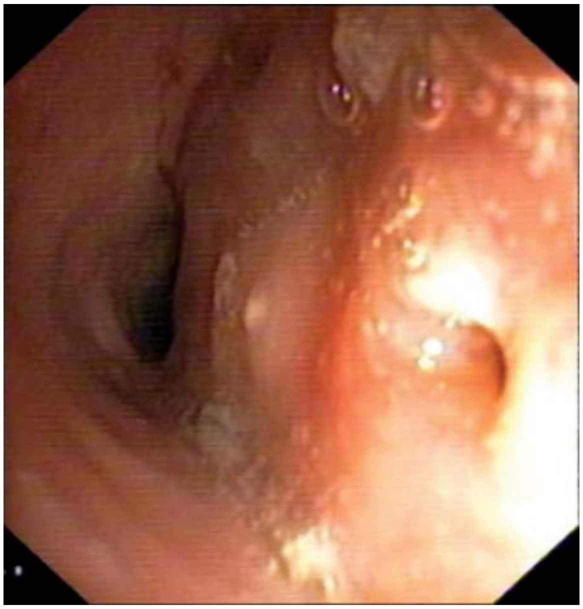

Fig. 31.7: Fistula between left main bronchus and esophagus

with specific regard to their normal anatomy, anatomical variations and pathological involvement. Specific inspection of the airway lumen can be done during inspiratory and expiratory movements. Congenital, post-traumatic, postsurgical and/or pathological disruptions in the integrity of the bronchial lumen can be visualized, e.g. bronchoesophageal fistula (Fig. 31.7).

Assessment of Tracheobronchial Mucosa

The normal mucosa of the tracheobronchial tree is pale-pink (Fig. 31.8). The presence of changes like hypervascularity (Fig. 31.9), ulcerations and granulation tissue point towards the pathological involvement. The use of photosensitizers have been used for cancer detection. The Laser Imaging Fluorescence Endoscope (LIFE), which is used in auto fluorescence bronchoscopy, generates images which are about 30,000 more times powerful than images taken with usual endoscopic cameras, by which the detection and subsequent biopsy of lesions leads to the early diagnosis of dysplasia and carcinoma *in situ*. Optical Coherence Tomography (OCT), a technique

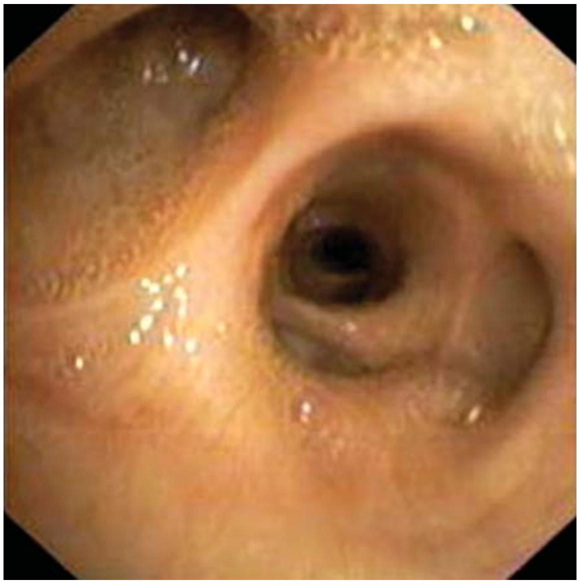

Fig. 31.8: Normal bronchial mucosa

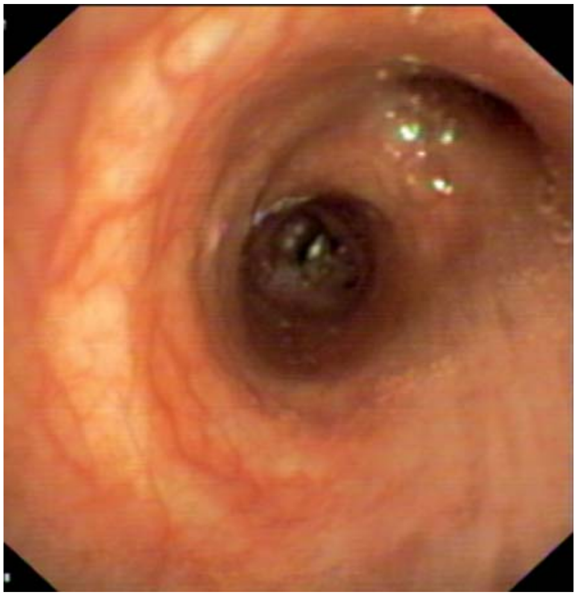

Fig. 31.9: Hypervascularity of bronchial mucosa

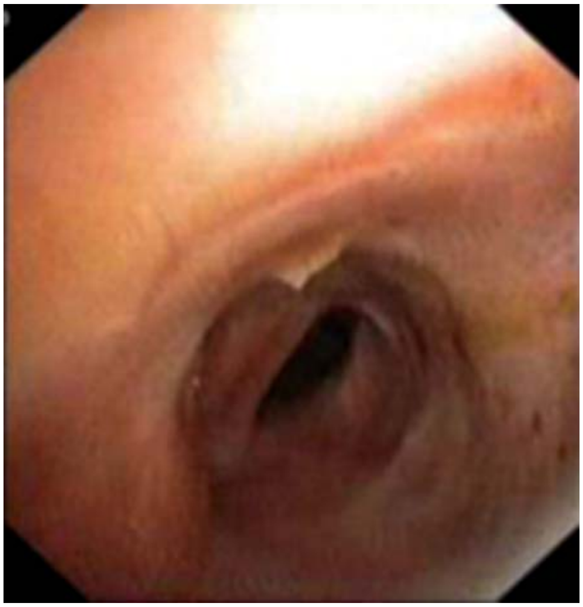

Fig. 31.10: Tracheal stenosis of lower one-third of trachea

similar to ultrasound imaging, uses infrared rather than acoustic waves.

Evaluation of Cough

Bronchoscopy is one of the recommended investigations in evaluation of patients with chronic cough especially when there is a change in the character of the cough and with an association of smoking.

Evaluation of Wheezing

Lesions like foreign bodies, tracheomalacia, vascular abnormalities, tracheal stenosis (Fig. 31.10), extrinsic or intrinsic tracheal obstructions due to mass lesions may present clinically with wheeze and may require further evaluation by bronchoscopy.

Evaluation of Stridor

Stridor is a life threatening sign of upper airway obstruction. Prior to the evaluation of likely causes (in adults), such as infections, Wegener's granulomatosis, bilateral vocal cord paralysis, tracheal tumors, tracheal compression due to mediastinal and esophageal lesions, the bronchoscopist must ensure that adequate facilities are available for emergency intubation and tracheotomy, if required.

Evaluation of the Hoarseness of Voice

It has been found that 36% of vocal cord paralysis were due to neoplastic diseases of which, 55% were from lung cancer.[9] Left hilar lesions, which may contribute to left recurrent laryngeal nerve paralysis may be sampled by TBNA.

Evaluation of Inhalational Injury

Inhalational injuries may occur due to smoke inhalation, toxin exposure or thermal injury due to steam or superheated air. Bronchoscopy is done for the initial assessment of inflammation, mucosal edema, ulceration and swelling of the laryngeal airway. It can also be used for fibreoptic intubation.

Evaluation of Hemoptysis

Bronchoscopy in the evaluation of hemoptysis helps in the identification of the location and source of bleeding. Early bronchoscopy (within 48 hours) has a greater diagnostic yield than late bronchoscopy, but an overall impact of timing on the patient management has not been found.[10] Though the rigid bronchoscope has better control of the airways and greater suction capacity, the flexible fibreoptic bronchoscope makes visualization of the smaller airways possible.

Evaluation of Superior Vena Cava Syndrome (SVCS)

TBNA of the mediastinal masses or lymph nodes causing SVCS can be done. Diagnosis can be established by bronchoscopic biopsy in about 60 to 70 % of cases.[11]

Evaluation of Peribronchial Structures

The changes, pathological or developmental, of the mediastinal structures and their effects on the tracheobronchial tree can be appreciated through bronchoscopy (Fig. 31.11). Procedures like TBNA and TBNB can be done to sample the mediastinal lymph nodes. Diagnosis and staging of lung cancer is an important indication of TBNA. The use of Rapid Onsite Evaluation (ROSE) of TBNA samples, where a cytopathologist is present in or near the bronchoscopy suite, ensures that the material is prepared in the best possible manner, with improvement in yield, and reduction in the number of inadequate specimens. It also avoids the need for further sampling, if the samples are satisfactory. Use of methods like CT fluoroscopy, EBUS and electromagnetic guidance, increase the yield of TBNA. Newer generation EBUS bronchoscopes allow for concurrent lymph node visualization and performance of TBNA.

Evaluation of Interstitial Lung Disease

Procedures like BAL have been found to be useful in studying the cells causing inflammatory response in

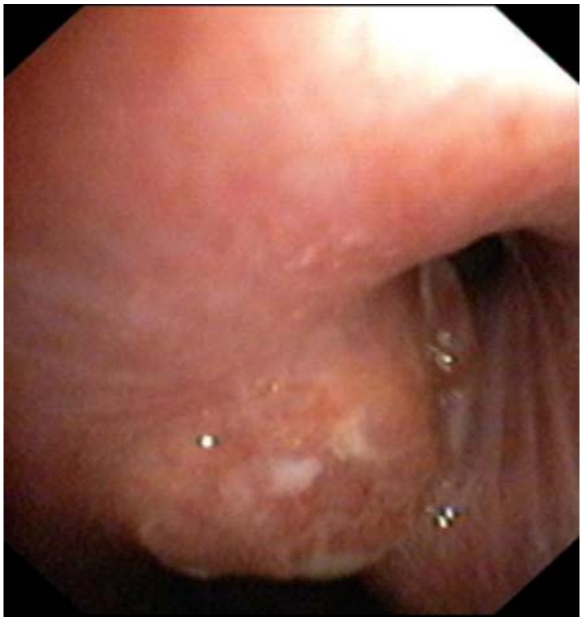

Fig. 31.11: Right hilar lymph node eroding into bronchial lumen

Idiopathic Pulmonary Fibrosis (IPF). Use of BAL and Bronchoscopic Lung Biopsy (BLB) have increased the diagnostic yield in diffuse parenchymal conditions such as sarcoidosis, histiocytosis X and lymphangitis carcinomatosa.

Evaluation of Infections

Bronchoscopy with BAL is a safe method of sampling the lower respiratory tract secretions. Bronchoscopy is more likely to have a better yield if the radiological infiltrates have been present for more than 30 days, are multilobar or segmental and if the patient is less than 55 years of age.[12]

Evaluation of Lobar Collapse

The yield of diagnostic bronchoscopy is highest, when lobar collapse is being investigated, up to 65% of patients undergoing bronchoscopy for lobar collapse had endobronchial masses.[13]

Evaluation of Pleural Effusions

Presence of hemoptysis, cough, a parenchymal lesion in addition to the pleural effusion, increase the yield of bronchoscopy in pleural effusion.

Evaluation of Chest Trauma

In patients with both blunt and penetrating thoracic trauma, bronchoscopy is an essential tool to assess the airway damage. It is also useful for fiberoptic intubation of patients, as well as to deal with post-trauma complications like mucous plugging and aspiration.

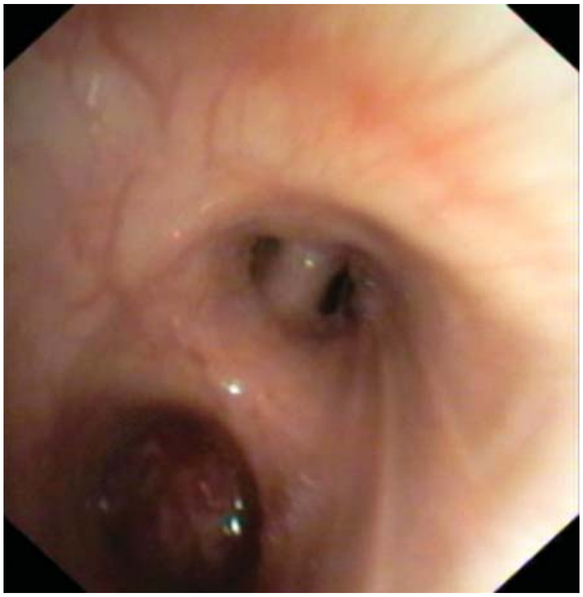

Fig. 31.12: Endobronchial mass occluding right bronchus intermedius

Evaluation of Lung Masses

Lung masses, especially those which present with endobronchial lesions (Figs 31.12 to 31.14) can be visualized through the bronchoscope and biopsied with

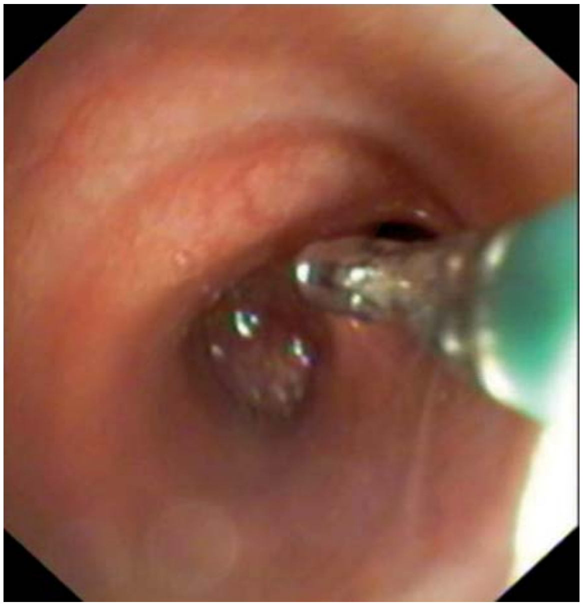

Fig. 31.13: Endobronchial mass in right bronchus intermedius being biopsied

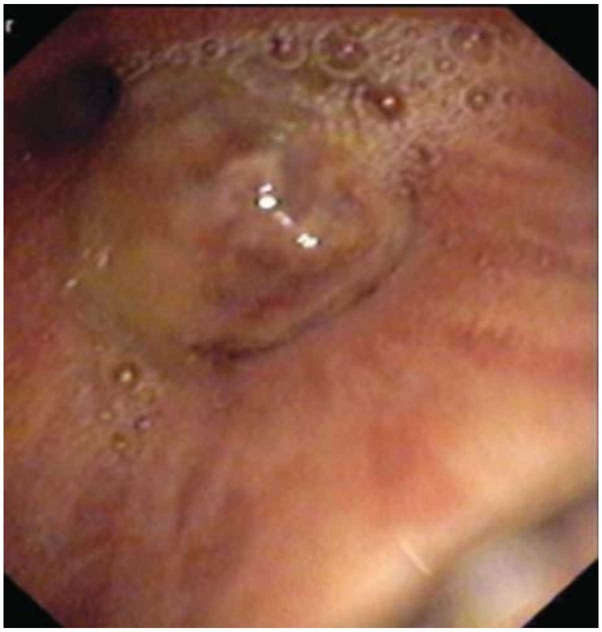

Fig. 31.14: Endobronchial mass in right lower lobe common basal segment

forceps. Three to four samples have been found to be sufficient for diagnosis.[14] The use of a combination of sampling techniques, including wash, brush, forceps and TBNA have shown to increase the yield of the diagnosis of bronchogenic carcinoma.[15]

Evaluation in Lung Transplantation

Bronchoscopy plays a valuable role in patients undergoing lung transplantation. It is useful in evaluating the presence and treatment of various airway complications like infection and stenosis, and also to differentiate between rejection and infection.

DIAGNOSTIC PROCEDURES

Bronchoscopic Lung Biopsy

Bronchoscopic lung biopsy is the technique by which biopsy of the lung parenchyma can be obtained by either the rigid or the flexible fiberoptic bronchoscope. It is also referred to as transbronchial or transbronchoscopic lung biopsy. Although found to be useful in diffuse parenchymal diseases, its use has generally declined.

The use of CT imaging in the diagnosis of diffuse lung disease has lead to a decrease in the number of bronchoscopic lung biopsies. Moreover, there are several contraindications for bronchoscopic lung biopsy[16] (Table 31.3). EBUS has shown promise in accessing peripheral pulmonary nodules, may even throw light on differences in the nodule architecture of malignant and benign lesions.

TABLE 31.3: Contraindications of bronchoscopic lung biopsy

Absolute Contraindications
1. Inability of patient to cooperate with the procedure
2. Inability to undergo general anesthesia (when required) for obtaining BLB
3. Unstable cardiovascular status
4. Acute severe asthma
5. Severe hypoxemia
6. Inadequately trained bronchoscopist or bronchoscopy team
7. Inadequate instruments for procedure performance

Relative Contraindications
1. Uncontrollable cough, during procedure
2. Untreated hemorrhagic diathesis
3. Advanced renal failure
4. Significant hypoxemia in a patient with single lung
5. Extensive bullous changes in areas to biopsied
6. Radiological suggestion of vascular malformations adjacent to areas to be biopsied

Pulmonary hypertension has been considered as a contraindication to BLB, but no significant difference was found in post BLB complications in the patients of interstitial lung disease with latent pulmonary hypertension in comparison to those patients without pulmonary hypertension.[17]

Sampling of Airway and Alveolar Constituents

The techniques used for sampling the tracheobronchial tree include the bronchial washing, bronchial brushing and BAL. The specimens can be sent for various microbiological and cytological analyses.

Bronchoalveolar Lavage

This is a relatively safe and easy procedure, which involves the instillation of measured aliquots of saline and its recovery through the bronchoscope so as to get a sample of the epithelial lining fluid of the small airways and alveoli. It is useful in the diagnosis of conditions like pulmonary alveolar proteinosis, eosinophilic granuloma and eosinophilic pneumonia.

Quantitative Microbiological Techniques

In the setting of patients with ventilator associated pneumonias, it is essential to get a sample from the bronchial tree, which is free from the contamination or

TABLE 31.4: Therapeutic bronchoscopy–indications

Removal of Foreign Bodies
Pulmonary Toilet
Stent Placement
Bronchoalveolar Lavage
Lobar Collapse
Intubation
Airway Maintenance
Management of Malignant and Benign Endobronchial Tissue
Electrocautery
Argon Plasma Coagulation
Laser Photodynamic Therapy
Cryotherapy Brachytherapy
Endobronchial Valve Placement
Bronchial Thermoplasty
Thoracic Trauma
Pneumothorax

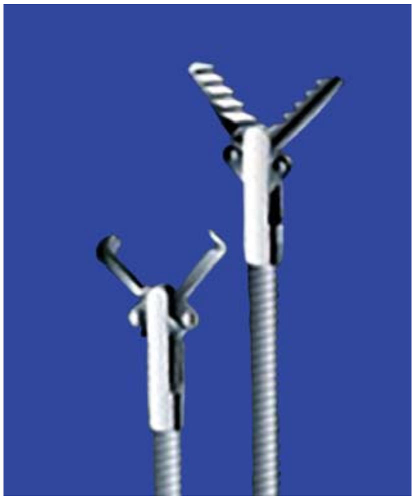

Fig. 31.15: Foreign body grasping forceps

colonization of organisms. Procedures like Protected Specimen Brush (PSB) and quantitative BAL help in acquiring representative samples.

THERAPEUTIC BRONCHOSCOPY

Bronchoscopy is also employed for several therapeutic indications (Table 31.4).

Foreign Body Aspiration and Removal

Bronchoscopy finds a major role in the removal of foreign bodies. Traditionally, the rigid bronchoscope had been the instrument of choice for foreign body removal, but now the flexible fiberoptic bronchoscope is being increasingly used. It offers greater access to the periphery and can be used with ease in patients on mechanical ventilator and those who have unstable neck. The various instruments used for foreign body removal include snares, balloon catheters, retrieval baskets and grasping forceps (Fig. 31.15).

Control of Hemoptysis

Bronchoscopy is useful for both diagnosis and emergency management of hemoptysis. An instrument with a larger working channel is required, the use of rigid bronchoscopy is recommended. Various measures like instillation of iced saline solution and epinephrine, may be tried. Catheters to offer tamponade on bleeding segments, including Fogarty balloon catheter may be tried. In the event, a visible source of bleeding is seen and laser photocoagulation can be attempted.

Pulmonary Toilet

Clearing of tracheobronchial tree of secretions called toileting, is the most common application of therapeutic bronchoscopy. Bronchoscopes with large suction channel are to be used. This is commonly required in ICU practice.

Bronchoalveolar Lavage

Whole lung lavage in patients with Pulmonary Alveolar Proteinosis (PAP) has a therapeutic, as well as diagnostic role. About 50% of patients will suffice with a single treatment (Fig. 31.16), multiple lavages are required in other patients.[18]

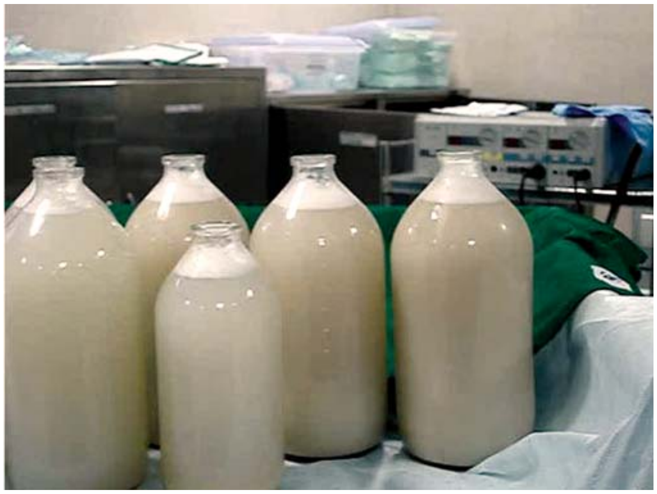

Fig. 31.16: Lavage fluid from the whole lung lavage of pulmonary alveolar proteinosis

Electrocautery and Argon Plasma Coagulation

Electrocautery can be used via the bronchoscope channel in a contact or noncontact mode. It has the advantage over laser because it requires a shorter procedure time and lesser investment for instrument overheads. Indications for electrocautery include the treatment of malignant and benign lesions, debulking of tumors and removal of granulation tissue, hemoptysis management, immediate hemostatic control and coagulation.

Cryotherapy

It is one of the modalities used for the treatment of malignant endobronchial lesions. The principle of treatment is to create the fastest possible cooling of the target tissue in order to provoke intracellular freezing. The cooling agents used are liquid nitrogen, nitrous oxide and carbon dioxide.

Laser Photoresection

The use of laser in obstructive endobronchial lesions allows the establishment of airway patency and the subsequent ventilation of the distal lung and drainage of the postobstructive pneumonia. Other lesions treated by laser photoresection include tracheal granulomas, tracheal stenosis, endobronchial amyloidosis and tracheopathia osteoplastica.

Photodynamic Therapy

Photosensitizers are used to cause tissue necrosis. The likely indications for this therapy include the treatment of early lung cancer or palliation of unresectable bronchogenic carcinoma causing tracheobronchial obstruction.

Balloon Dilatation

It is used to establish airway patency in patients with retention pneumonia, atelectasis, lung abscess or the symptomatic stenosis of tracheobronchial tree.

Tracheobronchomalacia

Tracheobronchomalacia is diagnosed by flexible bronchoscopy. The treatment of choice for diffuse involvement is the insertion of standard or bifurcated silicone tracheobronchial stents. Pneumatic stent with concomitant noninvasive ventilation is another treatment option.

Fistula Closure/Repair

Identification of fistulae beyond the reach of flexible fibreoptic bronchoscope is done by the serial insertion of occluding balloons and checking for air leak. Various sealants like gel foam, autologous blood patches, cryoprecipitate and silver nitrate can be used to close the fistula. Up to 83% of tracheoesophageal fistulas can be detected by bronchoscopy, further treatment can be planned by concomitant esophagoscopy.[19]

Stents

Stents are placed bronchoscopically, to relieve endoluminal obstruction. Both flexible and rigid bronchoscopes are used for stent placements. Patients with primary airway tumors may benefit from endoluminal stenting, if surgery is not indicated. Other tumors that occur adjacent to the airway and produce obstruction by direct invasion or extrinsic compression, may also be successfully palliated with endoluminal treatments combined with stent placement. Patients with postintubation tracheal stenosis are occasionally good candidates for airway dilation and stenting.

Endobronchial Valves (EBV)

Bronchoscopic lung volume reduction using endobronchial valves for selected patients with hyperinflated lung from heterogeneous emphysema has been attempted. The use of endobronchial valves to treat persistent pulmonary air leaks has been shown as an effective and minimally invasive procedure.[20]

ELECTRONAVIGATION BRONCHOSCOPY

It is a procedure, which incorporates the patient's CT chest images into a special computer software program, to mark the exact site of lesion by placing electronic markers. It is done for virtual guidance for the bronchoscopist to sample the specific lesion by biopsy, brush or TBNA. The procedure is done under conscious sedation, with the patient lying on a low frequency electromagnetic bed.

SAFETY FACTORS IN BRONCHOSCOPY

Bronchoscopy is a technique, which requires expertise and training. Knowledge of airway anatomy is essential. Adequate equipment, trained personnel and means of handling complications, which may arise are essential.

TABLE 31.5: Complications of bronchoscopy

Complications related to anesthesia
- Hypersensitivity to local anesthetic agents

Oxygen Desaturation
Fever
Infection
Airway Obstruction
Airway Perforation
Pneumothorax
Hemorrhage
Air Embolism

Standard safety precautions when handling the equipment and performance of procedures are essential.

COMPLICATIONS OF BRONCHOSCOPY

Bronchoscopy has a potential of hazards of anesthesia, as well as of the procedure and associated interventions (Table 31.5). The complications are more likely if the basic prerequisites like patient selection and preparation are not appropriate.

Anesthesia-Related Complications

The importance of having a limit on the amount of local anesthetic, which is used has been mentioned earlier. It is essential to remember that oxygen desaturation may occur during the procedure, especially when done under conscious sedation or general anesthesia. Significant desaturation occurs during BAL. An essential prerequisite therefore, is the administration of supplemental oxygen.

Fever and Infection

The occurrence of transient fever, after bronchoscopy especially after the performance of BAL has been noted. The use of prophylactic antibiotic prior to procedure, as recommended by the American Heart Association, is for patients with a predisposition to endocarditis and those with valvular heart problems. Prohylactic antibiotics are not required prior to flexible bronchoscopy.

Airway Perforation and Obstruction

Various airway complications, including burns, perforation and airway obstruction, may occasionally occur when lasers, stents or valves are used, and when the procedures are inappropriately performed.

Pneumothorax

The incidence of pneumothorax following a transbronchial biopsy is about four percent. The risk increases when the patient is immunocompromised with associated pneumocystis infection, when the patient has multiple bullae in the lungs and when the patient is on a mechanical ventilator.

Hemorrhage

Its occurrence due to the procedure itself, can be avoided by proper selection and evaluation. As per standard recommendations, bronchoscopy should not be performed if the platelet count is less than 50,000/mm^3. Other interventional procedures, including TBLB, laser and stents should be done only if the platelet counts are more than 75,000/mm^3.

Air Embolism

This a serious and fatal complication, which rarely occurs, especially after laser photoresection.

Inspite of the likelihood of several complications, which have been enumerated, the procedure of bronchoscopy is generally safe and risk free. It is however important that it is done by trained personnel with ready availability of backup facilities to handle any complication.

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32

Interventional Bronchoscopy

Praveen N Mathur, FD Sheski

DEFINITION OF INTERVENTIONAL PULMONOLOGY

Interventional pulmonology is a very young and rapidly growing field within pulmonary medicine that focuses on the use of advanced bronchoscopic and pleuroscopy techniques. This was first defined in 1995[1] and subsequently by the ERS/ATS guidelines.[2] Interventional pulmonology can be defined as "the art and science of medicine as related to the performance of diagnostic and invasive therapeutic procedures that require additional training and expertise beyond that required in a standard pulmonary medicine training program." Disease processes encompassed within this discipline include complex airway management problems, benign and malignant central airway obstruction, pleural diseases, and pulmonary vascular procedures. Diagnostic and therapeutic procedures pertaining to these areas include, but are not limited to, rigid bronchoscopy, transbronchial needle aspiration, autofluorescence bronchoscopy, endobronchial ultrasound, transthoracic needle aspiration and biopsy, laser bronchoscopy, endobronchial electrosurgery, argon plasma coagulation, cryotherapy, airway stent insertion, balloon bronchoplasty and dilatation techniques, endobronchial radiation (brachytherapy), photodynamic therapy, percutaneous dilatational tracheotomy, transtracheal oxygen catheter insertion, medical thoracoscopy, and imaging-guided thoracic interventions.[1,2]

Although this definition was established in 1995, there has been a surge of new procedures that now can be performed with a bronchoscope. This area continues to thrive with new innovation and venture capital. Some of them are: Endoscopic lung volume reduction for advanced emphysema, bronchothermoplasty for asthma, and newer spectroscopic imaging techniques. As we learned to perform these procedures safely we have not defined the value of these procedures in controlled trials.

In this chapter, only the interventional bronchoscopy is addressed.

Rigid Bronchoscopy

Bronchoscopy was first performed with a rigid bronchoscope in 1897 by Gustav Killian to remove a pork bone impacted in the airway of a farmer. Killian used a Mikulicz-Rosenheim rigid esophagoscope.[3] Killian continued to use rigid metal tubes in cadavers, he subsequently described the extraction of foreign bodies from the airway. Chevalier Jackson in Philadelphia was responsible for the development of rigid bronchoscopy in the United States. He improved and developed the modern rigid bronchoscope.[4] The development of the flexible bronchoscope leads to the decrease of the use of rigid bronchoscope. However, rigid bronchoscopy has regained usefulness due to the increasing use of interventional bronchoscopy.[5]

The rigid bronchoscope, also known as the open tube bronchoscope, is a nonflexible, straight, and hollow metallic tube made of stainless steel. The tube comes in various external diameters, which vary from 2 to 14 mm. They have the same diameter from the proximal to the distal ends, but most have a beveled tip to facilitate lifting of the epiglottis during intubation and also to core out an endobronchial lesion.

Telescopes were made with 0 degree and multitude of angles, allowing the visualization of upper and lower lobe bronchi. Many of the angled telescopes are not used as the fiberoptic bronchoscope, but are used through the rigid tube. Light sources using xenon or halogen lamps are currently used. Video cameras can be easily connected to the eyepiece of a rigid telescope. Accessory instruments often used during rigid bronchoscopy include biopsy forceps, suction tubing, and specific forceps that may become necessary for removal of foreign-body. This procedure is performed under general anesthesia. The teeth must be protected, a rolled blanket placed between the shoulder blades, which enables the upper trachea to move forward. Anesthesia could be intravenous; if inhaled anesthetic gases are to be used, it is necessary to pack with gauge the nose and mouth to avoid gas leakage. Ventilator support is provided using assisted spontaneous ventilation or closed-circuit positive pressure ventilation.

Several techniques are used for the intubation of the rigid bronchoscope: a. direct intubation is the method of choice for intubation; b. intubation with the help laryngoscope, or c. intubation alongside a small endobronchial tube.

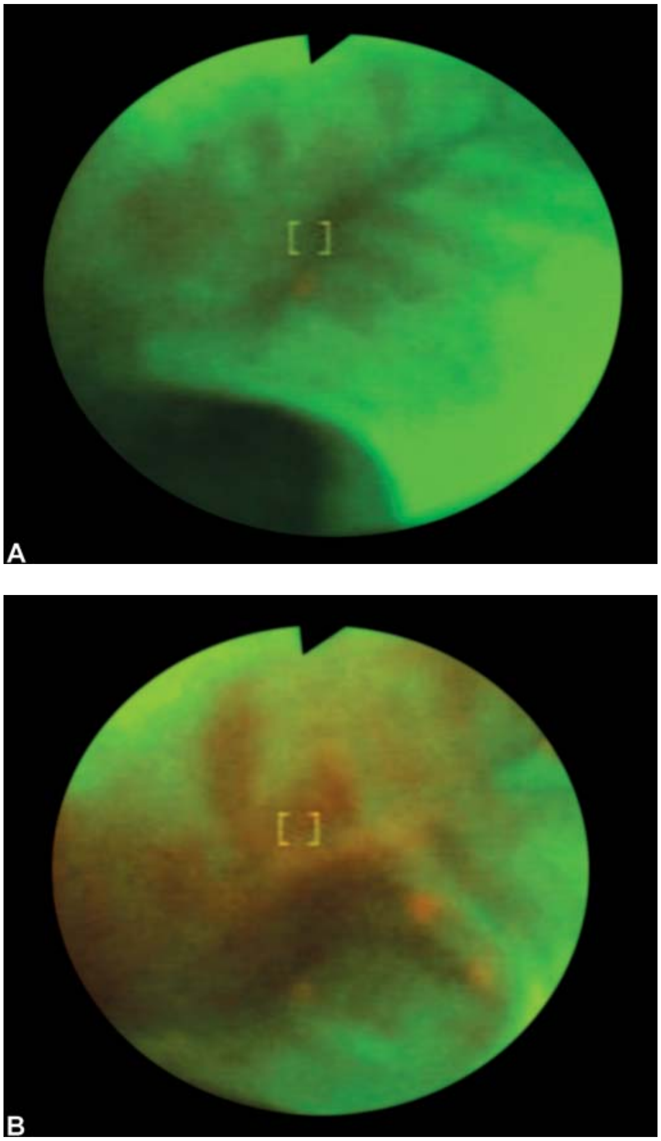
Complications are related to poor insertion technique such as trauma (to gums, teeth, lip) and laryngeal swelling.

The rigid bronchoscope is used for interventions, such as endoscopic resection of endobronchial masses with laser, electrocautery argon plasma coagulation or cryotherapy; placement of silicone stents, and finally for the removal of foreign bodies.

ADVANCED IMAGING BRONCHOSCOPY

Fluorescence Bronchoscopy

Lung cancer progresses through several stages, including metaplasia, dysplasia, carcinoma *in situ*, microinvasive carcinoma, and invasive carcinoma.[6] In order to identify this abnormal mucosa, a variety of techniques have been used. When a suitable wavelength is used to excite tissue to fluoresce, infiltrating tumor will alter tissue fluorescence. This difference in fluorescence is used to help in detecting abnormal mucosa in the airways. Photosensitizing fluorescent compounds were used to increase the intensity of the fluorescence, but this approach has been limited by skin phototoxicity.[7-10] Advances in image processing have improved the detection of subtle differences in fluorescence. Carcinoma *in situ* and microinvasive carcinoma exhibit a weaker red fluorescence and slightly weaker green fluorescence for normal tissues, when illuminated by light with a wavelength of 380 to 440 nm (Figs 32.1A and B). Several reasons suggested as this phenomenon are not well understood. This may be due to increased epithelial thickness, increased blood flow, and/or a reduced concentration of fluorophores in abnormal tissue.[11,12]



Figs 32.1A and B: Carcinoma *in situ* and microinvasive carcinoma exhibit a weaker red fluorescence (A) and slightly weaker green fluorescence for normal tissues (B)

The first fluorescence bronchoscopy system that was commercially available was the Light-induced fluorescence endoscopy (LIFE) device (Xillix Technologies Corporation, Vancouver, Canada).[13,14] This device used blue light from a helium-cadmium laser and collected fluorescence images via its imaging bundles. The red and green wavelengths reflected by the tissues were filtered and amplified by cameras. A variety of different manufacturers has used similar technology and also displayed numerically to provide quantification. A variety of different color schemes has been used by different manufacturers. Fluorescence and white light bronchoscopy is performed during the same session.

Most of the studies have performed conventional White light bronchoscopy (WLB), followed by Autofluorescence (AF) Bronchoscopy. Biopsies were taken from abnormal and normal areas. AF bronchoscopy was better at detecting airway lesions than WLF,[15] but was also more likely to give false positive results.[16] In one study, 95 out of 285 (33%) biopsies have taken from areas with abnormal fluorescence contained abnormal histology, a positive predictive value of only 33%.[17] There are no accepted indications for AF. It has a role in radiological occult sputum atypia, surveillance in patient with known carcinoma *in situ* or high grade dysplasia. AF bronchoscopy may be helpful in the evaluation of patients with invasive carcinoma who are being considered for curative endobronchial or surgical treatment.

Not all high grade lesions are premalignant and progression has been confirmed histological in fewer than 100 patients.[15,18] In addition, one study found that such progression probably occurred in 1 out of 3 patients; the rest regressed to normal.[18] The natural history is not well understood as there are difficulties due to the lack of agreement among pathologists.

High-Magnification Bronchoscopy

Neovascularization or increased mucosal microvascular growth[19,20] is a hallmark of early lung cancer. High-magnification bronchoscopy (HMB) uses this principal to identify abnormal mucosa. This system can provide information about the bronchial mucosa with a maximum magnification of 110 times. Such increased vascularity in the bronchial mucosa is also seen in asthma and chronic bronchitis. Areas of complex networks of tortuous vessels in the bronchial mucosa that are detected using HMB at sites of abnormal fluorescence may enable discrimination between bronchitis and dysplasia. The sensitivity and specificity of HMB is 70% and 90% respectively.[19] This promising work has not been duplicated at any other institution.

Narrowband Imaging

This neovascularization or increased mucosal microvascular growth can be observed, if a new narrowband filter is used instead of the conventional red/green/blue broadband filter. This narrowband imaging (NBI) technique uses a 415 nm blue light, which is absorbed by hemoglobin contained in the capillary network on the mucosal surface and a 540 nm green light that is absorbed by blood vessels located a bit deeper below the capillary layer.[21] NBI was shown to increase the rate of detection of dysplasia or malignancy by 23% when compared to WLB,[22] however when combined with AF bronchoscopy, there is no increase yield.[23]

Optical Coherence Tomography (OCT)

This is also a noninvasive technique for endoscopic imaging of *in vivo* tissue structure. Optical coherence tomography resembles ultrasound, but uses light rather than acoustic waves. On ultrasound, the resolution of the quality of image is often obscured due the presence of air, OCT overcomes this problem. Velocity of light is 200,000 times greater than the velocity of sound, thus the resolution is much improved, but the depth is only up to 2 mm.[24,25] The procedure can be performed with standard bronchoscopy. OCT can localize preneoplastic changes in the bronchial epithelium once identified by AF bronchoscopy. Carcinoma *in situ* (CIS) and invasive carcinoma can be identified from normal bronchial epithelium.[26,27] It may have role in understanding the airway remodeling in Chronic Obstructive Pulmonary Disease (COPD) and asthma as the details of airway can be visualized up to 2 mm.[28]

Confocal Endoscopy

Optical technological advances for endoscopic imaging continue to proliferate, confocal endoscopy endomicroscopy is another one such advancement. This has the capabilities for submicrometer-level resolution imaging, but has further limitations in the depth of penetration (approximately 0.5 mm compared with approximately 2 to 3 mm with OCT).[29] It is envisioned that sometime soon in future, the optical technologies will provide a window to intracellular structures *in vivo*, replacing the traditional *in vitro* analyses of cellular components using conventional tissue biopsy specimens.

ADVANCED BIOPSY TECHNIQUES

Transbronchial Needle Aspiration (TBNA)

Needle aspiration of mediastinal lymph nodes was initially recognized in 1949, its application via flexible bronchoscopy was later described in 1981.[30,31] However, the TBNA has been utilized in the diagnosis of endobronchial lesions, peripheral nodules, and mediastinal abnormalities.[32-34] The most common application of TBNA is the diagnosis and staging of lung cancer.

Technique

In order to perform optimal TBNA; a computed tomography of the chest is performed with contrast prior to TBNA. The relationship of the tracheobronchial tree to the lymph nodes and blood vessels are essential to know. The needle must reach the core of the lymph node to get optimal biopsy while avoiding nearby vascular structures. TBNA of lymph nodes in the subcarinal and right paratracheal regions detects metastasis with a higher sensitivity than TBNA of left paratracheal lymph nodes.[35]

When someone is going to perform TBNA, he first must learn and understand the mediastinal anatomy. As the bronchoscope is passed to the right of the distal third of the trachea the superior vena cava and the azygos vein is found. Directly anterior to the trachea, above the level of the primary carina is the innominate artery and the aortic arch. They cross the origin of the left main stem bronchus and then lie anterior and to the left of the distal third of the trachea, making an easily recognizable pulsatile imprint.[36] The main pulmonary artery divides into the right and left branches within the concavity of the aortic arch. The left pulmonary artery runs anterosuperiorly, in close approximation (within 3 to 5 mm) to the left main stem bronchus, while the right pulmonary artery lies anterior to the right mainstem bronchus and the origin of the upper lobe bronchus. The esophagus lies in close approximation (within 2 to 3 mm) to the posterior wall of the trachea and the left mainstem bronchus.[36]

Only the retractable needles should be used, as the damage to working channel is common and costly, the commonly used size is 22 Gauge (G) needle to obtain cytology. There is a larger 19 G needle that has been used for histology; however, it is cumbersome system with poor performance record. During insertion of the catheter, the flexible bronchoscope should be kept as straight as possible, with its distal tip in the neutral position in order to prevent damage to the working channel. The tip of the needle should be kept within the metal hub during its passage through the working channel.[37] The catheter should be retracted, and the tip of the needle kept in view distal to that of the fiberoptic bronchoscope. The bronchoscope is then advanced as a single unit to the target area, and the tip of the needle is anchored in the intercartilaginous space so as to penetrate the airway wall. The needle should be inserted with the metal hub against the tracheobronchial wall. When the needle is inserted, suction is applied at the proximal side port using a 60 ml syringe. The catheter is then agitated to and fro to obtain cytology with continuous suction. The needle is withdrawn from the target site after releasing suction.

The specimen for cytology is prepared by using air from a 60 ml empty syringe to spray the specimen onto the slide, smearing it using another slide, and immediately placing it in a 95% alcohol solution. If Rapid On-Site Evaluation (ROSE) service is available, then feedback from the cytologist is extremely helpful and reduces the number of punctures.[38] The cytopathologist reviewing the sample for adequacy has been demonstrated to increase diagnostic yield.[38] A trained assistant is essential for the success of TBNA and proper tissue handling.

Complications following TBNA are uncommon if appropriate precautions are taken and the proper technique is employed. Damage to the working channel of the bronchoscope is most common. There are no firm recommendations on antibiotic prophylaxis. Oozing of a minimal amount of blood from the puncture site may be encountered; infrequent complications include pneumothorax, pneumomediastinum and hemomediastinum.

Outcomes

A meta-analysis of 42 studies examining the accuracy of CT in detecting mediastinal nodes infiltrated with malignancy reported sensitivity and specificity of 79% and 78% respectively.[39] The sensitivity and specificity of TBNA for the diagnosis of non-small cell lung cancer was 39% and 99% respectively in other large meta-analysis of 113 studies.[40] TBNA establishes the diagnosis and provides staging information in a single procedure. A positive N2 or N3 lymph nodes for non-small cell lung cancer avoids surgical intervention. Positron Emission Tomography (PET) helps in defining, which lymph nodes should be sampled.

The utility of TBNA in the diagnosis of lymphoma has been limited, this usually requires larger samples of nodal tissue. Several reports have confirmed an increase in the diagnostic yield when both transbronchial lung biopsies and TBNA are performed in patients with suspected sarcoidosis.[41,42]

Endobronchial Ultrasound (EBUS)

This bronchoscopic technique uses ultrasound to visualize structures of the mediastinum adjacent to the airway wall to perform TBNA. EBUS can be used to guide bronchoscopic sampling of mediastinal lymph nodes, hilar lymph nodes, or peripheral pulmonary nodules.[43,44] EBUS is different than EUS. While both visualize and guide the sampling of mediastinal lymph nodes, EBUS is performed during bronchoscopy and EUS is performed during upper endoscopy.

Techniques

Various techniques for endobronchial ultrasound include the following:

i. *RP-EBUS:* Radial Probe EBUS (RP-EBUS) provides 360° images of the airway wall and surrounding structures, and visualize the layers of the airway wall. RP-EBUS is performed by placing the bronchoscope tip in the area of interest, inserting the radial ultrasound probe through the working channel and inflating its balloon sheath with water. Twenty MHz or Thirty MHz miniature radial probes are available, which provide a depth of penetration of 5 mm. An ultra-miniature radial probe can be extended into subsegmental bronchi allowing peripheral pulmonary nodules to be visualized. The probe and guide sheath are advanced through the working channel of the bronchoscope until the nodule is visualized, radial probe is removed, leaving the guide sheath in position. Biopsy forceps or a bronchial brush is then inserted through the guide sheath and the nodule to be biopsied. When RP-EBUS is used for TBNA the radial probe is removed from the working channel before the TBNA can be inserted, thus it is not performed in real time.

ii. *CP-EBUS:* Convex Probe EBUS (CP-EBUS) gives a view, which is parallel to the shaft of the bronchoscope. This allows real-time TBNA, color flow Doppler will help identify vascular and cystic structures. A 7.5 MHz convex ultrasound probe is a part of the bronchoscope at its tip. The ultrasound image and conventional bronchoscopy image can be displayed on the same monitor, but two separate monitors are preferred. A transbronchial needle system containing a 22 G retractable sharp beveled needle with an internal sheath is inserted through the working channel, just proximal to the ultrasound probe. Once the catheter emerges from the bronchoscope, the needle is advanced from the catheter and locked into position. It is then pushed through the inter cartilage space and into the target lymph node under ultrasound visualization (Figs 32.2A to C). Suction is applied with syringe and the catheter is slowly agitated. The needle is pulled into the flexible catheter after suction is released. The specimen is prepared in a similar manner as TBNA.

Outcomes

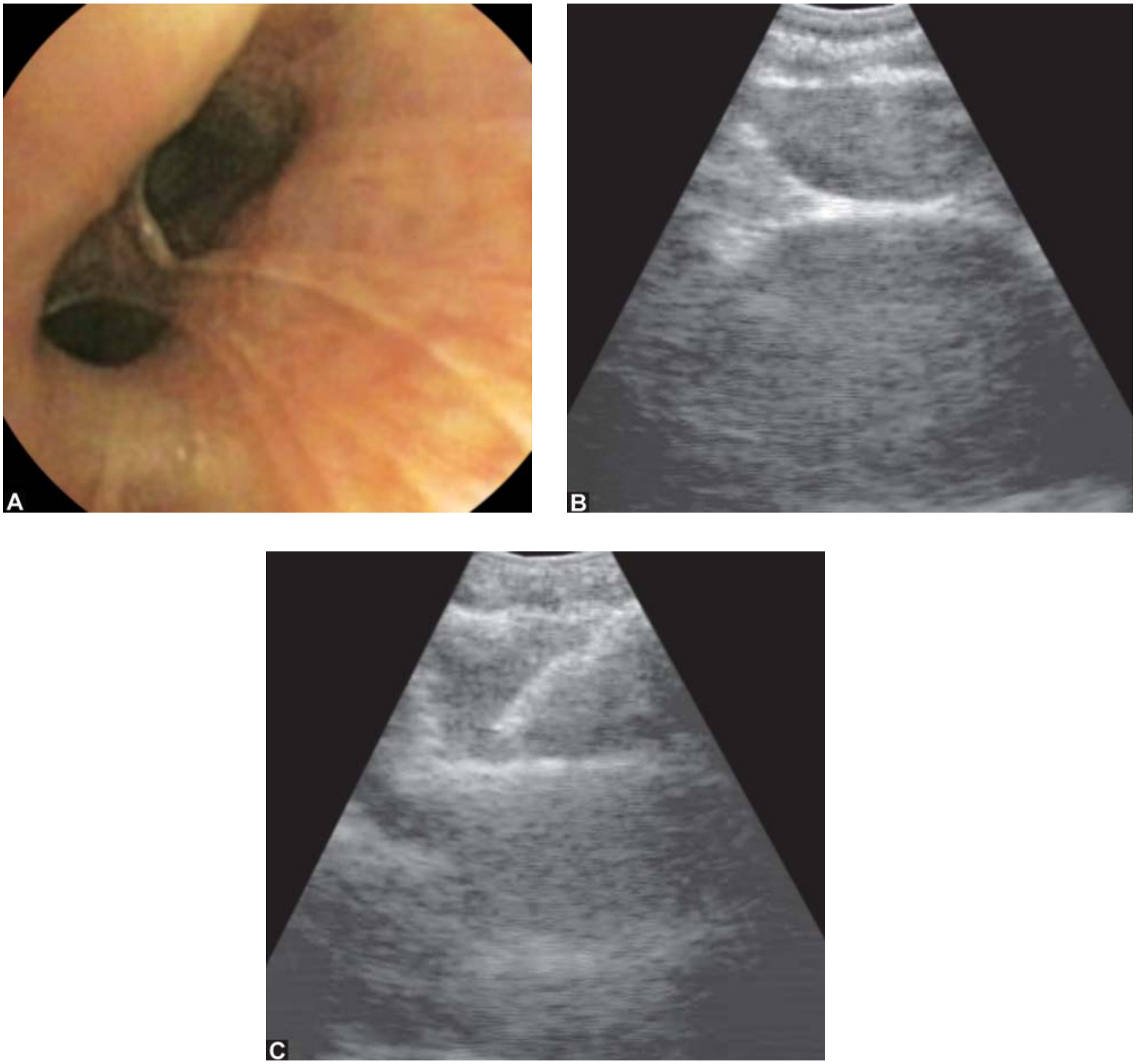
Various outcomes of endobronchial ultrasound include the following:

i. *Mediastinal lesions:* EBUS is employed once an enlarged mediastinal lymph node is identified by CT scan or is metabolically active on a PET.[45] In an initial clinical trial, RP-EBUS was used in suspected lung cancer.[46] Patients with lymphadenopathy were randomized to RP-EBUS and TBNA. Positive result was defined as yielded lymphocytes or a specific abnormality on cytology. In patients with lymph nodes, which were other than subcarinal, RP-EBUS-guided TBNA had an improved yield (84% vs 58%) when compared to TBNA. RP-EBUS did not add any further value when subcarinal lymph nodes were analyzed.

   CP-EBUS-guided TBNA could successfully sample mediastinal or hilar lymph nodes,[47] malignancy was detected with a sensitivity of 95% and the specificity of 100%, and diagnostic accuracy of 96%. Similar sensitivity and specificity were shown in a large meta-analysis of 11 studies.[48] When a combination of EBUS-guided TBNA and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is used to access mediastinum, there is a good possibility of making the entire mediastinum accessible thus decreasing the need for more invasive procedures. The combination appears to improve the diagnostic yield, when compared to either procedure alone.[49,50]

   CP-EBUS-TBNA has been used with to diagnose sarcoidosis. This has been demonstrated by a randomized study where EBUS has been shown advantageous than conventional TBNA.[51] EBUS had a sensitivity of 83% and specificity of 83%, while conventional TBNA had a sensitivity 61% and specificity of 100%. Similarly, EBUS is an effective method for diagnosing mediastinal lymphoma.[52]

   The EBUS have certain disadvantage as the bronchoscope is larger than the conventional bronchoscope with a poorer image quality. As the vision is 30° above, it is technically difficult to maneuver and requires practice. Due to its poorer



Figs 32.2A to C: Extrinsic compression (A) EBUS view of the lymph node (B) EBUS needle visible in the lymph node (C)

quality image, it should not be used for initial inspection. There is no histology needle available with EBUS, the size is the same as TBNA of 22 G.

ii. *Pulmonary nodules:* In a prospective study of 150 patients with peripheral pulmonary nodules, RP-EBUS-guided forceps biopsy using a guide sheath, was diagnostic in 77% of cases.[53] The yield was not impacted by lesion size. In comparison, prior studies when a guide sheath was not reported a diagnostic yield of up to 28% only. Other studies have similarly reported a diagnostic yield of approximately 79% when a guide sheath is used.[54] In a large randomized trial assigning patient to RP-EBUS-guided or conventional transbronchial biopsy,[55] RP-EBUS-guided transbronchial biopsy identified malignant disease with a sensitivity of 75% and accuracy 83% in nodules that were smaller than 3 cm. In contrast, conventional transbronchial biopsy identified malignant disease with a sensitivity of 31% and accuracy of 50%.

However, the yield is lower than with CT-guided percutaneous transthoracic needle aspiration. The RP-EBUS only provides an advantage if the lesion is smaller than 3 cm.

Navigational Bronchoscopy

Navigational bronchoscopy provides a virtual 3-D map to enable a physician to perform biopsy, place markers for radiation therapy or facilitate the surgeon to remove a small peripheral lesion. Bronchoscopic lung biopsy has been one of the methods to obtain tissue from a peripheral lesion. The yield for the lesion of less than 2 cm is very poor. Transthoracic needle aspiration with CT-guidance is commonly used where variable results on diagnosis and complication rates are reported. Depending on the author's intension, these variable numbers are used to either exaggerate or minimize the true impact.

Navigational systems use either an electromagnetic navigation assistance or computer assistance to identify the air columns to reach the final destination. This procedure requires several steps prior to the bronchoscopy. A CT is performed to the specification of the manufacturer. These images are transferred to laptop containing specific proprietary software and the planning is performed. Depending on the software, the virtual plan is generated. This virtual plan is placed in the navigational computer; finally bronchoscopy is performed with fluoroscopic assistance. A variety of steerable catheters can be placed in the working channel. The target is approached through an extended working channel and the navigational catheter with help of the navigation system. Once the target is reached, forceps or brushes are used to obtain tissue or fiducial markers placed.

Several studies have reported a diagnostic yield of 64 to 69%.[56,57] In a multicenter, randomized, controlled trial where EBUS, navigation system or EBUS combined with navigation system were used, the diagnostic yield was only 72%. The combined yield for EBUS with Electromagnetic Navigation Bronchoscopy (ENB) was 88%. This has not been reproduced anywhere else.[58]

The capital equipment cost is above 200,000 US dollars and disposable equipment for every case is above 1,000 US dollars, which make these systems currently prohibitive. Similarly, the EBUS systems are also in the same dollar range.

ENDOSCOPIC PALLIATIVE CARE

Begin or malignant tracheobronchial obstruction can lead to acute respiratory distress, even asphyxia and death. Endobronchial obstruction may present as an endobronchial lesion, an extraluminal obstruction or sometimes a combined lesion.

If curative resection is not possible, various endoscopic methods for palliation are available such as Neodymium-Doped Yttrium Aluminium Garnet (Nd:YAG) laser, cryotherapy, electrocautery, Argon Plasma Coagulation (APC) and photodynamic therapy. In case of extraluminal lesions, palliation is performed by balloon dilatation, stent placement, and/or external beam radiation.

These patients present with dyspnea, cough, chest discomfort, hemoptysis, stridor or localized wheeze. The history may include known cancer, aspiration of a foreign body, prior airway surgery or intubation, recurrent pneumonia, or other underlying illnesses that may involve the airways such as sarcoidosis or tuberculosis.

ND:YAG LASER

Using theories proposed on radiant energy in 1917,[59] Schawlow and Townes[60] formulated the hypothesis of laser light with the subsequent development of a ruby laser reported by Maimon in 1960.[61]

Laser technology makes use of the power of radiant energy and properties of light amplification, "laser" being an acronym for "light amplified by the stimulated emission of radiation". For the stimulated emission of light to occur, there must be an adequate population of excited electrons with the subsequent release of photons to produce the laser light. This phenomenon is termed population inversion, requires an outside energy source exciting a designated medium. Almost any solid, liquid or gas may act as a medium. Placing the substance to be excited in a chamber with mirrors at either end further facilitates population inversion. The effectiveness of laser light, as opposed to naturally occurring light, has to do with three important properties[62]—wavelength, spatial coherence and temporal coherence.

The amount of energy that is delivered to a lesion depends on the power setting of the laser expressed in watts, the distance from the laser tip to the target, and the duration of impact.[63] Light directed at a surface may also be reflected, scattered, transmitted or absorbed.[63] The depth of penetration, therefore, depends not only on the properties of the light, but also on the inherent properties of the tissue; the characteristics of the light produced also depend on the medium used.

In the CO_2 laser, the light is produced in the infrared spectrum at a wavelength of 10,600 nanometers. The CO_2

laser can be used as a precise cutting tool, with only minimal blood loss owing to a relatively shallow depth of penetration. The most widely used laser light for tracheobronchial lesions is the Nd:YAG laser, which is produced by the stimulation of an yttrium-aluminium-garnet glass, coated with neodymium. The Nd:YAG laser has a wavelength of 1,064 nanometers and is easily transmitted through pale tissues, with sizeable scatter and a potential penetration of up to 5 to 10 mm from the focal point.

The CO_2 laser therapy is most commonly used in the management of laryngeal lesions involving the area about the glottic opening. The CO_2 laser serves as an excellent scalpel since scattering is minimal; tissue vaporization is rapid with minimal damage to tissue. The Nd:YAG lasers, unlike the CO_2 laser, can cause deep tissue vasoconstriction, with a penetration depth of up to 10 mm, but has very good coagulation properties.

Indications and Contraindications (Tables 32.1 and 32.2)

Clinical contraindications are relevant in patients who may not tolerate the conscious or general anesthesia because of comorbid diseases. In addition, patients in whom atelectasis distal to the obstruction has been present for more than four to six weeks will probably not benefit from endoscopic laser resection because re-expansion of the involved lung is unlikely.

Complications

Complications of laser therapy are related to the laser equipment or instruments, the anesthesia used, and perioperative causes. However, despite the possibility of severe, often fatal complication, the overall risk is low. In one series, there were only 60 complications and 12 deaths associated with Nd:YAG laser therapy in 2,610 resection cases.[64]

TABLE 32.1: Contraindications for laser/cryotherapy/ electrocautery APC

Anatomic Contraindications
- Extrinsic obstruction without endobronchial lesion
- Lesion incursion into bordering major vascular structure (e.g. pulmonary artery) with potential for fistula formation
- Lesion incursion into bordering esophagus with potential for fistula formation
- Lesion incursion into bordering mediastinum with potential for fistula formation

Clinical Contraindications
- Candidate for surgical resection
- Unfavorable short-term prognosis without hope for the palliation of symptoms
- Inability to undergo conscious sedation or general anesthesia
- Coagulation disorder
- Total obstruction more than 4 to 6 weeks.

TABLE 32.2: Indications for laser/cryotherapy/ electrocautery/APC

Benign or malignant airway lesion associated with:
Dyspnea
Uncontrolled cough
Impending asphyxiation
Stridor
Inability to wean from ventilator owing to obstruction
Post obstructive pneumonia
Symptomatic or unresolving atelectasis
Nearly complete (>50%) obstruction of one major bronchus
Recurrent hemoptysis
Closure of bronchopleural fistula not responsive to conventional therapy.

A potential catastrophic intraoperative complication of laser therapy is endotracheal fire. Although the use of combustible anesthetic gases must be avoided, the use of supplemental oxygen should be less than 40%. Although the metal rigid bronchoscope cannot catch fire, the use of the Nd:YAG laser through an endotracheal tube deserves special consideration. An immediate danger to the patient and operating room personnel is that of intratracheal explosion, with the anesthetic gases or oxygen producing a "torch effect" with the ignition of the endotracheal tube; longer-term complication may result from the subsequent lower airway inhalation injury, with mucosal sloughing and airway obstruction caused by granulation tissue. Similarly, a silicone stent should be removed prior to the use of laser therapy.

Fatal hemorrhage is associated with perforation into an involved or contiguous vascular structure. Perforation may also occur into adjacent structures with the development of pneumothorax, pneumomediastinum and tracheoesophageal fistula. Systemic air embolism and the development of vascular communication with the tracheobronchial tree have been reported.

Technique

Physicians prefer to use rigid bronchoscopy with general anesthesia, although procedures can be performed through the flexible fiberoptic bronchoscope using topical anesthesia alone.[65,66] Laser resection is performed first with photocoagulation of the tumor. Coagulated tissue is then removed by the use of the beveled edge of the rigid bronchoscope. Complete laser vaporization of tissue may also be performed, but has high risk of endobronchial fire. The laser beam should always be aligned parallel to the bronchial wall and never be discharged perpendicular to the airway wall. Laser pulses of one second or less are usually employed. When using a flexible bronchoscope, the removal of devitalized tissue can be slow and difficult due to small forceps. In addition, the flexible bronchoscope is combustible.

Precautions

The patient's eyes should be protected with saline-soaked pads and aluminum foil to avoid injury from accidental laser scatter, and all personnel should wear protective goggles. Fraction of inspired oxygen should be kept below 40%. Flammable materials, such as endotracheal tubes and silicone stents should be removed prior to the use of laser. If a flexible bronchoscope is employed, the laser must be kept at a sufficient distance beyond the tip of the bronchoscope. Power settings of greater than 40 watts should not be used.

Outcomes

The indications depend on the anatomic characteristics of the obstructing lesion and the clinical conditions outlined in Table 32.2.[66,67] Benign and malignant airway endobronchial lesions causing symptomatic or obstructive complications do benefit from endoscopic laser photoresection.[68-72] Laser therapy has also been performed for stenosis related to prolonged intubation;[73] stricture produced by mycobacterial infection; anastomosis granulation tissue following lung transplantation;[74] suture granulomas;[75] and in systemic inflammatory conditions, such as Wegener's granulomatosis, Behçet's syndrome and relapsing polychondritis.[76,77] Laser therapy has been also used in symptomatic obstruction secondary to broncholithiasis.[78] Benign or low-grade tumors, such as hamartomas, spindle cell carcinomas, endobronchial Kaposi's sarcomas, and even diffuse papillomatosis have also benefited from Nd:YAG laser photoablation.[79-82] A primary goal of laser therapy is the safe, effective, and rapid palliation of symptoms owing to tracheal or bronchial obstruction.

Electrocautery

Electrocautery uses electric current to produce heat and destroy tissue. Strauss[83] used electrocautery for treating gastrointestinal tumors in 1913 and reported their experience on over 40 cases in 1935.

Electrocautery uses alternating current at a high frequency (105 to 107 Hz) to generate heat that coagulates, vaporizes or cuts tissue, depending on the power. The power applied to the electrocautery device (measured in watts) corresponds to the heat generated in the tissue, as related by the equation: Power = $(\text{current})^2 \times \text{resistance}$. Coagulation involves high amperage and low voltage, whereas vaporization uses high voltage and low amperage. Cutting tissue with the ability to coagulate blends these two settings. At the temperature of approximately 70°C, the tissue coagulates and at over 200°C, the tissue carbonizes. The degree of destruction depends on the applied power, the electrical properties of the tissue, the device-tissue, contact time, and the device-tissue contact surface area.

When a tissue is sufficiently heated, cellular water evaporates, thereby destroying the cell and then the tissue. Heating to higher temperatures leads to the chemical breakdown of the cell and the tissue constituents and eventual vaporization/carbonization. Electrocautery devices are monopolar; they require the bronchoscope, the generator, and the patient to be grounded to complete the circuit or otherwise shocks and burns may occur. The bronchoscope should be insulated. The generator should at least have an isolated power output to minimize current leakage and possible injury, if it is not grounded.

Indications

The indications and contraindication for electrocautery are similar to those Nd:YAG laser[84,85] (Tables 32.1 and 32.2). Similarly, laser therapy electrocautery produces the rapid debulking of a tumor, but at a lower cost.

Equipment and Technique

Insulated flexible bronchoscopes with working channels of 2.0 or 2.6 mm are used. Electrocautery blunt-tip probe snare is compatible with the most commonly used flexible bronchoscopes. The generator should regulate the high-frequency current, so that operator can adjust the setting depending on whether the procedure is intended to coagulate, cut, cut and coagulate, or vaporize. The monopolar unit must be grounded with an electrode pad.

The operator can use either a closed forceps or the blunt electrocautery probe to manipulate the lesion and thus to assess its size, mobility, friability/bleeding potential, and to locate any attachment to the airway. Polypoid lesions may be amenable to the snare. The snare is used to cut and remove tissue, a blended current is used to cut and coagulate, but not vaporize.

Outcomes

It had been shown that hemoptysis was controlled in 75% of the cases, dyspnea was alleviated in 67%, and cough or stridor was relieved in 55%.[86] In one series, 28 of 29 patients had symptomatic improvement after the removal of a lesion, with a snare while another showed that 15 of 17 treated patients had immediate restoration of a patent airway; eight had relief of dyspnea, and four had control of hemoptysis.[87,88] Most series involve predominantly malignancies, and success is defined as removing greater than 50% of the tumor; success rates of 70 to 95% have been reported.[89-91]

Complications

Two endobronchial fires have been reported during the electrocautery procedure;[90] both were associated with high inspired oxygen concentrations, and in one incident, a silicon stent also ignited. Several investigators have reported hemorrhage, in most cases minor. One death had occurred secondary to hemorrhage. Operator and patient burns and electrical shocks are frequently mentioned as possible complications, but published data are scant. Another concern is using electrocautery in a patient with a pacemaker or an automatic implantable defibrillator because the devices may malfunction. When used in animal models, airway stenosis and cartilage damage have been shown to occur with electrocautery.

In summary, similar to Nd:YAG laser therapy, electrocautery is an effective tool for palliation. It is also a cheaper alternative to laser therapy, and has no significant disadvantages.

Argon Plasma Coagulation (APC)

Argon plasma coagulation is an electrosurgical technique used to remove an obstructing lesion and/or to achieve hemostasis. The indications and contraindications are similar to that of laser or electrocautery (Tables 32.1 and 32.2).

APC was developed more than 20 years ago to improve surgical hemostasis. In the early 1990s, a flexible probe was introduced that facilitated its use during endoscopic procedures. APC was initially used during gastrointestinal endoscopy during polypectomy.[92] APC has been used during bronchoscopic procedures to debulk malignant airway tumors, control hemoptysis, remove granulation tissue from stents or anastomoses, and treat a variety of other benign disorders.[93-97] APC is a noncontact form of electrocautery.

Procedure

Similar to electrocautery, a grounding pad should be placed on the patient back. It is applied at a power of 30 watts and an argon flow rate of 0.8 to 1 L/min, the flow rate determines the length of the flame. Since the argon will seek biological tissue or any combustible object, the flame length is important in its airway application. The probe tip should be several centimeters beyond the bronchoscope's tip. This insures that the bronchoscope will not get burned. The probe tip should be within 1 cm of the target lesion. The electric current will not be conducted if the probe is farther from the target lesion. The probe tip should not contact the target lesion. Argon gas is expelled from the probe and a high voltage electric current is passed. When the electric current contacts the argon gas, the argon gas becomes ionized and conducts a monopolar current to the target lesion.[94,95] This argon plasma is applied to the surface in one to three second bursts. The net tissue effect is similar to that of electrocautery.

In the process of debulking of an endobronchial lesion, the Eschar is first formed (Fig. 32.3) with the application of APC and then removed with forceps or a cryotherapy probe. APC is then applied to the underlying fresh tissue. This process is repeated until the tumor is removed. If brisk bleeding is encountered, the argon gas can be used without ignition to blow the blood away, thus improving visualization.

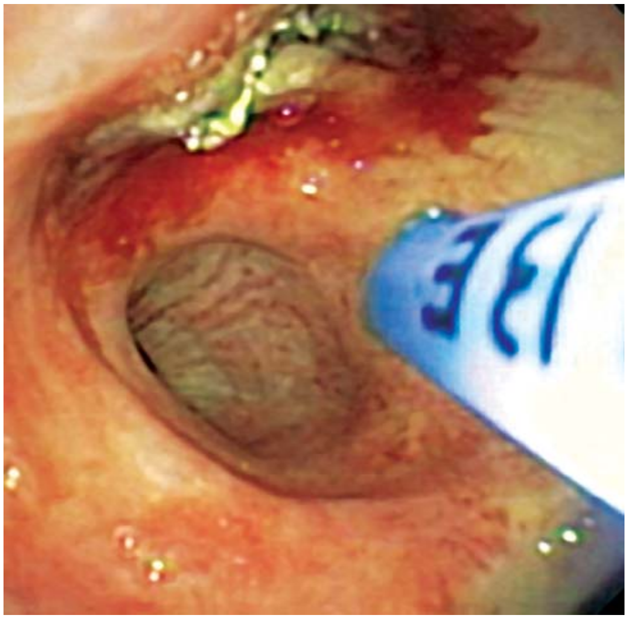


Fig. 32.3: APC use with an Escher formation

Outcomes

A prospective cohort study of 364 patients who underwent APC (482 procedures) reported a success rate of 67%, defined as hemostasis and/or full or partial airway recanalization; rigid bronchoscopy was used in 90% of the interventions.[96] In another study on 60 patients who underwent APC (70 procedures), treatment was immediately successful in 59 patients.[96] All of the patients had either hemoptysis or airway obstruction, with treatment success defined as the resolution of hemoptysis and/or decreased airway obstruction. Hemoptysis did not recur over a mean follow-up of 97 days, improved dyspnea persisted for over a mean follow-up of 53 days. A similar study of 47 patients reported a success rate of 92%, maintained for a mean follow-up of 6.7 months.[94] However, an average of more than three sessions per patient were required to achieve this result. APC has been successfully used to treat benign disorders, such as granulation tissue due to stents or airway anastomosis.[95,96]

Complications

Complications of APC are infrequent (less than 1% of procedures). They include airway burn and perforation, which can cause pneumomediastinum, subcutaneous emphysema and pneumothorax.[98] Gas embolism has also been described in a case series, leading to three cases of cardiovascular collapse and one case of death.[99] Such a complication is a reflection of the lack of experience by the operator. A burned bronchoscope has also been reported. Limiting the inspired oxygen concentration, the power (less than 40 watts), and the application time (less than 5 seconds) probably minimizes the risk of airway fire. Keeping the probe tip several centimeters away from any combustible material is also helpful to prevent airway fire.

Cryotherapy

Documents from 3500 BC described the use of cold as treatment for swelling and war wounds.[100] Hippocrates described the use of cold to treat orthopedic injuries.[100] Arnott described the use of salt solutions containing crushed ice at a temperature of about –8 to –12ºC to freeze advanced cancers of accessible sites, producing reduction in tumor size and improvement of pain.[101,102] The current cryoprobes function, according to the Joule-Thomson effect, i.e. the sudden expansion of a gas from a high to a low-pressure region.

The destructive effect of cold had been confirmed also by the healing of the tracheobronchial tree, with the restoration of a normal ciliated epithelium, without stenosis.[103-110] The first study from the Mayo Clinic, consisting of 28 patients with endobronchial tumors and concluded that cryotherapy did serve as a good alternative for palliation.[110]

Cryotherapy deals with the destruction of biological materials through the cytotoxic effects of freezing. The damage induced by freezing occurs at several levels, including at the molecular level, cellular level, structural level and the whole tissue. The effect of freeze injury is influenced by many factors and the survival of cells is dependent on the cooling rate,[111-113] the thawing rate,[114] the lowest temperature achieved[115] and repeated freezing thawing cycles.[116,117] Certain tissues are cryosensitive (skin, mucous membrane, granulation tissue), and others cryoresistant such as fat, cartilage, fibrous or connective tissue. The cryosensitivity depends on the water content of the cells (Table 32.3). Tumor cells may be more sensitive than normal cells.[118]

TABLE 32.3: Cryosensitive and cryoresistant tissues

Cryosensitive	*Cryoresistant*
Skin	Fat
Mucous membrane	Cartilage
Nerve	Nerve sheath
Endothelium	Connective tissue
Granulation tissue	Fibrosis

Cooling Agents

Several cooling agents can be used as cryogens. These are generally used in the liquid phase, on vaporization they remove heat at a constant temperature (heat of vaporization). The core temperature needed for a lesion to be destroyed is between –20 and –40°C. Freezing to –40°C or below at the rapid rate of –100°C per minute will cause more than 90% cell deaths.

Nitrous Oxide (N_2O) is the commonest cooling agent used. The vapor haze of N_2O occurs at the metal tip of the cryoprobe where it expands from a high pressure to atmospheric pressure (Joule-Thomson effect). This expansion lowers the temperature of the fluid and produces droplets of liquid and reaches equilibrium of –89ºC at atmospheric pressure.

Cryotherapy Equipment

The cryoprobes are rigid, semirigid or flexible; rigid and semirigid cryoprobes can only be used through a rigid bronchoscope, but flexible can be used through the channel of the fiberoptic bronchoscope. The diameter of the flexible probes requires a larger working channel (2.6 to 3.2 mm).

The monitoring of the freezing remains a problem,[119] there is no ideal solution. The empirical method relies on the experience of the operator, who depends on the change in color\consistency of the frozen tissue, and the length of freezing. In clinical studies,[120-123] each freeze-thaw cycle is about 30 seconds. The thaw phase is almost immediate with rigid probes that have a system of reheating, but with the flexible probes thawing is done by body temperature thus, increasing the freeze/thaw cycle times.

Indication

Cryotherapy is indicated for tracheobronchial obstruction. The selection criteria are similar to those of laser, APC or electrocautery (Tables 32.1 and 32.2) except when there is an urgency to treat. In addition, cryotherapy can be used for the extraction of foreign bodies, blood clots and mucous plugs.

Technique

The flexible cryoprobe is passed through the working channel, which is visualized and directly applied to the tumor area. The cryoprobe is activated with a foot pedal. An ice ball appears within 30 seconds on the tip of the probe; two to three freeze thaw cycles, each lasting for one minute, are applied to the same or the neighboring area. The tip can be applied perpendicularly, tangentially or driven into the tumor mass. The tissues are frozen at –30 to –40°C. The cryoprobe is deactivated by the removal of the foot from the foot pedal.

The metallic tip of the cryoprobe is placed on or pushed into the tumor that produces circumferential freezing of maximal volume. Two to three freeze thaw cycles are carried out at each site. The probe is then moved 5 to 6 mm and another three cycles carried out in the adjoining area. The hemostatic effect of freezing is often sufficient to stop hemoptysis.

Outcomes

Walsh[124] reported the effects of cryotherapy on dyspnea, hemoptysis, cough and stridor. In his study, symptoms, lung function, chest radiography and bronchoscopic findings were recorded serially before and after 81 cryotherapy sessions in 33 consecutive patients. Most patients reported the improvement of symptoms, stridor and hemoptysis, they had an overall improvement in dyspnea. Several other investigators have noticed a subjective improvement in symptoms.[125-127] Successful cryorecanalization was achieved in patients with endobronchial tumors.[128,129] The flexible cryoprobe for symptomatic endobronchial tumor stenosis was successful for immediate treatment, but the safety remained a cause of concern. This can be potentially dangerous in inexperienced hands. This method has been helpful in getting a bigger biopsy sample.[129] The mean transbronchial biopsy specimen area was 5.82 mm^2 taken by forceps compared to 15.11 mm^2 obtained using the cryoprobe.[130]

There has been a renewed interest in the treatment of early stages of lung cancers. The French experience[131] reported by the GECC (study group on cryosurgery) was based on 36 patients with 44 lesions (*in situ* or micro invasive tumors); 42% of these patients had been treated for an invasive ENT or bronchial cancer. At one year, there was complete clinical and histological control of the tumor was achieved in 88.8% with a mean follow-up of 32 months. The mean survival of this population was 30 months.

Benign Tracheobronchial Lesions

Benign lesions have been treated with cryotherapy with very good results, particularly for granulomatous tissues; 100% had favorable results with no recurrence months or even years after treatment. Granulation tissue is very sensitive to the effects of cold. Nevertheless, when surgery is not possible, treatment with cryotherapy can yield good results, and several cases of carcinoid, cylindromas, and laryngotracheal papillomas have been successfully treated.

Removal of Foreign Bodies

Foreign bodies have been extracted with success using cryotherapy, this is most useful to remove friable and biological matter such as pills, peanuts, tooth, chicken bones and others. This is extremely helpful in the removal blood clots mucus plugs and slough.

Future Work

In the treatment of lung cancer, a local cryotherapy has been used for palliative care.[132] Forest[133-137] has demonstrated differential biological effects of these therapies and the benefit to combine them. As vascular changes occur after cryotherapy, intratumoral angiogenesis was also studied. Tumors were treated by cryotherapy and chemotherapy by the injection of vinorelbine or both. Tumors treated by cryochemotherapy presented a significantly reduced volume and the lower T/C ratio, confirming the benefit of a combined treatment.

Photodynamic Therapy (PDT)

Photodynamic therapy is used for endobronchial destruction of tumor and also in the treatment of early superficial lung cancer with the only available agent, Porfimer (Photofrin®). A dose of 2 mg/kg is injected intravenously slowly over 5 to 10 minutes. There is preferential retention in tumor cells and in vascular endothelium, the cytotoxic reaction of porfimer is selective for neoplastic cells.[138] After 48 hours, the tumor is exposed to light energy, which triggers the cytotoxic reaction. The absorption peak occurs at a wavelength of 405 nm. A wavelength of 630 nm is used for adequate penetration and destruction to a depth of 5 to 10 mm.[139]

The most commonly used design is a cylindrical diffuser, which emits light in a 360 degree arc near its tip. It is recommended initially to apply 200 Joules/cm treated; additional energy may be applied during a follow-up bronchoscopy, two days later, 200 J are generally applied with a dye laser. Tumor is visualized, the light fiber is introduced through the working channel and the light is delivered to produce the cytotoxic reaction. A repeat bronchoscopy is performed in 48 hours. First the debris and secretion are removed, then a second treatment is applied.

The most common adverse event of PDT is photosensitivity of the skin. The patient teaching on photosensitivity precautions is important. The patient is at risk at 4 to 6 weeks after injection, protective gear must be worn till then.

Outcomes

PDT has shown to have an excellent cure rate in early stage endobronchial cancer, i.e. carcinoma *in situ*.[140-144] PDT has been used for palliation with similar results with other endoscopic techniques, but significant skin phototoxicity. The relief of symptoms is similar with PDT compared to Nd:YAG laser.[145] As there is a significant burden placed on the patient to protect themselves from phototoxicity, our preference has been to limit the use of PDT only in superficial early lung cancer.

PDT provides a safe endobronchial option of possible cure of early-stage lung cancer. New photosensitizers with more specificity for cancerous tissue and less associated photosensitivity have been used in different countries, however yet without data from large clinical trials.

Brachytherapy

Background

Endobronchial radiation therapy by the use of an implanted source of ionizing radiation (brachytherapy) was first used in the 1920s. Yankauer reported on the implantation of radium into an endobronchial tumor using a bronchoscope and having the radium in capsules attached to a string that exited through the mouth.[146] In the mid-1980s, publications distinguishing Low-Dose-Rate (LDR) from High-Dose-Rate (HDR) brachytherapy appeared. LDR brachytherapy is usually defined as less than 2 gray (Gy)/hour and a total dose between 1500 and 5000 Gy, given over 3 days; HDR involves more than 10 Gy/hour, in which the total dose and the dose per session (fraction) varies. Fractions have varied anywhere from approximately 300 to 1000 Gy, and total dose from approximately 500 to 4000 Gy.

Henschke developed the remote afterloading device, thereby reducing radiation exposure to the health care staff.[147] Almost 20 years later, the use of the flexible bronchoscope and the polyethylene catheter that holds the radioactive material for brachytherapy was described.[148,149] Iridium-192, the current radiation source was also described at this same time.[148]

Techniques and Dosage

Currently, intraluminal brachytherapy uses fiberoptic bronchoscopy for the placement of after loading with the radiation source manually or with a remote afterloader polyethylene catheter adjacent to the tumor, the placement is verified by bronchoscopy and by radiograph. The dose rate of brachytherapy depends on the radioactivity of the radionuclide used. The apparatus designed to deliver HDR brachytherapy uses iridium 192, which is the radionuclide of choice. HDR brachytherapy is usually delivered in fractionated doses to maximize its safety and effectiveness. The treatment schedules vary in clinical practice, most patients are treated once a week or once every two weeks rather than once a day to minimize patient discomfort.

Indications and Contraindications

The indications are similar to any other endobronchial therapy discussed earlier. The goal of brachytherapy is to palliate symptoms caused by airway obstruction by tumor. Brachytherapy, however, can also be used as an adjunct to external beam radiotherapy for treatment in otherwise unresectable lung cancer. Some investigators[150] have used it in patients who have histologically positive surgical margins after resection.

Absolute contraindications for endobronchial brachytherapy include known fistulas to nonbronchial tissue areas and lesions that are not proven malignancies. Patients with endotracheal carcinoma causing high-grade obstruction should be treated with Nd:YAG laser and the possible placement of stent before brachytherapy, because of the potential for postradiation edema and total airway obstruction.

Outcomes

Most studies on brachytherapy have reported on its use in combination with external beam radiation therapy. Subjective improvement after brachytherapy has ranged from 20 to 100%, depending on the symptom. Hemoptysis is relieved in more than 90% of the treated patient, cough and dyspnea have moderate to minimal relief, probably owing to an underlying chronic bronchitis or radiation fibrosis. In most studies, there was a greater than 50% improvement in the patency of the airway. The positive response of most studies persisted for six or more months.[151-158]

Conventional external-beam radiation therapy relieves the symptoms of hemoptysis, dyspnea, or chest pain in 50 to 80% of patients for three to four months.[156] There are no studies comparing external-beam radiation therapy with endobronchial brachytherapy directly. Based on existing data, however, endobronchial brachytherapy has been a second line treatment option offering effective palliation.

Complications

Brachytherapy has both early and late complications. The two most serious complications of endobronchial brachytherapy are massive hemoptysis and fistula formation to the mediastinum. Serious complications range up to 42% in several large series. Risk of massive pulmonary hemorrhage is likely related to the proximity of pulmonary arteries to the left upper lobe bronchus. Bedwinek[157,158] found a 32% rate of massive hemoptysis with recurrent tumors in the right upper lobe, right mainstem, and left upper lobe bronchus.

Flexible Fiberoptic Balloon Dilation

The successful use of a balloon to dilate a benign airway stricture was first reported in an 18-week infant with a postsurgical stricture.[159] Those initial reports utilized fluoroscopy or rigid bronchoscopy to guide the dilation procedure. Flexible fiberoptic bronchoscopy with balloon dilation was not described until 1991,[159] and since that time relatively few reports with small numbers of patients have been published.[160-166] This technique is useful in the treatment of benign strictures due to sequelae of long-term endotracheal intubation, bronchial reimplantation, anastomosis of transplanted lungs, granulomatous disease (e.g. tuberculosis, Wegener's granulomatosis) or smoke inhalation. A suitable lesion for balloon dilation is a web-like stenosis (Figs 32.4A to C), but if there is loss of supporting structures, the success is poor. Medical treatment of the cause of the stricture should be instituted prior to attempt at dilation. For example, local treatment of patients with strictures secondary to tuberculosis should not be attempted until adequate antimicrobial treatment is administered.

Technique

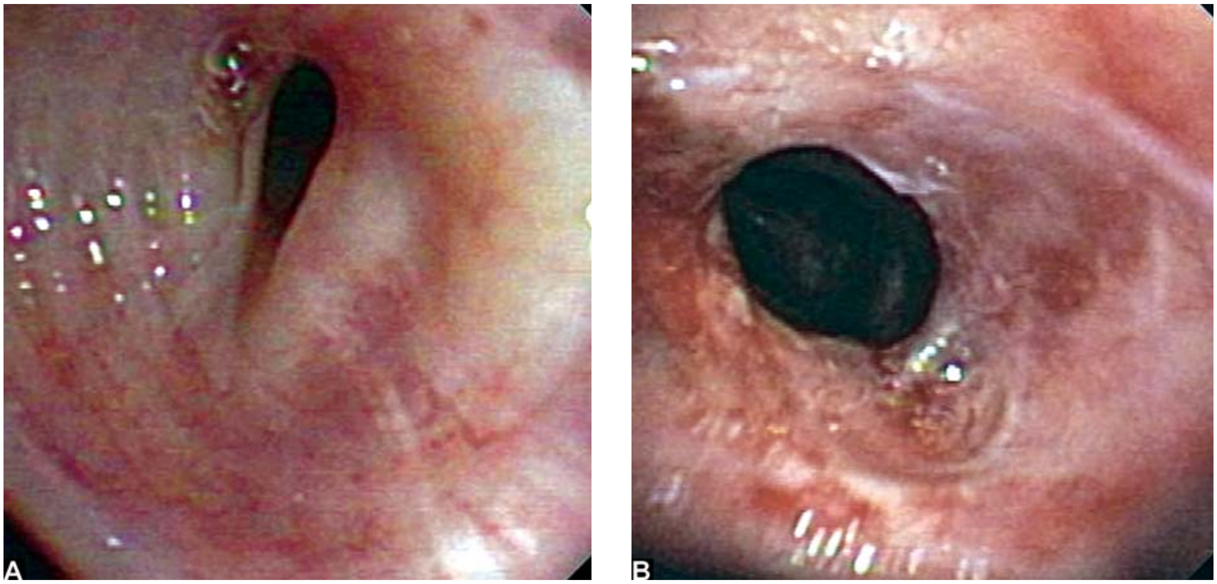
Bronchoscopic balloon dilation is a simple method to dilate a stenosis. A flexible fiberoptic bronchoscope is used in a standard manner with topical anesthesia and conscious sedation. After the identification of the stenosis, a 0.89 mm diameter guide wire is passed through the working channel and advanced beyond the stenosis and monitored fluoroscopically. The bronchoscope is removed once guide wire is in place. Next, a balloon catheter is passed, which has been selected based upon the diameter of the stenosis. The balloon has variable diameters, the dilation can start with the small size and then increased in size. The marking on the balloon, which is radiologically opaque, should protrude enough beyond each end of the stenosis for the dilation of the entire lesion. If the balloon does not extend distally enough, it tends to slip out of the stenosis upon inflation. If the balloon is ineffective, it should be replaced with a larger one. Repeated inflations can be performed with the same balloon if the result is inadequate. Immediate success or failure will be visible to the bronchoscopist (Fig. 32.5).

Complications

Excessive balloon inflation or a large length may lacerate or rupture the airway, but these complications have not been reported.

Outcomes

Several case series of fiberoptic bronchoscopic balloon dilation in adults have been reported. The largest series involved 19 stenoses in 16 patients; initial success was achieved in 13 of 19 bronchial stenoses; six dilations were unsuccessful because the stenoses were caused by localized bronchomalacia.[164-166] On an average about 50%



Figs 32.4A and B: Web like stenosis, which has been improved by balloon dilation

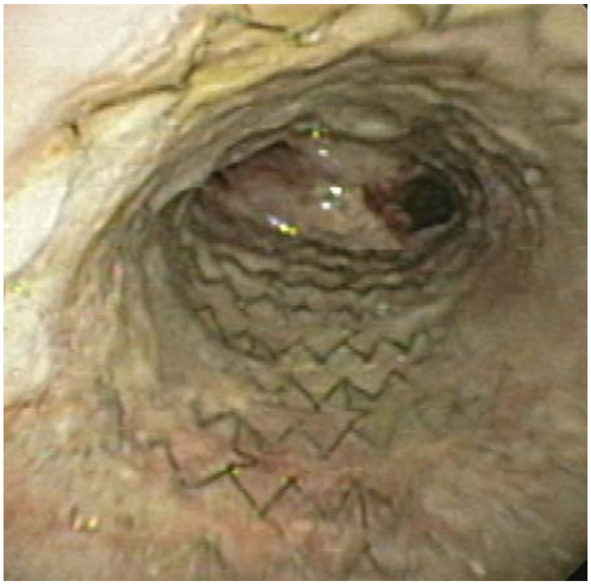


Fig. 32.4C: A metal placed

success rate has been reported without reinterventions. Surgical treatment of the stenotic segment is technically feasible in most patients. Endobronchial cryotherapy[166] in conjunction with balloon dilation has been used in two cases of benign airway stenosis with success. However, an airway stent is usually needed for support if there is damage to cartilage in the trachea or bronchi resulting in bronchomalacia.[166]

Airway Stents

The term "stent" honors a late 19th century British dentist, Charles R Stent, who developed a dental impression material that was later used as a template to support heal-ing skin grafts.[167] Today, the term stent connotes an artificial support that maintains patency of a hollow tubular structure. When the large airway is compressed by an extraluminal lesion (Figs 32.6A and B), airway

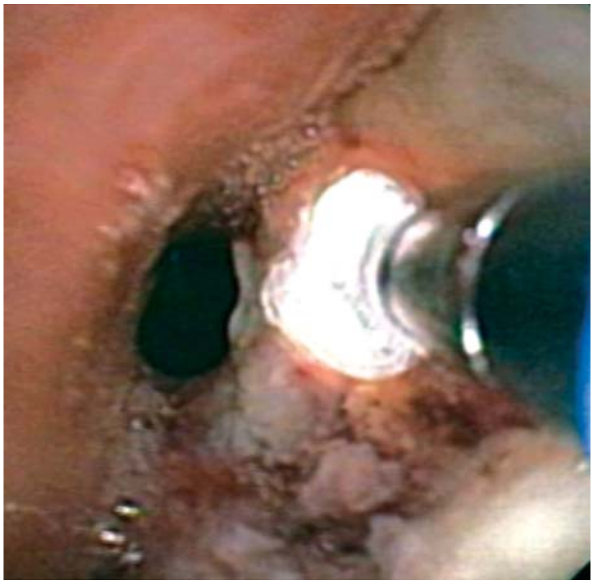
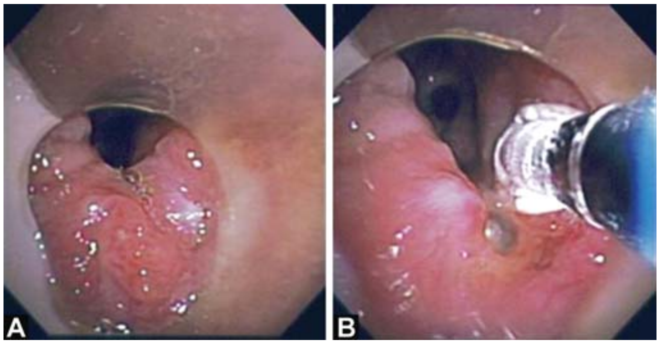


Fig. 32.5: Use of the cryotherapy



Figs 32.6A and B: Use of cryotherapy in granulation tissue formed after a stent placement

stents can play an important role. There is no ideal stent, but some characteristics make it more valuable, such as the ease of insertion and removal, infrequent migration, resistance to external forces, lack of tissue reaction, and improved mobilization of secretions.

Indications

Stent may be used alone or with other techniques for the palliation of dyspnea, cough, or respiratory insufficiency due to central airway obstruction. An airway stent supports the airway wall against collapse or external compression and can impede the extension of tumor into the airway lumen. Stents can be safely used in patients undergoing external-beam radiation therapy or brachytherapy.[64]

TABLE 32.4: Airways stents

Silicone Stents	*Metal Stents*
Rigid bronchoscopy	Flexible bronchoscopy
Removable	Extremely difficult to remove
High migration rate	Low migration rate
Thick caliber	Thin caliber
Infections	Infections
Mucostasis	Mucostasis
Granulation tissue formation	Granulation tissue formation

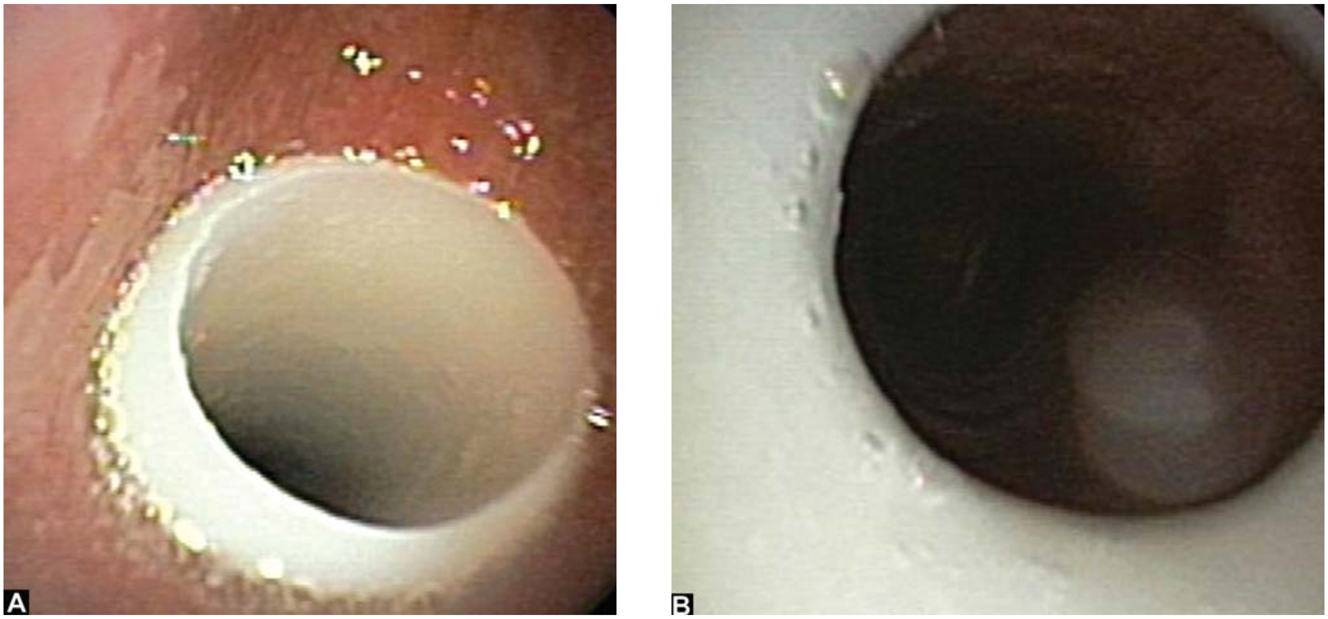
There is no survival difference between those patients without malignant airway obstruction who received palliative chemotherapy (median survival, 8.4 months) and others with airway obstruction who received treatment with laser, stent, or both followed by chemotherapy (median survival, 8.2 months).[168] The first choice to treat a benign stricture due to prolonged intubation, infectious or inflammatory diseases, and infectious diseases should comprise of a surgical repair. The patient may require stenting if there are comorbid conditions that do not allow surgery. There is an FDA black box warning against placing metal stent in a patient with benign stricture.

Types of Stents

Tracheobronchial stents can be grouped into silicone, metal or hybrid stents (Figs 32.7A and B). Silicone stents include Montgomery T-tube, Dumon, Polyflex, Noppen and Hood. The metal stents are available as covered or uncovered, include Palmaz, Wallstent Wallgraft, Ultraflex (Table 32.4). Finally hybrid stents are a combination of both such as Orlowski and Dynamic stents.

i. *Silicone stents:* The most widely used stent for central airway obstruction is the silicone stent. Silicone rubber is a synthetic substance made of silicone elastomers; it is firm, stable at high temperatures, and repels water. Silicone stents are relatively inexpensive and well tolerated. They can be repositioning and removed without difficulty. Disadvantages include stent migration, granuloma formation, mucous plugging, insufficient flexibility to conform to irregular airways, interference with mucociliary clearance, and a need for rigid bronchoscopy for their placement.

   Montgomery T-tube: In 1965, the Montgomery T-tube was introduced for the treatment of subglottic and tracheal stenosis.[169] A tracheotomy is needed to place this stent during operation or via rigid bronchoscopy.



Figs 32.7A and B: Silicone stent on the proximal end as well passing through the silicone stent

The limb protruding out of the tracheostoma is left open for cricoid or glottic stenosis, unplugged transiently for bronchial toilet, or closed to allow speech. Radial force is not required to hold this stent in position. Montgomery T-tube is a safe stent for subglottis stenosis.

Smooth-walled Hood stent: The smooth-walled Hood stent is one of the first silicone stents designed for use in the airway. It is a straight, smooth-walled silicone tube that can be ordered in varying lengths and diameters, or in the shape of "Y". This stent does easily migrate, the design has been now modified to include a small flange on its proximal and distal aspects. Nevertheless, stent migration still occurs.

Studded Dumon stent: Dumon[170] initially described his experience with a new dedicated tracheobronchial prosthesis made of silicone with studs to decrease the migration. The studded Dumon stent has become the most widely used airway stent in the world since its introduction and is now considered by many as the gold standard. The stent is manufactured in various diameters, lengths, and shapes, including straight, L-shaped and Y-shaped. The stent stays in place due to radial force and the studs, but still has a significant migration rate of about 10 to 13%.[171,172]

Reynders-Noppen Tygon stent: The Reynders-Noppen Tygon stent is not commercially available in the United States. It is a cylindrical tygon plastic tube molded into a screw-thread form, which is far more rigid than the silicone stents. It must be pushed into place along the outside of a specific introducer; it cannot be folded into an applicator with bronchoscopic introduction. One study compared the outcome of 50 patients treated with either studded Dumon silicone stents or screw-thread stents. Stent migration occurred in more patients who received Dumon stent (24% vs 5%), although the difference was not statistically significant.[173]

Polyflex stent: Polyflex stent is a self-expanding stent made of cross-woven polyester threads embedded in silicone. Stents of different lengths and diameters and tapered models are available for sealing stump fistula. In one study of only 12 patients, 16 stents were placed with a migration rate was at 75%.[174] These investigators have abandoned the use of polyflex stents.

ii. *Metal stents:* Various metals, such as stainless steel, tantalum, alloys incorporating cobalt, chromium, and molybdenum (Vitallium, Nobelium) are inherently inert and can be safely placed into living tissues. All metal stents are radiopaque, exhibit varying degrees of radial force, are easy to insert, and maintain ventilation when placed across lobar orifices. These stents can be further divided into fixed diameter stents, which require balloon dilatation, and self-expandable stents, which spring to a predetermined diameter once released. These stents could be either made of bare metal or have a thin coating with silicon, nylon or polyurethane. They can be placed in an outpatient

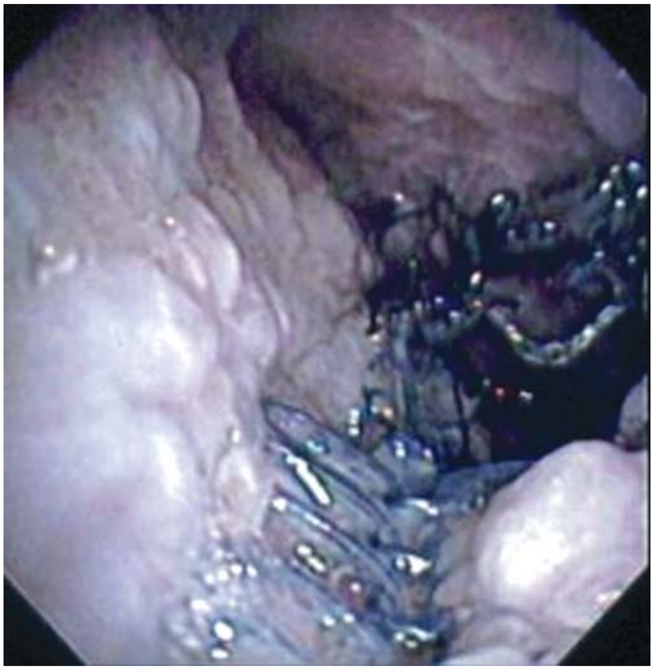


Fig. 32.8: Broken wire of a metal stent and granulation tissue

setting via flexible bronchoscopy under local anesthesia.[175,176] The ease of use has led to significant abuse and harm to patients. Its walls are thinner than a silicone stent and able to conform to tortuous airway. Similar to the silicone stent, granulation tissue formation does take place (Fig. 32.8). The disadvantage is the difficulty in removing and repositioning the stent; constant movement and metal fatigue leads to fractures of the wires. Metal stents migrate rarely (<1%).

Palmaz and Strecker stents: The Palmaz and Strecker stents are fixed-diameter balloon-expandable stents. These stents do not exhibit any intrinsic radial force, thereby compressive forces, such as breathing and coughing leads to the collapse of the stent, which in turn obstructs the airway. The plastic behavior of the Palmaz stent makes it unsuitable for use. Both these stents are of historical value and should not be used in the airway.

Gianturco stent: The Gianturco stent is made of a continuous loop of stainless steel wire, can be compressed into a narrow cylinder before bronchoscopic placement. Once expanded, the stent maintains an expansive force, and the small hooks embed in the airway mucosa to retard migration. Complications can lead to tracheopharyngeal fistula, and fatal erosion of pulmonary artery. The combination of high radial force exerted over the airway mucosa at selected contact points where the hooks are fixed can lead to mucosal ischemia and perforation.[177] Due to the severity of reported complications, this stent should also not be used.

Wallstent: Wallstent is a self-expanding device made of cobalt-alloy braided filaments in the form of a tubular mesh. It has a special feature of outward radial force provided by its integral design. It is inserted in a constrained form and once deployed expands to a preset diameter. The stent can be loaded into a delivery catheter. Various lengths and diameters are available. The covered form of the Wallstent prevents tumor and granulation growing through the spaces between the thin wire mesh. In a report of 52 Wallstents, stent-related obstructive granuloma occurred in 11% of patients, stent migration was not found. [178]

Ultraflex: The Ultraflex is a self-expanding stent made of nitinol, which is an alloy with shape memory, which deforms at low temperatures and regains its original shape at higher temperatures. Immediate relief of dyspnea is achieved in over 80% of the patients and migration is not observed.[179] The Ultraflex stents could be placed satisfactorily without fluoroscopy.[180] The complication rate was 0.06 complications per patient-month. The most common complications were infectious tracheobronchitis and obstructing granulomas requiring interventions to restore airway patency. Tumor growth and stent fracture were also seen.[180]

Alveolus stent: Alveolus stent is also self-expanding, completely polyurethane covered metallic stent. It has been claimed that it can be easily removed, but there is no data on this. The Alveolus stent is constructed from a single piece of nitinol, with concentric rings held in position by nitinol strands, this feature also makes it to crack vertically very easily. Due to its structure, it is amenable to length modification. Because it does not foreshorten with deployment and is completely covered in polyurethane coating, the stent keeps to its trimmed length and structural integrity.[181]

iii. *Hybrid stents:* Several stents incorporating both silicone and metal have been designed in an attempt to remedy some of the drawbacks of purely silicone or metal devices. Hybrid stents consist of expandable metal struts that resist compression, but are covered by a silicone membrane, which limits infiltration by tumor or granulation tissue.

The Rusch Y-stent: The Rusch Y-stent it is a Y-shaped stent made of silicone with a firm anterior wall that consists of horseshoe-shaped metal strut, which simulate the anterior trachea wall; the posterior wall is made of soft silicone, simulating the pars membranosa of the trachea. The stent can be difficult to insert. It is placed during rigid laryngoscopy by the means of a specially designed forceps, and the two distal limbs are inserted into the left and right main bronchi.[182] However, its length makes it difficult for patients to effectively clear airway secretions, and removal can be difficult if it becomes obstructed. It is used for strictures of the trachea, main carina and/or main bronchi; tracheobronchomalacia; tracheobronchomegaly and esophageal fistula.

Choice of Stent

The first issue to address is the proper selection of stent size. The length and diameter in relation to the dimensions of the trachea or bronchus are also important to avoid stent-related complications. Metal stents are more expensive than silicone. They are difficult, if not impossible, to remove. Silicone stents require specialized equipment, along with rigid bronchoscope, whereas metal stents can be inserted via flexible bronchoscopy. The ease of placement should not lead to the erroneous choice of the easiest stent over the best one to treat a given condition. The immediate and long-term complications should be thought of before a stent is placed. A check list suggested by Lee[183] is as follows:

1. Is a stent required?
2. Will the patient benefit from stent placement in terms of quality of life or prognosis?
3. Does the stent interfere or prohibit a curative surgical procedure later?
4. Do I have the expertise, equipment, and team to place the stent?
5. What is the underlying airway pathology and which stent is ideal?
6. Is it safe to place a stent in this anatomic site?
7. What are the required stent dimensions (length and diameter)?
8. Do I have the optimal stent or should I order a more appropriate one?”

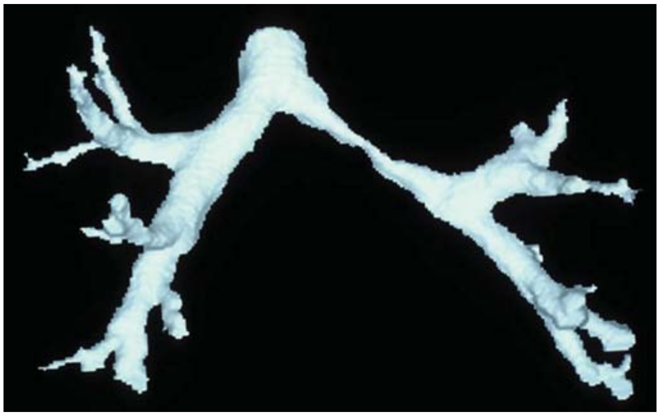


Fig. 32.9: Bronchial tree reconstruction shows an extrinsic compression of the left main stem bronchus

This check list will avoid errors and do less harm to the patient. In benign strictures, only silicone stent should be used as they are easy to remove and replace.

Technique

Bronchoscopy should be first performed in all patients with tracheobronchial stenosis. When a stenosis is evaluated, the distance from the vocal cords and the length and diameter of the lesion should be documented. A spiral CT scan with 3-D reconstruction is extremely helpful in the sizing of the stent that will be needed (Fig. 32.9). The largest possible prosthesis should be selected.

If a lesion is not amenable to endoscopic removal, bronchial dilatation should be done so that the stent of greatest diameter can be inserted.

The self-expanding stent that is mounted on an introduction catheter with crochet knots or is pushed out from the delivery system. The distal release model is easier to deploy than the proximal release design. The Polyflex stent with its pusher system is deployed with the help of a rigid bronchoscope. Insertion of the Dumon stent is facilitated by the use of the dedicated Dumon-Efer rigid bronchoscope and stent applicator set. Placement of dynamic and other bifurcated stents is facilitated with dedicated forceps.

In conclusion, airway stenting is a valuable adjunct to other therapeutic bronchoscopic techniques used for relieving central airway obstruction. Each stent has its unique features and complications. The technology is still in evolution, and design modifications strive to find the perfect stent.

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INTRODUCTION

Thoracoscopy or pleuroscopy is an invasive procedure to explore the pleural space through an incision in the chest wall. Thoracoscopy together with laparoscopy, was introduced in 1910 by Hans-Christian Jacobaeus, who at that time worked as an internist in Stockholm, Sweden. He published his first experiences in a paper entitled "On the possibility to use cystoscopy in the examination of serous cavities."[1] Jacobaeus himself initiated the therapeutic application of thoracoscopy for the lysis of pleural adhesions by means of thoracocautery to facilitate pneumothorax treatment of tuberculosis (Jacobaeus operation).[2] Between 1950 and 1960, a generation of chest physicians already familiar with the therapeutic application of thoracoscopy began to use the technique on a much broader basis for pleuropulmonary biopsy even for localized and diffuse pulmonary diseases. The excellent results of laparoscopic surgery and the tremendous advances in endoscopic technology stimulated many thoracic surgeons to develop minimally invasive techniques, which were termed therapeutic or surgical thoracoscopy, as well as Video-Assisted Thoracoscopic Surgery (VATS).[3-6]

Thoracoscopy is normally classified as:

- *Medical thoracoscopy:* This is a minimally invasive procedure, carried out mainly for diagnostic purposes by physicians, generally under local anesthesia and conscious sedation.
- *Surgical thoracoscopy:* Popularly known as VATS, is done by surgeons under general anesthesia for both diagnostic and therapeutic applications.[2]

MEDICAL THORACOSCOPY

Medical thoracoscopy is an invasive technique that should be used only when other, simpler procedures are not helpful. The technique is similar to chest-tube insertion by means of a trocar. In addition, the pleural cavity can be visualized and biopsy specimens can be taken from all the areas of the pleural cavity, including the chest wall, diaphragm, mediastinum and lung. An absolute prerequisite for thoracoscopy is the presence of an adequate pleural space, which should be at least 6–10 cm in width. If not present, a pneumothorax is induced under fluoroscopic or sonographic control, immediately or the day before thoracoscopy.

Medical thoracoscopic examination can be performed under local anesthesia or conscious sedation after premedication, without the support of an anesthesiologist. Furthermore, medical thoracoscopy is less expensive, can be safely performed with nondisposable instruments in an endoscopy suite.

Different techniques are used by the pulmonologists.[7,8] One of the methods consists of a single entry with a 9 mm thoracoscope with a working channel for accessory instruments, optical biopsy forceps and local anesthesia. The other method involves two entries, one with a 7 mm trocar for the examination telescope and the other with a 5 mm trocar for accessory instruments, including the biopsy forceps. Recently, minithoracoscopy was introduced mainly for the diagnostic purposes. The minithoracoscopy requires a rigid thoracoscope of 3 mm size, done under local anesthesia. For taking biopsy, a second port of entry is required unlike with the standard equipment.[9,10] Ultrasound can safely and reliably identify entry sites for the trocar placement during medical thoracoscopy, even in patients with pleural adhesions. The use of ultrasound may replace the practice of pneumothorax induction before medical thoracoscopy.[11]

Apart from the conventional white light, other imaging procedures that are said to yield more information especially for the presence of a pleural tumor, have been investigated, but the evidence has remained limited.[12-14] Narrow Band Imaging (NBI) is a new alternative light wavelength capture system that takes advantage of the altered blood vessel morphology. Wavelengths of light in the visible spectrum are filtered from the illumination source with the exemption of narrowbands in the blue and green spectrum centered at 415 nm and 540 nm, coinciding with the peak absorption spectrum of oxyhemoglobin making blood vessels more pronounced when viewed in NBI mode.[15] Imaging of vascular structures in deeper layers of thickened pleura can give some indication of where from the biopsy should best be taken. Moreover, NBI facilitates detection of any previously unobserved pleural dissemination.

Electrocoagulation is useful for the cauterization of adhesions and blebs or in the cases of bleeding after biopsy. For pleurodesis of effusions, 8 to 10 gm of sterile, dry, asbestos-free talc is insufflated through a rigid or flexible suction catheter with a pneumatic atomizer. Alternatively, 3 gm of talc may be used as slurry for nonmalignant effusion. Use of talc slurry is convenient and associated with excellent outcome and minimal complications.[16] For pneumothorax, 2 to 3 gm of talc is generally sufficient. Immediate suction through the chest tube is always applied following the procedure.

Equipment

Rigid instruments as they were from the beginning, are still in use (Fig. 33.1). They are preferred over the flexible instruments, which have several disadvantages compared to the rigid thoracoscope. The flexible instruments provide less adequate orientation within the pleural cavity, the biopsy specimens are small and frequently inadequate. A recently developed modification with a semiflexible tip can become an acceptable alternative.[17] Medical thoracoscopy can be performed either under direct vision through the endoscopic optics or indirectly by video transmission.[18] Single entry-site technique is usually done with a 9 mm diameter trocar and a cannula with a valve. Optical devices exist with various fields of view (0°, 30°, 90°). Trocars are also available with diameters of 5 and 3.75 mm for performing thoracoscopy in children. Biopsy forceps with straight optical devices, as well as accessory instruments, such as the puncture needle, cautery electrode, probe, combined suction and cautery cannula with valves and various biopsy forceps and scissors, are available. A talc atomizer (Fig. 33.2) is used for talc pleurodesis.[19,20]

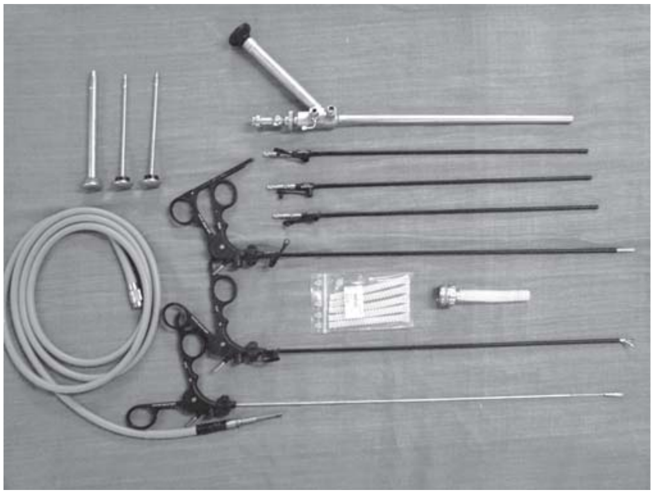

Fig. 33.1: Rigid thoracoscope and accessories

In the case of semirigid pleuroscope, the design including the handle is similar to a standard flexible bronchoscope, the proximal part being stiff (22 cm) with a bendable distal end (5 cm with angulation of 100 and 130 degrees). The outer diameter of the shaft is 7 mm. A working channel with a diameter of 2.8 mm allows the use of standard instruments that are available for flexible bronchoscope. The semirigid pleuroscope has the advantage that the skills involved in operating the instrument are generally familiar to the practicing bronchoscopist. Moreover, it is compatible with the existing video processors and light sources, so that little additional equipment is required to be added to the endoscopy suite. Its main disadvantage compared to the

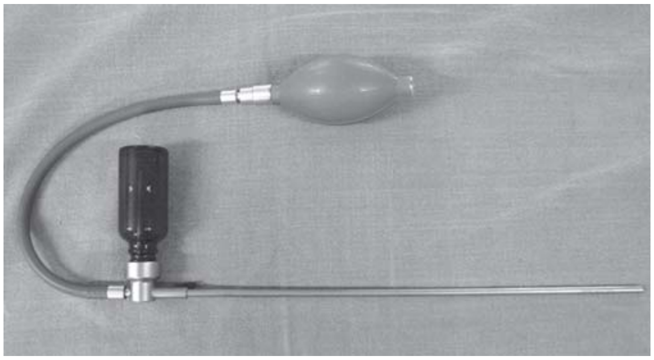

Fig. 33.2: Talc atomizer for pleurodesis

TABLE 33.1: Indications of medical thoracoscopy

Diagnostic	*Therapeutic*
Evaluation of undiagnosed exudative pleural effusion	Pleurodesis for malignant/recurrent pleural effusion/pneumothorax
Staging of malignant mesothelioma and lung cancer	Lysis of adhesion in pneumothorax/empyema
Biopsy from lung, diaphragm, mediastinum and pericardium	Sympathectomy

rigid thoracoscopic instruments is the smaller biopsy specimen. However, the flexible tip allows very homogeneous distribution of talc on all pleural surfaces where pleurodesis is required.

Procedure

Basic monitoring for medical thoracoscopy involves Electrocardiography (ECG) and pulse oximetry. Patient should lie in lateral decubitus position with the healthy lung on the dependent side. Ipsilateral arm should be placed above the head, so that the intercostal spaces become wider. Adequate local anesthesia should be given. The trocar is introduced with a rotating motion perpendicular to the chest wall. Once the trocar is introduced, suction is applied in the case of pleural effusion to remove the fluid. Adhesions can be lysed with a biopsy forceps or cautery. Exploration of the pleural space should be done by a slow circular motion of the scope. Biopsy can be taken from any abnormal lesion. At the end of the procedure, a chest drain is introduced in all patients.

Indications

Medical thoracoscopy unlike surgical thoracoscopy, is primarily used as a diagnostic procedure, but can be applied for certain therapeutic indications also (Table 33.1). The most common indications include the evaluation of the unknown exudative pleural effusion, staging of diffuse malignant mesothelioma or lung cancer, and treatment by talc pleurodesis of malignant or other recurrent effusions and empyema.[21] Medical thoracoscopy is also used for pleurodesis in recurrent pneumothorax. Other diagnostic indication is to obtain biopsies of the diaphragm, lung, mediastinum and pericardium. These procedures are safe in experienced hands, at the same time physicians should be aware of their limitations when indulging in procedures requiring more time and dissection.

Pleural Effusions

Even after extensive diagnostic evaluation of a patient with pleural effusion, the etiology often remains unclear.[22] Thoracoscopy is the standard diagnostic procedure for investigating exudative pleural effusion, it leads to a conclusive diagnosis for 95% of patients.[21] This should be performed in patients with undiagnosed effusions because of its high diagnostic sensitivity for malignant and tuberculous etiologies. The tissue obtained will usually provide a higher yield of the positive tubercular cultures, and greater histological proof of lung and pleural malignancies. The application of medical thoracoscopy allows the simultaneous insufflation of talc powder, which currently offers the best results in pleurodesis. Talc was used in 65% of 110 reported cases of nonmalignant pleural effusion that were treated with chemical pleurodesis, with a success rate of nearly 100%.[16] Further therapeutic advantages include complete fluid removal and adhesolysis in tuberculous effusion and empyema.

Malignant effusion: Malignant pleural effusion is the leading diagnostic and therapeutic indication for medical thoracoscopy.[23] In a prospective intrapatient comparison in 208 patients, the diagnostic yield of medical thoracoscopy was 95% versus 62% for pleural fluid cytology and 44% for percutaneous needle biopsy. Medical thoracoscopy showed a significantly higher sensitivity than needle biopsy plus cytology, which were positive in 74%. All methods taken together were diagnostic in 97% of cases of malignant pleural effusions. These results have been confirmed by others.[24,25]

In another series, no difference was noted in the yield for the different types of malignant pleural effusions: 96% in 67 cases of lung carcinoma, 96% in 154 cases with extrathoracic primary tumors, and 92% in 66 cases with diffuse malignant mesothelioma. The reasons for false-negative thoracoscopy results included insufficient and nonrepresentative biopsies, experience of the thoracoscopist, and the presence of adhesions (which denied access to neoplastic tissue).[23]

Medical thoracoscopy is helpful in the staging of lung cancer, diffuse malignant mesothelioma and metastatic cancer.[26] In the case of concomitant pleural effusion in lung cancer that otherwise appears resectable, medical thoracoscopy is indicated as a staging procedure to distinguish malignant from paramalignant effusion.[27] The latter condition would allow for the resection of the tumor; however, in 80 to 95% of the patients, the effusion is due to the tumor spread and surgical cure is not possible. Thus, medical thoracoscopy can help avoid unnecessary thoracotomy.

In diffuse malignant mesothelioma, medical thoracoscopy provides an earlier diagnosis, more precise histologic classification due to a larger, more representative biopsy, and more accurate staging.[26,27] This may have important therapeutic implications, as better responses to local immunotherapy or chemotherapy in stages I and II have been observed. Thoracoscopy is also helpful in the diagnosis of benign asbestos-related pleural effusion, which is a diagnosis of exclusion. Fibrohyaline or calcified, thick, pearly white pleural plaques indicate probable asbestos exposure. Thoracoscopic biopsies from lung and from certain lesions on the parietal pleura may demonstrate high concentrations of asbestos fibers, providing further support to the diagnosis of asbestos disease.[28]

In metastatic pleural effusions, biopsies of the visceral and diaphragmatic pleura are possible only under direct vision. Because the chest wall pleura is often not involved (in approximately 30% of cases) in early stages, it is not possible in these cases to provide a diagnosis by blind needle biopsy. With the large size of biopsy specimens obtained by thoracoscopy, it may be easier for the pathologist to suggest the origin of the tumor. In metastatic breast cancer, tissue can be obtained for the determination of hormone receptors. Even with lymphomas, the diagnostic yield, as well as the morphologic classification, are improved.[29]

Local treatment of pleural malignancies: The main therapeutic option offered by medical thoracoscopy is the prevention of recurrent effusion with pleurodesis. Under direct visual control, 8 to 10 gm of asbestos-free, sterilized talc (French talc) is insufflated into the pleural space so that the powder is equally distributed on the parietal and visceral pleura. Talc poudrage is probably the most effective, conservative option for pleurodesis.[19,20]

Tuberculous pleural effusion: Tuberculosis remains an important cause of pleuropulmonary involvement in developing countries. In extrapulmonary tuberculosis, pleural involvement is second only to lymph nodes. Although the yield of blind needle biopsy is higher than in pleural malignancies, the diagnostic accuracy of thoracoscopy is greater, because the pathologist is provided with multiple, selected biopsy specimens, and because the bacteriological culture proof of tubercle bacilli is more frequently positive. In a prospective intrapatient comparison, the histologic diagnosis of 100 patients with TB was established by thoracoscopy in 94%, compared with only 38% with needle biopsy, allowing an early start of antituberculous chemotherapy. The combined yield of pleural histology and mycobacterial culture was 99% for medical thoracoscopy, 51% for needle biopsy, and 61% when combined with fluid culture. The percentage of positive TB cultures was twice as high from thoracoscopic biopsy specimens, including cultures from fibrinous membranes (78%), compared with the percentage in pleural effusions and needle biopsy specimens, combined (39%). This had the advantages of an early bacteriologic confirmation and drug susceptibility testing. Resistance against one or multiple antituberculous drugs, which influenced therapy and prognosis, was found in 5 of the 78 positive cases (6.4%).[7]

In another prospective study of 40 patients from South Africa, thoracoscopy had a diagnostic yield of 98%, in comparison with an 80% diagnostic yield with Abrams' needle biopsies (three biopsy specimens were obtained, each examined histologically and microbiologically).[30] This led to the conclusion that in areas with a high prevalence of TB, Abrams' needle biopsy could contribute significantly to the diagnosis. In a further study on the effect of corticosteroids in the treatment of tuberculous pleurisy, the same authors found that the initial complete drainage of the effusion, performed during thoracoscopy, was associated with greater symptomatic improvement than with any subsequent therapy.[30]

Other pleural effusions: Thoracoscopy may provide clues to the etiology when effusions are neither malignant nor tuberculous as in the cases of rheumatoid arthritis, effusions following pancreatitis, hepatic hydrothorax, extension of disease from the abdominal cavity, or in effusion related to trauma. Although the history, pleural fluid analysis, physical and other examinations are usually diagnostic in these conditions, thoracoscopy is indicated in problematic cases. When pleural effusions are secondary to an underlying lung disease (such as pulmonary infarction or pneumonia), the diagnosis can frequently be made based on macroscopic examination, confirmed microscopically on lung biopsy. Thoracoscopy is also useful for the diagnosis of benign asbestos-related pleural effusions, which by definition present a diagnosis of exclusion.[31]

By the virtue of thoracoscopy, the proportion of so-called idiopathic pleural effusions usually decreases to less than 10%, whereas studies in which thoracoscopy was not applied, diagnosis is not established in more than 20% of cases. These figures will also depend on the

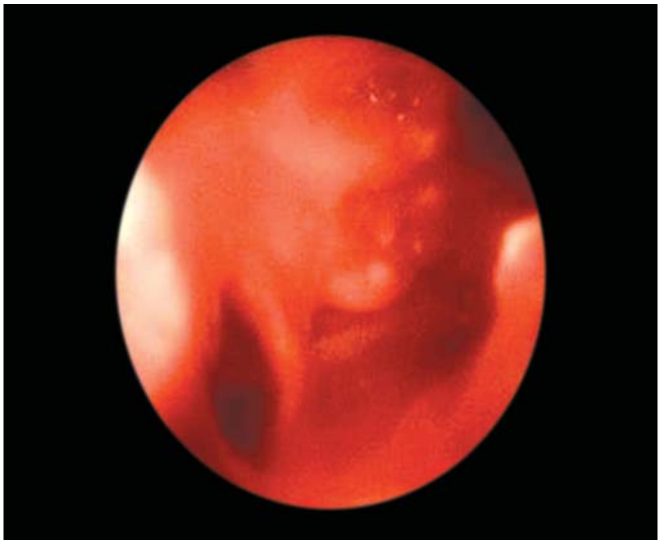

Fig. 33.3: Multiple nodules on visceral pleural surface in a case of hemorrhagic pleural effusion

selection of patients and the definition of an "idiopathic effusion".[32] In the selected cases of the recurrent pleural effusions of nonmalignant etiology, including chylothorax, pleurodesis may be induced by applying talc poudrage during medical thoracoscopy.[29]

The diagnostic accuracy of thoracoscopy in the setting of undiagnosed pleural effusions, varies widely with a range of about 60 to 90%.[28] Because of its high diagnostic accuracy, thoracoscopy is an excellent option in exudative effusion in which the etiology remains undetermined after pleural fluid analysis (Fig. 33.3). In a case series of 42 patients who underwent thoracoscopy at our center, 29 were done for diagnostic purposes, of whom 15 were diagnosed as malignant, 3 tuberculous and 10 of nonspecific inflammatory origin.[33]

Empyema

Medical thoracoscopy can be effectively used in the management of empyema.[24] This can help in breaking thin fibrinopurulent adhesions to remove multiple loculations and create a single cavity that can be drained and irrigated more successfully (Fig. 33.4).[34] This treatment should be instituted early in the course of empyema, before adhesions become too fibrous and adherent (Fig. 33.5). If a chest tube drainage is indicated and if the facilities are available, medical thoracoscopy should be performed at the time of chest-tube insertion itself. Medical thoracoscopy is a procedure similar to that of chest-tube insertion, at the same time it helps in visualizing the pleural cavity and allows better local treatment. In carefully selected cases, medical thoracoscopy can be useful, especially when performed early after the failure of chest tube drainage.[35] In more complex cases, VATS would be the preferred choice.[36,37]

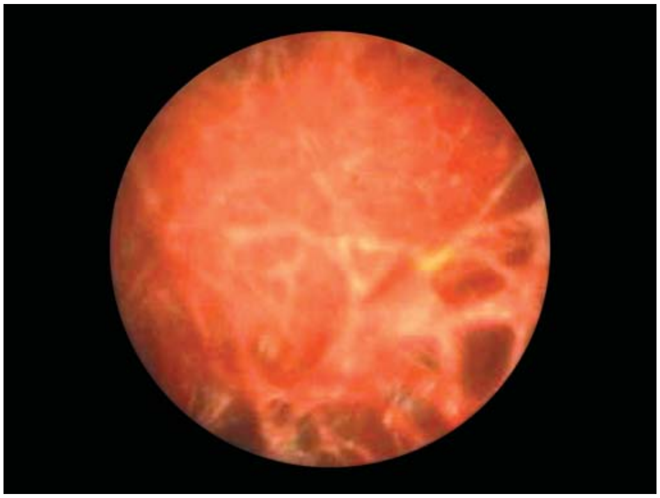

Fig. 33.4: Thoracoscopic view showing multiple thin adhesions

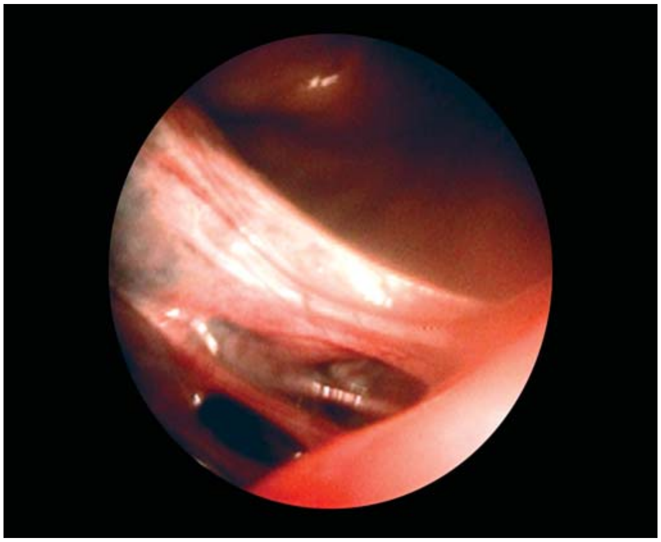

Fig. 33.5: Thick adhesion in tuberculous pleural effusion

Spontaneous Pneumothorax

In spontaneous pneumothorax, medical thoracoscopy can be used for both diagnostic and therapeutic purposes.[38] In particular, if a chest tube is introduced by a trocar technique, it is easy to visually inspect the lung and the pleural cavity before inserting the chest tube through the cannula. On inspection during medical thoracoscopy, the underlying lesions can be directly assessed according to the classification of Vanderschueren: Stage I with an endoscopically normal lung; Stage II with pleuropulmonary adhesions; Stage III with small bullae and blebs (< 2 cm in diameter); and Stage IV with numerous large bullae (> 2 cm in diameter).[39] Although the detection rates of blebs and bullae are higher in the series with VATS or thoracotomy, larger bullae, blebs or fistulae are likely to be detected during medical thoracoscopy.[38,39]

Medical thoracoscopy offers the possibility of combining pleural cavity drainage with the coagulation of blebs and bullae, as well as of pleurodesis by talc poudrage. Talc poudrage achieves the best conservative treatment results with the recurrence rates of less than 10%. In stage IV with numerous large bullae, VATS or thoracotomy should usually be performed. Talc poudrage and/or coagulation of bullae are performed only in patients in whom surgery is contraindicated because of the respiratory insufficiency secondary to advanced pulmonary disease.[16] Medical thoracoscopy is justified in all patients with spontaneous pneumothorax when tube drainage is indicated, as it provides a chance to assess the underlying lesions under direct vision; direct treatment by coagulation of blebs and bullae; severance of adhesions; administration of talc poudrage; and selection of the best location for chest-tube placement.

Advanced Indications

Lung biopsy: Forceps lung biopsy with or without electrocautery can be performed by pulmonologists using medical thoracoscopy (Fig. 33.6).[40] The results are comparable with surgical VATS biopsies in the diagnosis of diffuse lung diseases. Larger VATS biopsies are superior for conditions where lung vascular examination is necessary (e.g. vasculitis).

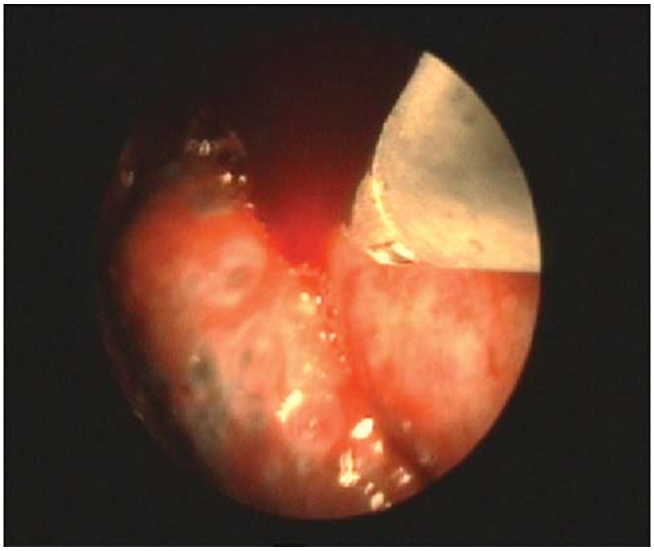

Fig. 33.6: Thoracoscopic pleural biopsy

Other thoracoscopic procedures, such as sympathectomy for the control of severe hyperhidrosis, can be easily performed by a well-trained thoracoscopist. Short- and long-term results are similar to those obtained by typical VATS interventions with a lesser degree of mortality.[4]

Contraindications

An obliterated pleural space is an absolute contraindication.[41] Relative contraindications include the presence of bleeding disorders, hypoxemia, unstable cardiovascular status, and persistent, uncontrolled cough.

Complications

During the procedure, cardiorespiratory function should be monitored by ECG, blood pressure measurement and continuous oximetry. Complications, such as benign cardiac arrhythmias, blood pressure instability, or hypoxemia can virtually be prevented by the administration of oxygen.

The reported mortality rates are very low (< 0.01%) (Table 33.2). Several liters of fluid can be removed during thoracoscopy with a little risk of pulmonary edema, since immediate equilibration of pressures is provided by the direct entrance of air through the cannula into the pleural space. If lung re-expansion appears to diminish, only low-pressure suction should be applied through the pleural drainage tube, which is always placed at the conclusion of the thoracoscopic procedure.

Following lung biopsy, a bronchopleural fistula may occur, requiring a longer period of suction than the usual three to five days, particularly in patients with poorly compliant lungs. After talc poudrage, fever may occur.

TABLE 33.2: Complications of thoracoscopy

1. During the procedure
    - Significant bleeding
    - Hypoxemia, cardiac arrhythmias, hypotension, occasionally death
    - Subcutaneous emphysema
2. Later complications
    - Local site infection
    - Empyema
    - Bronchopleural fistula
    - Respiratory failure
    - Neoplastic invasion of thoracoscopic tract

Local site infection is uncommon and empyema is rare. In the cases of mesothelioma, radiotherapy may be performed 10 to 12 days after thoracoscopy to prevent the late complications of tumor growth at the entry sites.

SURGICAL THORACOSCOPY

Video-assisted thoracoscopic surgery, often referred to as VATS, is done in a theater-suite under general anesthesia. Surgeons often use multiple ports to introduce the thoracoscope, biopsy forceps and suction cannulae. VATS is used to examine the chest cavity from within and to perform diagnostic procedures such as the lung, diaphragmatic and pleural biopsies.[42] Increasingly complex procedures are now being performed such as the lung resections, bullectomy, evacuation of pleural based problems, decortication, antireflux procedures, diaphragmatic plication and mediastinal node biopsy.[42,43] Thoracoscopic approach for the microsurgical removal of herniated thoracic disks is also described.[44] Compared to medical thoracoscopy, VATS is used for more complex, and time consuming procedures, replaces thoracotomy in many instances.

Post Thoracoscopic Management

Following thoracoscopy, a chest tube should be introduced into the pleural space. The tube is fixed in place by a skin suture. The tube is removed when there is no further air leakage or when the fluid production is less than 100 ml/day.[10] In uncomplicated cases, intercostal drain is removed after 48–72 hours.

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Section

6

RESPIRATORY DISEASE IN THE DEVELOPING WORLD

SK Jindal

34

The Burden and Clinical Spectrum of Respiratory Diseases

SK Jindal

INTRODUCTION

Infections, ever since they were first recognized, have dominated the scene of respiratory diseases all over the world for the past several centuries. It is only in the last fifty years or so that differences have cropped up in the spectrum of respiratory diseases between the developed and the developing countries. These are largely attributed to the differences in the economic, environmental, social and political standards, different health practices and the availability of health care infrastructure. It is apparent that the burden of infectious diseases in the developed countries has markedly diminished. On the other hand, the infections and the communicable diseases continue to pose a bigger challenge in the developing countries. What is most concerning is the observation that the burden of noninfectious or noncommunicable diseases in these countries is as enormous as that in the developed countries.[1,2] The future onslaught of respiratory diseases in countries, such as India, is expected to rise by manifolds. While infectious diseases will continue to persist, the noncommunicable, chronic diseases will increase at a rate even faster than that in the developed countries. This dual burden of both infectious and noninfectious diseases, which has already overstrained the health care infrastructure, will pose a major threat to its very existence.

RESPIRATORY DISEASE BURDEN

Respiratory diseases have a wide spectrum extending from acute conditions (such as pneumonias) at one end to the chronic conditions (such as the obstructive lung diseases) at the other end. The acute problems are often life-threatening, but the burden is difficult to assess. Community-acquired pneumonias may account for about 4–10 cases per thousand population per year.[3,4] Chronic respiratory symptoms together constitute the most frequent cause of outpatient clinic visits at primary levels of health care. In the community, there is about 12% prevalence of chronic chest symptoms such as cough and expectoration. Worldwide, in the Global Burden of Disease Study (GBDS), the Lower Respiratory Infection (LRI) was the first and tuberculosis, the seventh most common cause of disability assessed by using a standard unit, the Loss of Disability Adjusted Life Years (DALYs).[5] In the same study, Chronic Obstructive Pulmonary Disease (COPD) and tuberculosis were the sixth and seventh most common causes of mortality.[5] It has also been estimated that in the developing countries, by the year 2020, the diseases, such as COPD, LRI and TB, will continue to stay in the list of ten leading causes of loss of DALYs, with COPD being the fourth most common cause.

The total magnitude of the respiratory disease is expected to enormously expand in the next few decades. This is attributed to an increase in the total population, as well as to an increase in the exposure to the various risk factors, especially tobacco-smoking and the exposure to the environmental pollutants. The chronic respiratory disease is also a major cause of increased health care costs and economic burden in the community. The overall burden of several different chronic respiratory illnesses have now been recognized worldwide. This is also corroborated by the assessments of the Global Alliance against Chronic Respiratory Diseases (GARD), which aims at jointly fighting against this challenge and in improving the global respiratory health in accordance with the local needs.[6]

CLINICAL SPECTRUM OF RESPIRATORY DISEASES IN INDIA

There are four broad groups in which the respiratory problems can be broadly categorized: Acute diseases (both tubercular and nontubercular, bacterial, fungal and viral infections); airways and lung parenchymal diseases (e.g. asthma, COPD and interstitial diseases); neoplastic diseases (e.g. lung cancer and tumors of the mediastinum, pleura and chest wall); and respiratory critical illnesses (e.g. acute respiratory failure, severe pneumonia, sepsis, acute respiratory distress syndrome, pulmonary thromboembolism and others). Presently, the public burden of respiratory diseases in India is primarily constituted by tuberculosis, asthma and COPD (Table 34.1), but diseases, such as interstitial lung diseases, vasculitides, cardiopulmonary problems, lung neoplasms and sleep apnea syndromes are other major illnesses, which are being increasingly encountered in clinical practice.

TUBERCULOSIS

Tuberculosis, which continues to lead the list of major, but preventable health problems in India, accounts for nearly one-third of the total global burden. Nearly 40% of the Indian population is infected with the *Mycobacterium tuberculosis* and about 8.5 million individuals are estimated to suffer from "active" or "probably active" TB.[7,10] It also accounts for about 415 thousand deaths and for losses of more than 300 million in direct costs, each year.[7,10] The burden of TB is further aggravated because of the coexistence of problems of Multidrug Resistance (MDR), Human Immunodeficiency Virus (HIV) coinfection and other comorbidities. The rate of MDR-TB in new cases in India ranges from 0 to 3% at different sites, while it occurs in upto 13.0% of previously treated cases.[11] The problem of drug resistance is a major challenge, which is expected to rise in the immediate future. The recent recognition of Extreme Drug Resistant (XDR) TB in several different countries, including India, is an issue of grave concern.[11,12]

TABLE 34.1: Population prevalence rates (%) of major respiratory illnesses in general population in India

1.	Tuberculosis[7]	
	Infection	40.40%
	Prevalence: Sputum positive	0.23%
	Mortality	0.046%
	Overall prevalence	0.51%
2.	Bronchial asthma[8]	
	Children	2.3–12.5%
	Adults	2.4–3.5%
3.	Chronic Obstructive Pulmonary Disease (>35 years of age)[9]	
	M:	5.0%
	F:	3.2%

Fortunately, one can hope that the problem of TB will decline fast, once the results of successful implementation of the control programs are achieved. The Revised National TB Control Program (RNTCP), introduced in India since 1993, is now being implemented throughout the country.[10] The Program is aimed at the prevention and control of TB to achieve the Millennium Development Goals (MDGs) and related Stop TB Partnership of the World Health Organization. It adopts the strategy of Directly Observed Therapy (DOT) to prevent noncompliance and ensure the treatment of the diagnosed cases of TB. The evidence available till date shows a high success rate, promising a great degree of optimism.[13,14] The Program not only covers the governmental health-service institutions, but also the private sector, the medical colleges and other agencies engaged in providing health care. It also coordinates with the National AIDS Control Organization for patients with TB and HIV infection. It has already entered into the next phase of Stop TB Partnership with DOTS-Expansion to cover treatment for MDR-TB.

NON-TUBERCULOUS RESPIRATORY DISEASES

Bronchial Asthma

There is a lot of variability in the prevalence rates of asthma reported from different countries.[15,16] These variations can be attributed to the differences in the environmental and climatic risk factors, the genetic predisposition and the inheritance patterns.[15] Other important reasons, which can be counted for the difference include the differences in the definitions used for the diagnosis of asthma, the type of sample selection and the methodologies employed in different studies.[15-17] Frequently, the episodes of upper respiratory tract catarrh (especially when recurrent), chronic bronchitis, bronchiectasis and miscellaneous causes of cough, breathlessness and other respiratory symptoms are also inadvertently misdiagnosed as asthma. The prevalence rates and burden will also differ if one employs the definitions of "ever-asthma" or "current asthma," "symptomatic asthma" or "asthma, including bronchial hyperresponsiveness." Several of the global estimates of "current-asthma" point to variable rates from 1.2 and 3.7% in Belgium to as high as 25.5% in Australia.[15] The prevalence rates are also different if one uses the definition of "diagnosed asthma," "recent wheeze" or "Airway Hyperresponsiveness (AHR)".

The mean prevalence of clinical asthma for Southern Asia (Bangladesh, Bhutan, India, Nepal, Seychelles and Sri Lanka) was assessed to be 3.5% for a total population of 1.21 billions,[15,16] but several of these estimates, based on limited data from a particular region, do not truly represent the overall population prevalence. From India, the prevalence rates as high as over 10% among school children are reported in some studies. The field prevalence of diagnosed asthma is about 5% in children and about 3% in adults (Table 34.2).[8,18-30] The average population prevalence was 2.4% amongst 73,605 adults of over 15 years of age, studied at four different centers in Phase I of the Indian Multicentric Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARCH) when a validated questionnaire and a relatively stringent definition of "ever-asthma" were used.[21]

The most recent Phase II of the INSEARCH Study conducted in 12 different centers in a population sample of 1,69,575 individuals has reported a mean prevalence of 2.05% of current asthma[31] (Fig. 34.1). This reflects an enormous overall burden of asthma in India. For a total population of 1.028 billion (including children and adults) as per Census of India (2001), the minimum burden of asthma is about 21 millions for all age groups. The figure could actually be higher considering the higher prevalence rates in children. If one uses more sensitive criteria, such as the "wheeze alone" or the presence of bronchial hyperresponsiveness, the estimates are likely to be higher. These prevalence rates, although somewhat lower than those described from the West, are similar to those obtained from other Asian countries.[16,32] Some of the possible explanations, which have been advocated for a lower prevalence of asthma, may include the presumably protective influence of a higher incidence of childhood respiratory infections and ambient atmospheric pollution, which may partially suppress the allergic immune responses. A higher likelihood of breastfeeding in the Asian children may also be partially protective.

Asthma is more common in boys in childhood, but in women it is more commonly encountered among adults.[31] Residence in the urban areas and lower socio-economic status are other important factors likely to increase the occurrence of asthma. House-dust mites, contact with domestic-pets and exposure to a number of aeroallergens can precipitate and manifest asthma. Pollens of several plants, such as prosopis, ricinus, argemone, amaranthus, cannabis, parthenium, etc., have been implicated in the causation of asthma in India. Tobacco smoking of all types, including the cigarettes, "bidis" and "hukkah," as well as the passive exposure to Environmental Tobacco Smoke (ETS) form other important factors, which may provoke asthma.[33,34] Both "inutero" and childhood smoking exposure may also have an important role in the causation of asthma and

TABLE 34.2: Summary of the important population studies from India on prevalence of asthma

			Study population			
	Author	*Region*	*Group*	*No.*	*Age (years)*	*Prevalence (%)*
	Adults					
1.	Viswanathan (1966)[18]	North	Urban	15805	All ages	1.8
2.	Chowgule (1998)[19]	West	Field	2313	20-44	3.5
3.	Jindal (2000)[20]	North	Field	2016	18-70	2.8
4.	Aggarwal (2006)[21]	Multicentric	Field	73605	> 15	2.4
	Children					
5.	Chhabra (1998)[22]	North	Schools	2609	4–17	11.6
6.	Shah (2000)[23]	Multicentric	Schools	37171 31697	13–14 6–7	3.7–4.5
7.	Gupta (2001)[24]	North	Schools	9090	9–20	2.3
8.	Paramesh (2002)[25]	South	Schools	6550	6–15	16.6
9.	Chakravarthy (2002)[26]	South	Field	855	<12	5
10.	Mistry (2004)[27]	North	Schools	575	13–14	12.5
11.	Awasthi (2004)[28]	Lucknow	Schools	3000	13–14 6–7	3.3–2.3
12.	Pakhale (2008)[29]	West	Schools	3668	13–14	7.3
13.	Lai (2009)[30]	West	Schools	-	6–7	2.4

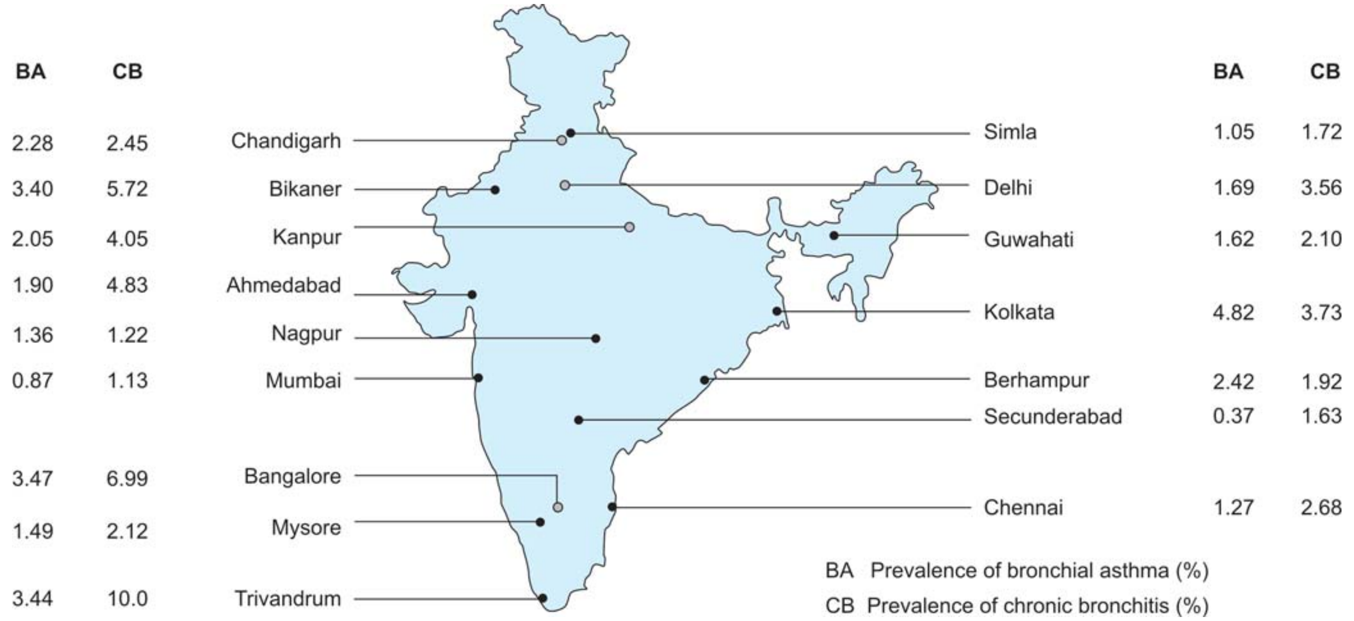

Fig. 34.1: Prevalence of asthma and chronic bronchitis in different parts of India

bronchial hyperresponsiveness in children, as well as in adults. Indoor exposure at home to pollutants from solid-fuel or fossil-fuel combustion may act in a similar fashion as the tobacco smoke. Their role in causing asthma, as well as in producing exacerbations has been described in the past, as well as in the INSEARCH Study.[31,35,36]

Food is commonly blamed for asthma in India, although only a few types of food can be definitely identified as triggers. The presence of Gastroesophageal Reflux (GER) is considered as an important trigger especially in patients with nocturnal asthma, though the relationship of GER with asthma has recently been disputed. It was shown in a large double-blind trial that silent GER was not a likely cause of poorly controlled asthma. Allergic Bronchopulmonary Aspergillosis (ABPA) is frequently recognized in about 10 to 15% of asthmatic individuals in India.[37] This is an important cause of difficult or poorly controlled asthma. At the primary health care levels, more than half of the ABPA patients are known to have received antitubercular treatment because of the similarities in the clinical and the radiological findings before the diagnosis is established.

Guidelines for the management of asthma formulated by the Global Initiative for Asthma (GINA) are now available for global use.[15] These guidelines are quite useful in the hands of physicians and the pulmonologists, especially those who practice at referral hospitals. A symptom-based, Practical Approach to Lung Health (PAL) is advocated for use at the primary health care.[38] Similarly, in India, a simple consensus-approach based on the global guidelines was developed under the initiative of WHO-Government of India Biennium program for use by the general practitioners and physicians, at the primary levels of health care.[39] The Indian guidelines for the primary levels of care follow a common and feasible algorithm to the management of asthma, in accordance with PAL plan.[39]

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease poses a huge burden from its disabling morbidity and mortality. Globally, it is perhaps the only leading cause of death that is increasing in prevalence.[40] The term COPD, which includes chronic obstructive bronchitis and emphysema in its ambit, has remained a source of confusion and controversy in the past. It was because of the lack of precise definitions and overlapping criteria for the diagnosis of chronic bronchitis and emphysema that the term was coined.[41] It is now globally accepted that COPD may be defined as a disease state characterized by airflow limitation that is not fully reversible and is associated with some systemic manifestations; the airflow limitation is usually progressive, but may show some degree of reversibility.[42] It is associated with an abnormal inflammatory response of the lungs to the noxious smoke and dusts.

Chronic obstructive pulmonary disease is distinct from asthma as it occurs in adults, generally over 40 years of age. Prevalence is high all over the world.[42,43] The burden of COPD is high in most of the Asian and the other developing countries, including India.[43-47] A prevalence of about 2 to 10% has been reported over the past 50 years in the form of several small reports (Table 34.3).[48-61] In the earlier multicenter Indian study on its epidemiology, the prevalence of 5% in men and 3.2% in women was reported amongst approximately 3,52,950 adult individuals who were over 35 years of age.[9,62] The INSEARCH (Phase II) Study at 12 centers, similarly reports the prevalence of 4.3% amongst men and of 2.7% amongst women.[31] The INSEARCH study had used only the standardized and validated bronchial-symptom questionnaire for the diagnosis of chronic bronchitis, as a prototype of COPD. On the other hand, the Burden of Obstructive Lung Disease (BOLD) initiative had used the questionnaire, as well as the spirometric parameters before and after bronchodilator administration.[44] The estimated population prevalence of COPD of Gold II stage from 12 sites amongst 8,775 adults was 10.1 ± SE = 4.8% overall.[44] Similarly, the PLATINO Study from Latin America, which employed spirometry, reported a prevalence estimate of 14.3%, the proportion of subject in Stages II-IV of the Gold classification was 8.6%.[45]

The disease is distinctly more common in smokers, with the smoker: nonsmoker ratio varying from over 2.65 to 1.[9] There is also a strong dose relationship, i.e. an increased risk of COPD with an increase in the amount and duration of smoking. All different forms of smoking prevalent in India, i.e. cigarettes, bidis, hookah, chilum and chutta are almost equally responsible for the causation of COPD. About 25 to 45% of patients of COPD have never smoked. A substantial incidence of COPD of 2.8 cases/ 1000/year in young adults was reported in an international cohort, comprising of 5,002 subjects without asthma from 12 countries in the year 1991-2002, for the framework of the European Community Respiratory Health Survey II.[63] Importantly, the presence of chronic cough and phlegm was helpful to identify a subgroup of subjects with a high risk of developing COPD, independent of their smoking habits.[63] Several different risk factors are important in such patients. Amongst nonsmoker individuals, especially the women, the indoor air pollution from passive exposure to tobacco smoke from others (e.g. husbands) and combustion of solid fuels are important risk factors.[9,31,63,64] Ambient air pollution from the dust, smoke and exhausts of vehicles and industrial units are significant contributory factors for the presence of chronic respiratory symptoms, as well as of COPD.[64,65]

The natural history of COPD is characterized by the progressive deterioration of lung functions, clinical symptomatology and frequent acute exacerbations usually due to recurrent respiratory infections. It is the most important and common cause of pulmonary hypertension, chronic cor pulmonale and chronic respiratory failure. The progression of COPD can be slowed and complications prevented with an appropriately devised treatment strategy. Smoking cessation is the most essential component of any treatment and rehabilitation plan for COPD. Long-term domiciliary oxygen therapy is the only other treatment option, which has shown to prolong survival and improve quality of life.

TABLE 34.3: Summary of important population studies from India on the prevalence of chronic bronchitis/COPD

	Authors	*Population*		*COPD prevalence (%)*			
		Place	*No.*	*M*	*F*	*M:F Ratio*	*S:NS ratio (Males)*
1.	Wig et al (1964)[58]	Rural, Delhi	3767	3.36	2.54	1.32	1.98
2.	Viswanathan (1966)[18]	Patna	15805	2.12	1.33	1.59	-
3.	Sikand et al (1966)[59]	Delhi	14460	7.0	4.3	1.63	25
4.	Bhattacharya et al (1975)[55]	Rural, U.P.	1140	6.67	4.48	1.49	-
5.	Viswanathan and Singh (1977)[53]	Delhi—Rural	993	4.7	3.5	1.34	9.57
		—Urban		8.0	4.3	1.86	4
6.	Thiruvengadam et al (1977)[50]	Madras	817	1.9	1.2	1.58	10.2
7.	Charan (1977)[60]	Rural, Punjab	7132	2.28	1.63	1.4	-
8.	Radha et al (1977)[54]	New Delhi	2098	8.1	4.6	1.76	1.8
9.	Malik (1986)[52]	N.India—Rural	4372	9.4	4.9	1.92	5.5
		—Urban		3.7	1.6	2.31	7
10.	Jindal (1993)[57]	N.India—Rural	2804	6.2	3.9	1.59	9.6—
		—Urban		4.2	1.6	2.6	
11.	Ray et al (1995)[61]	South India	9946	4.08	2.55	1.6	1.6
12.	Jindal et al (2006)[62]	Multicentric	35295	5.0	3.2	1.56	2.65

M: Male; F: Female; S: Smoker; NS: Nonsmoker; COPD: Chronic Obstructive Pulmonary (Lung, Airway) Disease

The importance of diagnosis, management and prevention of COPD is one essential step in the preservation of lung health. Based on the global Guidelines for Obstructive Lung Disease (GOLD), the Indian guidelines for its management, developed similarly as for asthma, are also available for use at the primary levels of health care.[42,66] One essential component in the comprehensive management of COPD is the need to recognize COPD as a distinct disease apart from asthma. The PAL strategy covers both asthma and COPD in the overall management and prevention plan.[38]

Environmental and Occupational Lung Diseases

There is an enormous increase in the incidence of general health problems and respiratory illnesses from exposure to different environmental pollutants. Outdoor atmospheric ambient-air pollution resulting from vehicular and industrial exhausts mostly in the urban areas is responsible for the increased presence of nonspecific respiratory symptoms and occurrence of pneumonias in children. Besides being responsible for causing and precipitating acute exacerbations of asthma and COPD, the continued exposure may also cause gradual and progressive decline in lung function. The limited number of studies, which are available on the subject from India, clearly point to a significant morbidity and mortality due to the problem.[67-70] In Delhi, a single-pollutant model based on air pollution levels and daily variations in respiratory morbidity during 2004-2005 showed that a 10 $\mu g/m^3$ rise in pollutant levels caused a statistically significant relative risk of respiratory morbidity.[67] In another study from Delhi, the chronic respiratory symptoms, as well as the prevalence of asthma and COPD were consistently and significantly more in the residents of higher-pollution areas.[69] Similarly, the residence in an industrial town in Punjab was associated with chronic respiratory symptoms and spirometric ventilatory defects, independently of other demographic variables.[68] Emergency hospital-visits and mortality were higher in the Delhi hospitals amongst patients from higher pollution areas.[70]

Indoor air pollution is similarly responsible for chronic nonspecific respiratory symptoms, respiratory infections and acute exacerbations of chronic respiratory and cardiovascular disease in India.[71-74] Indoor air pollution is an important issue of concern in both the urban and the rural areas. Indoor pollution in the ill-ventilated urban dwellings of multistorey buildings is attributable to large concentration of volatile organic hydrocarbons from the construction and building materials, paints, resins, cosmetics and toiletries, in addition to the presence of indoor allergens and microorganisms. The resultant "sick-building syndrome" characterized by mucosal irritation, respiratory symptoms and neurobehavioral impairments is now commonly reported amongst the inhabitants of all large towns and cities in India. Indoor radon-exposure is now listed as the second most common cause of lung cancer. On the other hand, indoor combustion of solid fuels for domestic cooking and heating is the most important source of indoor pollution in the rural and semi-urban areas, as well as the urban slums. In India, about 3.5% of the national burden of disease and over 0.4 million deaths are attributable to solid-fuel use.[72] Respiratory symptoms were observed in 13% of 3,608 nonsmoking women using domestic cooking fuels.[73] Use of Biomass-fuels was reported as an important factor for deterioration of lung function in both female and male subjects.[74]

Occupational exposure to inorganic dusts, chemicals, gases and fumes is rather rampant and largely unregulated in the developing world. This is especially so at the vast number of unorganized industrial and mining sites.[75,76] Unfortunately, we do not have systemically collected information on most of these problems. It is apparent from the reports appearing from time to time that pneumoconioses (such as silicosis, asbestosis and anthracosis) have a huge prevalence in India.[76-79] Silica is widely reported in upto 50% or more of miners and in workers engaged in iron and steel foundries; manufacturing of pottery, ceramic, glass, paints and rubber; slate-pencil and stone cutting units; and quartz-grinding, metal casting, scaling, polishing and other manufacturing processes.[76]

India imports about 1,00,000 metric tons of asbestos per year for mining and milling of small-scale asbestos.[79] Surveys showed a significant degree of occupational exposures, early radiological and lung function changes amongst asbestos-exposed workers.[79] It is anticipated that asbestos-related disease will account for more than a million deaths in the developing countries.[78] By the year 2020, the number of deaths is likely to begin to rise in the developing countries when it is likely to start declining in the developed countries.[78] Toxic-gas exposure due to industrial leaks or exhausts is another common problem of which the Union-Carbide disaster in Bhopal is an important reminder.[80] Reports on organic dusts exposure especially at work-places, which are responsible for hypersensitivity pneumonias are there, albeit anecdotal and small. Incidences of farmer's lung disease, byssinosis, bagassosis and aspergillosis have been reported from different places.[81-83]

Interstitial Lung Diseases

Interstitial Lung Disease (ILD) is a broad term, which encompasses over 150 different conditions and diffusely involves the lung parenchyma. ILDs in the past were either misdiagnosed or only those which occurred in association with systemic diseases especially the Connective Tissue Disorders (CTD), were recognized. "Lone" Interstitial Pulmonary Fibrosis (IPF), sarcoidosis, pulmonary vasculitides and even hypersensitivity pneumonias were generally considered rare. However now, both general and pulmonary physicians confront and diagnose these problems more frequently in their day-to-day practice. Several reports on these diseases have appeared in the Indian literature in the last two decades.[84,85] This trend is partly attributed to an increased awareness and a wider availability of better diagnostic techniques, but a genuine increase in the occurrence and incidence of these diseases is also understandable.

The two important ILDs, which have made a significant impact on the clinical practice, are sarcoidosis and the Idiopathic Interstitial Pneumonias (IIP).[86] The recent surge in the number of patients with these disorders, diagnosed in the medical and chest departments of mostly the large hospitals bears testimony to their increased occurrence. Sarcoidosis known in India since past four decades, has always posed a challenge in the differential diagnosis particularly from tuberculosis. The distinction between the two diseases is of great relevance especially because of the need of anti-inflammatory corticosteroid treatment for sarcoidosis, which in the case of tuberculosis is avoided for its harmful effects.[87] The characteristic clinical and radiological picture, supported by a negative Mantoux test and demonstration of noncaseating granulomas in transbronchial lung biopsy specimens, is fairly diagnostic of sarcoidosis.

The high-resolution Computed Tomographic (CT) scan has made it possible to diagnose and classify the idiopathic interstitial pneumonias. However, the recognition of several of the ILDs especially those of infectious origin, some of the IIPs, such as the organizing pneumonias and vasculitides, which require additional immunological tests and/or histological evidence for confirmation and, staging as well as for exclusion of alternate diagnoses remains somewhat unsatisfactory.[88,89] Transbronchial lung biopsy is fairly diagnostic in diseases such as sarcoidosis. One requires a transthoracic (thoracoscopic) or open-lung biopsy to reach a conclusive diagnosis for other conditions. It is quite likely that a large number of these patients are missed in India in the absence of a wider availability of some of the high-end diagnostic facilities.

Neoplastic Disorders

Respiratory malignancies, especially the lung cancer, have definitely increased in prevalence largely due to the widespread habit of tobacco smoking and exposure to environmental carcinogens.[90-93] Lung cancer occurrence in India has now overtaken the incidence of oropharyngeal cancer, which was earlier the most common form.[92] Lung cancer in India is shown to affect people of a relatively lower median age than that in the West. A significantly higher number of nonsmoker individuals are also affected. Passive exposure to environmental tobacco smoke is an important identifiable cause of lung cancer amongst nonsmoking spouses.[94] Atmospheric, environmental and occupational exposures are the other likely causes.[95] The grave threat from occupational asbestos has been listed earlier in this chapter.[78,79] Indoor radon exposure is another important cause. Unfortunately, the exposure information in India on most of these carcinogens amongst the general public, as well as the specific populations is highly unsatisfactory.

The epidemiology of lung cancer in India has not really changed over the past three decades. Perhaps, there has been no change in the smoking pattern of the population.[96] One can hope that recent implementation of tobacco-control policy by the Government of India may change the scene in the future. The epidemiology of lung cancer in India has not really changed over the past three years. Perhaps, there had been no change in the smoking pattern of the population.[96] One can hope that the recent implementation of tobacco-control policy by the Government of India may change the scene in the future. The management modalities, however remain limited partly because of the overall inadequacy of treatment of lung cancer and partly because of the scarcity of dedicated thoracic surgical and radiotherapy centers.[97] Most of the patients have advanced and nonoperable disease when first diagnosed. Surgical options for treatment at present are not very optimistic. Chemotherapy, widely employed for treatment is costly and unaffordable by most patients. The cost benefit ratio for most patients is not encouraging. Presently, primary prevention by tobacco cessation and control remains the most useful strategy to reduce the disease burden.

FUTURE SCENE OF PULMONARY MEDICINE IN INDIA

Pulmonary medicine, which developed as a superspeciality of medicine has now diversified to include several other subspecialities. Consequently, the spectrum and the scope have enormously expanded. As earlier discussed, the problems of tuberculosis, pneumonias and other respiratory infections will continue to constitute the major acute burden. On the other hand, respiratory allergies, such as asthma, COPD, environmental and occupational disorders, ILDs and lung cancer are likely to significantly increase over the next few decades. The introduction of endoscopic and image-guided procedures and interventions through bronchoendoscopy, thoracoscopy and mediastinoscopy, which have already improved our diagnostic and therapeutic skills, is bound to enlarge the boundaries of the speciality.

Pediatric and neonatal pulmonology are the other major pulmonary subspecialities in a rapid phase of development. Similarly, the increase in lifespan over the past few decades has widened the scope of geriatric-pulmonology. Pulmonary rehabilitation, palliative and end-of-life care are some of the resultant issues, which are rapidly emerging. There are several other groups of diseases and problems with the overlapping areas of interest with general medicine and other super or subspecialities. Some of these areas are still evolving in the developing countries. Occupational, industrial and rehabilitation medicine, sleep medicine, cardiopulmonary-medicine, diving, aviation, space and high altitude, trauma and disaster medicine are other important fields of health care, where pulmonary clinicians and scientists have a major share to contribute.

The most significant change in the scene has occurred with the introduction of respiratory critical care in the overall ambit of pulmonary practice. Critical care is a multispeciality discipline, but the respiratory physician plays the key role. Acute respiratory illnesses, severe pneumonias, sepsis, acute respiratory distress syndrome and pulmonary thromboembolism are some of the important problems encountered in all kinds of acute and chronic medicosurgical disorders, which require respiratory critical care. Malaria, tuberculosis, leptospirosis and acute viral syndromes, which may also present with acute respiratory distress syndrome are not uncommonly encountered in clinical practice.[98-100] Endotracheal intubation, bronchial hygiene, oxygen therapy and assisted respiratory support are some of the essential components of critical care for which the pulmonary intensivists are more actively required. Respiratory therapists and nurses now play a greater role in the disease management program.

Critical care has introduced a significant degree of skepticism and dilemma in the minds of health administrators and policy makers in India. Enormous inputs are required to provide costly care to a limited number of patients. The outcomes of critical care, especially in the presence of chronic diseases are also debatable. The ethical, moral, legal and social perspectives of critical care for the few, at the cost of a minimal level of care for all, have been debated and criticized.[101] This is especially so in the public health sector when the costs are borne by the governments. On the other hand, there is no denying the fact that the provision of the critical care makes all the difference between life and death for innumerable number of patients with catastrophic illnesses as well as for the victims of trauma and disasters. There is an enormous need and scope for the expansion of critical care services in India. The country has to evolve its own strategies and approaches to resolve the conflicting issues.

Lastly, there is a greater need for the development of both the clinical and the basic pulmonary sciences. Thoracic surgery in particular, is required to expand to cope up with the ever increasing list of indications. There is a wide gap in our knowledge and infrastructure to cope with the tremendous disease-magnitude. Although the scientific facts related to disease and management, are universal and globally applicable, the local problems are required to be handled with local perspectives. It is crucial to define the issues and find out their solutions through augmented efforts and inputs in research and development.

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35

Practical Approach to Lung Health

Salah-Eddine Ottmani

INTRODUCTION

The Practical Approach to Lung Health (PAL) was initiated by the World Health Organization (WHO) in 1998.[1] It is a patient-centered approach to improve the quality of diagnosis and treatment of common respiratory illnesses in Primary Health Care (PHC) settings. It seeks to standardize service delivery through the development and implementation of clinical guidelines and managerial support within the district health system. It is intended to coordinate among different levels of health care and between Tuberculosis (TB) control and general health services.

The Practical Approach to Lung Health is included in the Stop TB Strategy developed by WHO and the Global Stop TB Partnership to control TB.[2] In this framework, PAL is assumed to contribute to strengthening health systems while addressing the quality of the management of patients with respiratory conditions, among whom TB cases should be identified. It also defines how the process of this management should be adapted to the health resources and infrastructure.[3,4] This is why PAL aims at improving the following:

- The quality of care in patients who seek attention for respiratory symptoms in PHC settings
- The efficiency of respiratory service delivery within health systems with a focus on the district health system.

This chapter describes the rationale behind the development of the PAL strategy, highlights its objectives, explains its components and why it should be adapted to the specific country health environment, specifies the successive steps needed to develop and implement PAL, reports the first country experiences in PAL development, and implementation and outlines its potential impacts.

DEMAND OF CARE FOR AND MANAGEMENT OF RESPIRATORY PATIENTS

The demand for respiratory care is common in PHC settings. Patients who seek care for respiratory symptoms account for up to one third among patients aged 5 years and more who attend PHC facilities for any reason.[5-8] Most of the surveys have reported that among respiratory conditions encountered in PHC, 60 to 90% are associated with Acute Respiratory Infections (ARI) while TB accounts for a very small proportion, most often less than 2%.[5-11]

In most developing countries, there are often clear guidelines on how to manage, in PHC, a TB patient irrespective of her/his age and children below five years of age with ARIs. However, for non-TB patients who account for more than 98% of respiratory patients aged 5 years and over, there are no clear indications on how to manage. Respiratory patients are usually managed on the basis of symptoms, in non-systematic and non-standardized manner, by PHC workers. As a result, the quality of diagnosis of respiratory diseases is often poor, the treatment prescriptions are often inappropriate and unnecessarily costly and there are no clearly defined criteria for referral. For instance, two studies carried out in PHC facilities in Jordan and Syria have shown that more than 85% of respiratory patients were prescribed antibiotics;[8,11] another study undertaken in Kyrgyzstan, reports that 40% of respiratory patients are referred from first level health facility to an upper health level.[7] It is clear that this contributes to wasting resources for the patients as well as for the health system.

The development and implementation of a comprehensive, standardized and integrated symptom-based strategy to manage respiratory patients in PHC is likely to improve the quality of care and, subsequently, create conditions resulting in improving the identification of TB cases. These principles are the key elements in the development of PAL.

OBJECTIVES OF THE PAL STRATEGY

The Practical Approach to Lung Health is an integrated and syndromic approach to manage respiratory patients aged 5 years and over. It focuses on priority respiratory illnesses encountered in PHC.

Clinical Objectives

The Practical Approach to Lung Health targets in priority to improve the quality of respiratory care services. Indeed, it aims at the following:

- Improving the quality of TB diagnosis in patients with sputum smear-negative microscopy, particularly in People Living With Human Immunodeficiency Virus (PLHIV)
- Enhancing TB screening in patients with a chronic respiratory condition
- Strengthening the quality of care for TB patients
- Ensuring TB treatment success
- Standardizing an appropriate management of ARIs
- Improving the management of respiratory infections in PLHIV
- Upgrading the quality of treatment of asthma attacks and Chronic Obstructive Pulmonary Disease (COPD) exacerbations
- Organizing and monitoring the long-term management of patients with Chronic Respiratory Diseases (CRD).

Managerial Objectives

These objectives focus on increasing the efficiency of the operations to implement PAL activities through

- Setting criteria for the request of laboratory tests, thorax radiography and other complementary tests
- Standardizing the drug treatment of respiratory diseases
- Promoting the essential drug lists of countries
- Establishing clear criteria for referral and counter-referral for respiratory patients within district health systems
- Defining the role of each health worker category in respiratory care management according to the health care level
- Defining planning parameters and contributing to rationalizing the management of health resources
- Monitoring and evaluating the performance of the health service delivery for respiratory conditions through the utilization of the existing Health Management Information System (HMIS) and TB control information system.

Economic Objectives

These are intended to decrease the cost of management procedures and to promote cost-effective health care interventions for respiratory illnesses by

- Reducing the managerial cost per respiratory patient while improving her/his quality of life
- Reducing the absenteeism associated with asthma and COPD
- Reducing the attendance at emergency room and intensive care unit by patients with CRD
- Increasing the number of respiratory patients managed in PHC settings while reducing hospital morbidity associated with respiratory diseases.

COMPONENTS OF THE PAL STRATEGY

In order to improve the quality of respiratory case management and the efficiency of health care services for respiratory illnesses, PAL includes two important components:

- Standardization of clinical care
- Coordination.

Standardization of Clinical Care

The standardization of respiratory care needs the elaboration of clinical guidelines. The process of PAL guidelines preparation needs to follow the national procedures to develop guidelines. The guidelines should be in line with the following:

- The international recommendations on the management of lower ARIs and pneumonia[12-16]
- TB management as specified by WHO[17]
- The management of asthma and COPD as recommended by international initiatives[18-20]
- The rules on drug prescription.[21]

The development of PAL guidelines should take into account the existing national guidelines, such as the National TB Program (NTP) guidelines, HIV/ Acquired Immuno Deficiency Syndrome (AIDS) guidelines, the Integrated Management of Adolescent and Adult Illness (IMAI) guidelines or other clinical guidelines. The PAL guidelines should clearly specify the categories of health workers who will use these guidelines and at which health care level and define the tasks that the latter will carry out. The main component of the PAL guideline is a section, which includes a clear description of the standardized clinical management of respiratory illnesses; this section specifies the clinical criteria for which respiratory patients should be referred or counter-referred. The drugs specified in the guideline should be as much as possible in line with the national essential drug list or with the national essential drug program.

The drugs and the equipment needed to carry out the tasks described in the PAL guidelines should be clearly identified in individualized sections. The process to monitor and evaluate PAL activities should be described; this process should use as much as possible the existing information systems such as the Health Management Information System (HMIS) and the NTP information system.

The PAL guidelines also include a component dealing with health education for patients. This should focus on these objectives:

- Ensuring that TB patients cooperate with directly supervised treatment and contacts are screened for TB
- Ensuring that asthma and COPD patients adhere well to self-medication
- Helping asthma patients to avoid asthma attack-triggering factors
- Advising all respiratory patients who smoke, to stop smoking
- Promoting prevention against tobacco use among respiratory patients.

The PAL guidelines should be developed in priority for health workers practicing in first level health facilities. The clinical approach described in this guideline should be patient-centered, symptom-based, integrated and standardized. The management should use a minimum number of signs and symptoms that are effective to determine the degree of severity, classify the disease and make the appropriate decision, namely:

- Urgent referral to the hospital for urgent management
- Referral for complementary investigations
- Investigation for TB diagnosis
- Treatment and observation at the health unit
- Specific home treatment
- Symptomatic home treatment.

A specific PAL guideline can be developed for the first referral level health facilities. This guideline is usually more disease-based with details on differential diagnosis. It includes three sections in function of the respiratory conditions usually encountered in:

- Emergency room
- Outpatients department of clinical medicine or TB and chest clinic
- Hospital ward

This guideline needs to clearly define the role of the first referral health level and standardize complementary investigation, including pulmonary function tests.

Furthermore, it should help health workers practicing at this level identify respiratory patients who need to be referred to the second referral health level for more specialized investigations or care; it also provides indications on when to counter-refer patients to first level health care network.

When these two guidelines are, both, adopted and developed in the same country, they should have well established connections.[21]

Coordination

Coordination in the PAL strategy refers to the identification and involvement of the key components of the health system in the organization and the efficiency of health care service delivery for respiratory illnesses. Country experience showed that these components are many and may vary among countries.

To be successful, coordination also needs to clearly define the involvement, in respiratory case management, of each health care provider category and of each health care level. This results in coordination between first level health facilities and referral facilities, contributing subsequently, to full integration of respiratory case management within the health system, particularly at district level.

The development and implementation of the PAL strategy also requires coordination with the following:

- National health resource planning
- NTP, HIV/AIDS program, IMAI initiatives, PHC services and the management of general health services for training, supervision, logistics and communication
- HMIS to monitor PAL activities
- The essential drugs program in order to make drugs available and affordable for respiratory patients.

ADAPTATION OF THE PAL STRATEGY

The Practical Approach to Lung Health must be adapted to the national health policies and resources. National health policies vary among countries in function of the health priorities, which depend on the national epidemiological challenges. For instance, in low income countries and in high HIV prevalence settings, infectious respiratory illnesses account for a higher proportion of the respiratory diseases burden than CRDs; this distribution tends to reverse with country income; in high income countries, CRDs represent the highest proportion of respiratory diseases' burden (Table 35.1). Therefore, in countries with epidemiological pre-transition, the control of tuberculosis and ARIs are likely to have preference over the need to improve case management for CRDs, while in settings with epidemiological transitional or post-transition, CRDs are likely to be considered as important health priorities.

The resources available within the health system widely differ among countries. These differences are related to various factors, such as:

- The number of health care levels
- The educational and training level of health staff
- The accessibility to laboratory facilities
- The availability of equipment, whether basic (e.g. functioning weighing scales, thermometers) or diagnostic (e.g. stethoscope, sphygmomanometer, peak flow meter, spirometer, X-ray) or therapeutic (nebulizers, sources of oxygen)
- The availability of a national essential drug program
- The existence of a scheme of health care cost coverage
- The accessibility to and affordability of certain drugs such as medications for inhalation use
- The accessibility to hospitalization
- The coverage of the health system by HMIS and NTP information system. For instance, comparison of Tables 35.2A and B highlights the similarities and differences between Peru and Syria with regard to the health resources available in their health care facility categories.

TABLE 35.1: Distribution, in percentage of DALYs, of respiratory diseases' burden in the population over 15 years of age by epidemiological profile and socioeconomic status of countries in 2000

Respiratory Conditions	*High HIV Prevalence Countries*	*Low Income Countries*	*Middle Income Countries*	*High Income Countries*
Acute respiratory diseases	70.8%	59.4%	32.4%	12.8%
Chronic respiratory diseases	16.0%	30.6%	58.0%	73.5%
Other respiratory diseases	13.2%	10.0%	9.6%	13.7%
Overall	100.0%	100.0%	100.0%	100.0%

Arranged from:
http://www3.who.int/whosis/menu.cfm?path=evidence,burden,burden_estimates,burden_estimates_2000,burden_estimates_2000_V3, burden_estimates_2000_V3_Subregion&language=english

TABLE 35.2A: Health resources in health care facilities in Peru, 2002

Health Facilities	*Health Worker*			*Equipment*						*Access to Inhaled Medications*			*Hospital Accessibility*	*HMIS register*	*TB information system*
	Nurse	*GP*	*Specialist*	*TB lab.*	*Chest X- Ray*	*Peak Flow*	*Spirometry*	*Nebulizer*	*O_2*	*$ß_2$ Agonist*	*Steroids*	*IB*			
Health Post	+++	±						±	±				±	+	+
Health Center	++	+++		+	+			±	+	+			+	+	+
Referral Level (Hospital OPD)	+	±	++	+	+	±	±	±	+	+	+	±	+++	+	+

TB: Tuberculosis; GP: General Practitioner; IB: Ipratropium Bromide; HMIS: Health Management Information System; OPD: Outpatient Department; O_2: Oxygen

TABLE 35.2B: Health resources in health care facilities in Syria, March 2004

Health Facilities	*Health Worker*			*Equipment*						*Access to Inhaled Medications*			*Hospital Accessibility*	*Consultation register*	*TB information system*
	Nurse	*GP*	*Chest Specialist*	*TB lab.*	*Chest X- Ray*	*Peak Flow*	*Spirometry*	*Nebulizer*	*O_2*	*$ß_2$ Agonist*	*Steroids*	*IB*			
Peripheral health post	+++	±											±	+	+
PHC health center	++	+++								±			+	+	+
Comprehensive health center	++	+++	±	±	±			±	+	±	±		++	+	+
Referral center (Hospital OPD)	+	±	+++	++	++	+	±	+	+	±	±		+++	+	+

TB: Tuberculosis; GP: General Practitioner; IB: Ipratropium Bromide; HMIS: Health Management Information System; OPD: Outpatient Department; O_2: Oxygen

STEPS TO INTRODUCE THE PAL STRATEGY IN COUNTRIES

To initiate PAL strategy in a country, a stepwise approach is required. This approach includes approximately 10 steps that are described in detail elsewhere.[22]

Promotion of the PAL Strategy within Country

To stimulate the political commitment of the national health authorities for PAL and encourage the involvement of the potential stakeholders in the future PAL activities, one document or more on PAL should be prepared and distributed.

This/these document(s) should include the main background data that help to understand the foundations of PAL strategy, its objectives, components and perspectives based on the WHO recommendations on PAL[1,3-5,22-24] and the countries' experiences in PAL development and implementation.[6-8,10,11,25-32] Seminars, workshops or meetings involving influential health authorities and key stakeholders may be organized in order to explain the concept of PAL strategy as well as its advantages and implications on strengthening TB control, PHC services and district health system. Participants in these meetings may issue recommendations to the national health authorities and/or relevant health institutions of the country to initiate the process of PAL development.

Political Commitment

As a second step, the Ministry of Health (MOH) should issue an official statement announcing that PAL development should be explored in pilot sites and its perspectives of implementation and impact should be assessed. This statement should be circulated among the relevant programs and departments within the MOH. An official memorandum requesting their support in developing PAL strategy should also be issued whenever needed. A focal point within the MOH should be designated in order to coordinate the introduction of PAL.

National Working Group (NWG) on PAL

The establishment of a NWG on PAL is crucial for initiating PAL and provides essential leadership for the subsequent steps.[22] The role of the NWG is not only to lead the initial PAL activities, but also to ensure the involvement of all the relevant stakeholders in implementing PAL.

The NWG should include members who represent various entities, such as NTP, PHC services, IMAI initiatives, HIV/AIDS and essential drug programs, drug procurement policy, HMIS and health sector reform departments, health care service planning, chest specialists from academic institutions, physicians and nurses practicing in PHC settings and at referral levels, health insurance funds, nongovernmental organizations operating in communities, cooperation agencies and others.

Assessment of Health Environment to Adapt PAL

This assessment should be carried out under the responsibility of the PAL focal point and the NWG. The assessment findings are crucial to adapt PAL development and implementation to National Health Policy and priorities as well as to the existing health infrastructure and resources. Moreover, the assessment should aim at identifying any existing funding or institutional mechanism, which can facilitate PAL implementation as well as any further resource, which can support the NWG tasks in developing PAL. This assessment should be based on various elements,[22] such as:

- The Public Health Sector Policies in relation to: budgetary priorities, programs' integration, health care services' management, planning and financial procedures, essential package of health services and contribution of external support to the health sector
- The process of decentralization and health sector reform
- The managerial organization of the ministry of health at central, regional and district levels
- The managerial activities to implement interventions such as training and supervision
- The level of demographic and epidemiologic transitions, as well as the burden of respiratory illnesses within the national health system
- The situations of TB and TB control, as well as the level of HIV burden in the general population and risk groups
- Populations covered by health care services, particularly PHC and by a health insurance system
- Resources available within the health system to manage respiratory conditions
- The organizations of the referral system and of HMIS
- The organization of respiratory disease management, such as the existence of management guidelines for TB, pneumonia, asthma, COPD or any respiratory condition or the existence of organized referral system for CRDs and others.

PAL Guideline Adaptation and Development

The guideline development is the key element to standardize respiratory care provision. PAL guidelines should be developed by the NWG. The existing country guidelines and/or WHO guidance can help in developing PAL guidelines for a country.[22,24,28,30,33] Other elements and documents should be considered in the development of the PAL guidelines, such as:

- The national procedures to prepare a guideline
- The NTP guideline
- The national policy on HIV/AIDS care and control
- The respiratory disease-based guidelines already developed in the country by the MOH and/or medical professional associations
- The international recommendations on the managements of lower ARIs/pneumonia, asthma, COPD and TB,[12-21,34] as well as on smoking cessation.[35,36]

The guideline for first level health facilities should be symptom-based with a clear connection with the guideline for referral level. The guidelines should:

- Refer to the respiratory illnesses considered as health priorities in the country
- Clearly specify the equipment and the essential drugs needed to manage the respiratory conditions targeted
- Clarify the referral process for respiratory patients between the first level health facilities and the upper health care level facilities
- Specify the routine information system to be used based on the existing HMIS and involving the NTP recording and reporting system.

Training Material Development for PAL

The training material should be developed by the NWG after the finalization of PAL guidelines. It should target the appropriate utilization of PAL guidelines by health care workers in their daily tasks. The training of health workers is organized through workshops.[22]

The training material includes the following:

- The PAL guidelines
- A simplified document explaining the basic concepts and rationale of the PAL strategy
- A participant module, which explains the training objectives and activities, presents clinical cases as problems to be solved in terms of management, and describes necessary communication skills; the problem-solving approach should cover all the components of PAL guidelines
- A facilitator module, which gives the expected answer(s) to each clinical case and exercise and refers to the relevant sections of the guidelines
- A workshop director module, which provides guidance in the administrative and logistic requirements to effectively conduct the workshop.

PAL Site-Piloting

The NWG should test PAL strategy in selected health facilities, easy to supervise with motivated health professionals who provide care services to communities important in size. Testing PAL may focus on assessing the perception, by the health workers, on the usefulness and the quality of PAL guidelines, as well as on evaluating whether the guidelines could be expected to be effective in producing the desired changes in outcomes. For this, the Appraisal of Guidelines Research and Evaluation in Europe (AGREE) Instrument[37] can be used.[26]

The site-piloting can be also undertaken in the framework of a feasibility test of PAL. The objectives of this test are to assess the impact, in the short term, of the implementation of PAL guidelines on the knowledge of the health care workers and on health care delivery to patients with respiratory symptoms in PHC settings. The test is carried out in three phases and involves 80 to 100 health professionals practicing in selected PHC facilities.[22] In the first phase, the management of respiratory patients by the PHC workers is assessed for five consecutive days before any training on PAL. This assessment provides baseline data. The second phase consists of the training of the same PHC workers on the PAL guideline using the training material developed by the NWG. In the third phase, the management of respiratory patients by the trained PHC workers is reassessed in the same conditions as the baseline study. The data collected in the first and third phases are compared and analyzed in order to show whether the health care services for respiratory patients are more rationalized by the use of the PAL strategy.[6-8,10,11]

Development of PAL Implementation and Expansion Plan

The plan to implement and scale up PAL activities can be established for specific regions, in a first phase, or for the whole country. It needs to be elaborated in close coordination with the NTP and the national PHC department and discussed with the other relevant stakeholders. The plan should specify the equipment needed for each health care level in line with the directives included in the national guidelines on PAL. It should also establish a training agenda for heath professionals practicing in first health care level and referral level, including emergency room. To this end, a core of trainers needs to be organized at national level and, whenever needed, at region level.

The plan should clearly identify the entity, which will be responsible for the training. In Kyrgyzstan, the national training agenda on PAL was carried out by the Kyrgyz State Medical Institute of Postgraduate and Continuous Medical Education.[31] In Egypt, El Salvador, Jordan and Morocco, a core of national trainers from NTPs, PHC services and medical schools was constituted; this core is in charge of the implementation of the training program on PAL through a network of trainers at regional level. In the Free State Province, South Africa, the TB nurse coordinators' network was used to train the primary care nurse practitioners.[29]

Mobilization of Funds for PAL Implementation and Expansion

After the development of the plan to implement and expand PAL, the national health authorities should explore the potential sources of funding to implement the activities identified in the plan.

Government may provide funds for all the components of the plan or financially support specific parts of the plan. In some circumstances, funds can be mobilized through the process of the health sector reform or from potential donors. In Chile, the plan of PAL expansion was fully financed by the Chilean government in the framework of the health sector reform. In Kyrgyzstan, training on PAL was financially supported through the ongoing health sector reform, but the equipment needed was funded by the Ministry of Foreign Affairs of Finland. In Morocco, the training was financially supported by WHO, while the equipment procurement was financed by the MOH. In some countries, such as Brazil, India and South Africa, PAL development and implementation has not been financially supported by federal funds, but by state or province funding.

Sources of funding should also be explored through bilateral and multilateral cooperation with donors involved in the development of health care services within the country. As PAL is a subcomponent of the Stop TB Strategy, the Global Fund Against HIV/AIDS, Tuberculosis and Malaria (Global Fund), has financially supported many countries to implement PAL in order to contribute to strengthening health systems. To date, approximately 35 countries have received funding for PAL from the Global Fund. The amount of funds provided by the Global Fund increased from 1.9 million US $ at the Round 6 to 13.9 million US$ at the Round 9.

PAL Implementation and Expansion

PAL implementation and expansion should be under the leadership of a clearly identified coordination unit within the MOH. This unit can be under the responsibility of the NTP or PHC department. Other ministerial departments can take the leadership to implement and expand PAL. However, PAL activities should be always implemented in close collaboration with the NTP and

PHC services. In Bolivia, El Salvador, Jordan, Morocco, Nepal and Syria, PAL expansion is under the responsibility of the NTP, while in Chile it is under the responsibility of the PHC Department and in Kyrgyzstan under the responsibility of the Department of Health Sector Reform. Once funds are available, the PAL unit should proceed to their budgeting in order to procure equipment and organize the training sessions.

When PAL activities are carried out within district health system, the PAL coordination unit should, in collaboration with NTP, PHC services and HMIS, implement the monitoring and supervision system and collect information on a routine basis in order to evaluate the performance of PAL activities.

RESULTS FROM COUNTRY EXPERIENCES

The number of countries with PAL activities have increased since 2002. To date, there are approximately 50 countries with some form of PAL activities. Among them, 12 are at the phase of expansion; Chile and Kyrgyzstan have succeeded to implement PAL in all PHC facilities of the public sector. Many countries are still at the phases of the development of PAL guideline and training material or site-piloting. In other countries, even though the phase of PAL site-piloting was successfully carried out and the plan to expand PAL activities established, the funds needed to implement this plan have not been yet mobilized.

The available results have mainly come from the feasibility tests and operation research carried out in countries. The routine information system for PAL activities established in countries where PAL expansion is progressing has provided, to date, very few data. However, the available results suggest that the PAL strategy has an impact on respiratory case management.

PAL and the Integration of Respiratory Case Management in PHC Settings

The feasibility tests carried out in pilot sites showed that after training of PHC workers on PAL, the proportion of respiratory patients referred from first level health facilities to referral level either for hospitalization or for further clinical investigation decreased by 16% in Guinea, 26% in Jordan and approximately one-third in Bolivia and Kyrgyzstan.[6,7] These findings suggest that PAL strategy may facilitate the integration of respiratory case management within PHC services. However, these results were not confirmed in the feasibility tests of PAL carried out in Syria and Tunisia where the proportion of respiratory patients referred from first level health facilities was already low at the baseline assessment.[8]

A randomly controlled trial, carried out in South Africa, showed that the referral of respiratory patients who need urgent referral from PHC facilities improved with PAL.[25]

PAL and TB Control

Findings from the feasibility tests and operational research carried out in Algeria, South Africa, Syria and Tunisia suggest that training on PAL tends to increase the proportion of respiratory patients in whom sputum smear microscopy is requested.[8,10,25] Data from South Africa showed that PAL guideline, used by nurses practicing at outreach level, significantly contributes to accurately identifying patients with the high probability of carrying active TB.[28] Results of the feasibility tests undertaken in Bolivia, Syria and Tunisia highlighted that PHC workers trained on PAL proceed to a better selection of TB suspects among respiratory patients.[6,8] In contrast, these findings were not observed in the feasibility test carried out in Kyrgyzstan.[7]

Results showing an impact on TB detection are still not yet widely available. The randomly controlled trial carried out in South Africa showed that the probability of detecting TB among patients with respiratory symptoms increased by 72% in PHC centers with nurses trained on PAL in comparison to PHC centers with nontrained nurses,[25] while the feasibility test undertaken in Algeria reported that the proportion of TB cases identified among respiratory patients increased by 120% after training of PHC workers on PAL.[10] The feasibility tests carried out so far in the other countries have failed to yield such results on TB detection. The approach used to carry out a feasibility test is probably not the appropriate method to show such impact, given that the study populations involved are often too small to detect small proportions of TB cases among respiratory patients.

PAL implementation is far advanced in Chile and Morocco. PAL impact on TB detection is not visible in these two countries since both of them had a high TB case detection rate (more than 80%) before PAL implementation. However, this impact might be more significant in countries with a low TB detection rate. Data regarding PAL impact on TB case detection need to be collected on routine basis in countries where PAL is scaling up.

In countries with high detection rate, PAL may improve the quality of TB diagnosis. Indeed in Morocco where PAL services were initiated in 2002 and are presently available in 75% of the public PHC facilities, the routine information system on TB control showed an increase in the bacteriological confirmation of pulmonary TB: from 83% in 2001 to 87% in 2007. The effect of PAL on TB treatment outcome is very scarce. Only one study undertaken in South Africa reported a significantly higher treatment success rate in retreatment of TB patients.[32]

PAL and Drug Prescription

Country experiences in PAL implementation suggest that PAL is likely to decrease drug prescription, particularly at the expense of antibiotics and adjuvant drugs, and to increase the prescription of drugs for inhalation use. The feasibility tests carried out in Algeria, Bolivia, Jordan, Kyrgyzstan, Morocco, Syria and Tunisia[3,6-8,10,11] showed that, with PAL, the number of drugs prescribed per respiratory patient significantly decreased by 10 to 19% and the proportion of respiratory patients who were prescribed antibiotics, by 10 to 33%. Significant decrease in the prescription of adjuvant drugs, such as expectorants and vitamins was consistently observed with PAL in the country feasibility tests.[6-8,10,11]

The cluster randomized trial, involving PHC facilities in Nepal, reported that PAL guidelines' implementation significantly reduced the average prescription by six drugs for every 10 prescriptions and tended to increase the prescription of drugs from the essential drugs' list.[27] The data collected in the feasibility test carried out in Bolivia, Jordan, Kyrgyzstan, Syria and Tunisia highlighted that, after training on PAL, there was a significant decrease in prescription of bronchodilators and corticosteroids; however, among patients who received bronchodilator or corticosteroid prescription the proportion of those who were prescribed inhalers was significantly higher after training on PAL. In addition, data from Morocco highlighted a higher prescription of inhaled β2-agonists with PAL guideline while the randomly controlled trial carried out in South Africa[25] and the routine data collected in Chile[38] showed a significant increase in the prescription of corticosteroids for inhalation use in PHC facilities with PAL services.

PAL and Cost of Drugs Prescribed

Most of the data collected in the countries where PAL has been initiated, highlighted a decrease in the cost of drug prescription with PAL. The feasibility tests carried out in Algeria, Bolivia, Jordan, Kyrgyzstan, Morocco, Syria and Tunisia[3,6-8,10,11] reported a decrease by 8 to 32% in the average cost of drugs prescribed per patient after training of PHC workers on PAL. This decrease is most often associated with significant reductions in the average costs of the prescriptions of antibiotics and adjuvant drugs.[6-8,10,11] The data of some of these feasibility tests showed that after training on PAL there was a decrease, by 16 to 26%, in the average cost of antibiotic prescription among the respiratory patients who were prescribed antibiotics.[6-7,10]

Such findings suggest that PAL is likely to promote a cheaper antibiotic prescription. This can be explained by the fact that the utilization of the PAL guidelines developed in the countries involved the prescription of antibiotics specified in the national essential drug lists. Furthermore, the operational research study undertaken in Nepal reported that patients visiting PAL facilities, on an average, spent less on health care-related costs per respiratory episode, including expenses for drugs, fees and diagnosis tests, as well as on non-health care related costs.[39]

PAL and Quality of Life

PAL is expected to improve patients' symptoms and quality of life. The studies on these aspects are very scarce and difficult to undertake, given that PAL deals with a broad spectrum of respiratory disorders. However, a few findings have been reported from countries where PAL has been introduced. Indeed, a sample selected from the data collected on routine basis in the PAL sites in Chile shows that after one year of follow-up of 250 asthma patients, the number of hospitalizations and emergency room visits, as well as sleep disturbance and daily life limitations in these patients, have significantly decreased after PAL implementation.[38] The cluster randomized trial carried out in Nepal suggested that there was a greater effectiveness of treatment services provided in the PHC facilities with PAL in patients with difficult breathing with a nonchronic cough in comparison to PHC facilities with no PAL services.[39]

Using generic health-related quality-of-life measurements adapted to the local setting, the authors of this study showed that patients with a chronic cough treated in health facilities providing PAL services had better health-related quality of life outcomes than those who were treated in health facilities with no PAL services.[39]

PAL and Cost-Effectiveness

The cost-effectiveness of PAL has not been yet fully studied; the data on this issue are very rare. However, a cluster randomized controlled trial carried out in South Africa, in which nurses were trained on PAL, using an educational outreach method, reported that PAL intervention increased TB case detection, as well as the proportion of respiratory patients appropriately managed; the cost generated was $68 more for each extra patient with TB detected and $15 more for each extra respiratory patient appropriately managed. The authors of this study concluded that the extra cost of increasing TB case detection was comparable to the usual cost for passive TB case detection. Moreover, the intervention increased cost-effectiveness by also improving the care of other conditions.[40]

In the cluster randomized trial undertaken in Nepal, the findings generated by mathematical modeling procedures suggested that PAL implementation is relatively cost-effective. Implementing PAL services at all first level public health facilities in Nepal would cost $111 per quality-adjusted life year gained compared with no PAL implementation. Using a threshold of $150 per quality-adjusted life year gained the probability for PAL to be cost-effective is 54%.[39]

CONCLUSION

PAL is a subcomponent of the Stop Strategy aiming at improving respiratory care in PHC setting while contributing to strengthening health system, particularly at district level.[2] Country experience suggests that PAL can contribute to improving TB case detection as well as the qualities of TB diagnosis and TB care. It provides an essential and integrated health care package in order to address the challenging burden of respiratory illnesses in PHC setting. Country experience suggests that PAL upgrades the skills of PHC workers. Therefore, PAL is likely to strengthen PHC services and increase their utilization by meeting the needs of patients with respiratory symptoms.

PAL is believed to facilitate planning of health resources within the district health system, since standard case management should clearly define the training needs, equipment, drugs and other supplies for the first-level health facilities and the referral level. Data from countries indicate that PAL significantly improves drug prescription while decreasing drug prescription costs. Preliminary findings from Nepal and South Africa suggest that PAL may be cost-effective as a health intervention.

Most of the results of PAL implementation that have been reported, to date, mainly show a short-term impact of PAL, observed in the framework of feasibility tests or operational research studies. The outcomes of the long-term application are still unknown and need to be fully analyzed. It is expected that the appropriate application of PAL on routine basis will do the following:

- Increase the proportion of respiratory patients managed in PHC as a result of the improvement of the integration of respiratory care in PHC
- Decrease the proportion of respiratory cases in hospitals because of the improvement of respiratory care in PHC
- Improve the quality of the diagnosis of pulmonary TB among respiratory patients
- Decrease the number of asthma attacks and exacerbation of COPD particularly in emergency rooms and hospitals
- Reduce the cost of respiratory case management and improve the quality of life of respiratory patients particularly those with chronic respiratory conditions.

These characteristics should be documented in countries where PAL is in the process of expansion.

The WHO (India) and the Government of India have developed National guidelines for the management of CRD (COPD and asthma) at primary and secondary levels of health care in accordance with the PAL strategy.[41] The PAL implementation is likely to follow soon.

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Section

7

TUBERCULOSIS

SK Jindal

36

Epidemiology of Pulmonary Tuberculosis

VK Chadha

INTRODUCTION

Tuberculosis (TB), among the ten leading causes of death worldwide, remains a major public health problem in many countries.[1] It is estimated that about the one-third of world's population is infected with tubercle bacilli.[2] The absolute incidence of all types of TB cases globally during the year 2008 was estimated at 9.4 million, at the rate of 139 per 100,000 population.[3] The worldwide point prevalence was 11.1 million at 164 cases per 100,000 population.[3] About 1.3 million people presumably died due to TB at the rate of 20 per 100,000 population.[3] Of the 199 countries, 80% of the global incident cases each year are concentrated in 22 High-Burden-Countries (HBCs).[3]

Organized TB control programs were introduced from the middle of the 20th century. The very first scientific, community-based effort was implemented all over India from the year 1962 in the form of National Tuberculosis Program (NTP). However, TB continued to be a major public health menace especially in most developing countries due to the ineffective implementation of planned strategies, primarily attributed to managerial deficiencies and lack of sufficient resources. In recent years, new found political will has motivated health providers to consolidate managerial skills to bring in focus on target-oriented results. To give further impetus on control, Directly Observed Treatment Short-Course (DOTS) which is an internationally recommended TB control strategy, was introduced worldwide during 1990s. DOTS has since been further energized by enlarging its scope and content by the Stop TB strategy, which emphasizes on addressing the coepidemic of TB-Human Immunodeficiency Virus (HIV) and Multidrug-Resistant Tuberculosis (MDR-TB), needs of the poor, empowering people through Advocacy, Communication and Social Mobilization (ACSM) activities, engaging private providers and Nongovernmental Organizations (NGOs).[4]

The ultimate aim of TB control programs is to reduce the incidence of TB in the community. The Millennium Development Goals (MDGs) of the United Nations provide a framework for evaluating the progress in TB control. The principle target of MDGs for TB control is to ensure that incidence rates of TB decline globally by 2015. This is envisioned in the annual targets of case detection of new smear-positive PTB cases under DOTS strategy and their treatment success, set earlier by the World Health Assembly in 1991 and also adopted by Stop TB Partnership[5] (Table 36.1). The supplementary targets, are to halve the prevalence of TB and TB mortality rates by 2015, keeping 1990 as the base year (Table 36.1). These targets were based on a resolution at a meeting of the Group of Eight (G8) industrialized countries held in Okinawa, Japan in the year 2000. The year of 1990 was chosen as the baseline, since it was in this year that TB was declared a "global emergency" by the World Health Organization (WHO) leading to conceptualization of DOTS strategy. Stop TB Strategy further aims for the elimination of TB by 2050.

NATIONAL DYNAMICS OF TUBERCULOSIS

The study of "natural dynamics" aims to understand the basic or fundamental laws, which govern all events that take place between the tubercle bacilli and community

TABLE 36.1: Goals, targets and indicators for TB control

(a) Millennium development goal 6: Combat HIV/AIDS, malaria and other diseases	
Target 8	Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases.
Indicator 23	Prevalence and death rates associated with tuberculosis.
Indicator 24	Proportion of tuberculosis cases detected and cured under DOTS (the internationally recommended strategy for TB control).
(b) Stop TB partnership targets	
By 2005	At least 70% of people with sputum smear-positive TB will be diagnosed (under the DOTS strategy), and at least 85% cured.
By 2015	The global burden of TB (per capita prevalence and death rates) will be reduced by 50% relative to 1990 levels.
By 2050	The global incidence of active TB will be less than 1 case per million population per year.

under natural conditions, where active interference in the form of organized control measures is not in place.

The transmission of tubercle bacilli happens through the air when people with active tuberculosis cough or sneeze. For infection# with *M. tuberculosis* to take place, an infectious patient must be able to produce airborne infectious droplet nuclei$ containing tubercle bacilli. Therefore, only cases of pulmonary TB can transmit infection. Majority of the transmission in a community happens from sputum smear-positive cases of pulmonary TB and smear-negative cases are only one-fifth as infectious as the smear-positive cases.[6] On exposure to an infectious TB case, certain factors determine the risk of infection among the exposed susceptible individuals. Once infection occurs, the probabilities of the infected individual to develop TB disease and death due to the disease depend upon a multitude of factors. Thus, there are four stages in the natural course of TB in an individual—exposure, infection, disease and death.

Exposure to Tuberculous Infection

Exposure is said to have taken place when an infectious case of TB and a susceptible person share the same air space where complete air exchange has not taken place between the visits of the two persons. Most transmission of infection occurs in confined spaces because airborne droplets are dispersed rapidly reducing the numbers of droplets per unit volume of air outdoors. Further, the bacilli are killed rapidly due to sunlight and drying. Nevertheless, transmission can also take place outdoors depending on case-contact proximity, when the case coughs directly on the mouth of the other person or talks in very close proximity. It has been estimated that five minutes of loud talk is equivalent to one forceful cough.

The risk of exposure primarily depends upon the incidence rate of cases in the community, the average duration of their infectiousness and the intensity of contact between cases and the susceptible individuals. The risk of exposure is also dependent upon the duration of infectiousness of the case. An untreated case stays infectious for a longer period than the one diagnosed and treated well in time.[7] Given the average delay between the onset of disease and diagnosis, a particular case has the potential to infect about 30 to 40% of her/his contacts before diagnosis.It implies that the proportion of contacts that acquire infection can be reduced by reducing the delay in diagnosis. This underlines the importance of pro-activism of diagnostic and treatment services in drastically reducing the transmission of infection in the community.

Infection transmission also depends on the average number of susceptible individuals that come in contact with a given case. A case in a household with larger family size will expose more persons than in a family of small size. For the same reason, the average number of persons who get exposed to a single case is considerably higher in urban than rural areas due to higher population density.

Infection with Tubercle Bacilli

Once exposed, the risk of becoming infected depends on the size of infectious droplet nuclei produced by the patient on coughing or sneezing and their density in the air. Droplets larger than 10 Microns (μ) in size settle to the ground rapidly whereas smaller droplets remain buoyant for a prolonged period of time. Even if inhaled, almost all droplets larger than 10 μ and the majority between 5 and 9 μ get trapped in the upper respiratory tract. Therefore, only the droplets of less than 5 μ have the potential to establish infection.[8] On an average, an untreated smear-positive case infects about 7–10 persons a year.[9] The average duration of an untreated smear-positive case is about 2 years beyond which either natural cure or death occurs.[10] Therefore, about 20 susceptible

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#*Infection implies that the organism after introduction is able to establish itself in the body with the potential of either multiplication or development.*

$*The droplets, which contain one or more bacilli and are buoyant in air are called “droplet nuclei”.*

individuals would be infected by each smear-positive case, about 10% of whom would develop TB during their lifetime.[11] Therefore, the numbers of TB cases emerging in the community keep doubling over the course of one human generation, in the absence of control interventions.

TB cases who smoke are likely to associate their symptoms to their smoking habit and postpone taking remedial measures. This results in longer delay to initiate anti-TB treatment. The rates of success with anti-TB treatment have also been found to be poorer among smokers with higher rates of relapse of TB disease and death.[12] These factors along with increased frequency of coughing lead to the higher risk of infection among contacts of such cases. Given the mode of transmission, covering the mouth and nose during coughing and sneezing reduces the number of infectious droplets. However, wearing surgical masks by the exposed is not an efficient method of preventing transmission since these masks are not effective in filtering particles less than 5 μ and do not provide a tight seal around the mouth.[13,14]

Tuberculosis Disease

Given that the bacillus has established itself in the human body, numerous hosts related factors determine the risk of infection breaking down into disease. Most of the infected persons may never manifest with TB disease. The risk of developing TB largely depends upon the competency of immune system. The bacilli remain dormant in the body and may cause disease many years later when there is a decline in host immunity.

Factors Which Increase the Risk of Progression to TB Disease

The risk of breakdown and developing disease is very high during the first year following infection. While, the lifetime risk of a newly infected young child to develop TB is about 10%, half of this risk falls within the first 5 years of infection.[11] Therefore, 5 years has been arbitrarily chosen as the cut off point to demarcate primary TB from post-primary TB. In general, the younger the age of primary infection, the higher the risk of primary TB.[11] This also provides the basis for advocating chemoprophylaxis for young child contacts of TB cases.

Even though, the individual risk of developing TB is highest among the recently infected,[15,16] majority of the disease incidence is contributed by the remotely (more than 5 years) infected people. This is because the total numbers of remotely infected people are many times more than the recently infected.

The transmission of *M. tuberculosis* from man-to-man is more efficient than other mycobacteria. The risk of disease following infection with *M. tuberculosis* has also been found to be substantially higher when compared with infection with other mycobacteria like *M. bovis*.[17] Similarly, certain strains of *M. tuberculosis* are more virulent in causing disease.[18,19]

Significant differences in TB incidence by age and sex are largely attributed to differences in the risk of exposure. Community-based surveys generally reveal increasing trends in the incidence of pulmonary TB with age, which is partly due to increase in the prevalence of infection with age.[20, 21]

Incidence rates are generally two to four times higher in males compared to females.[20,21] However, given the same level of exposure to infectious cases, the risk of developing TB following infection has been observed to be higher among females especially in early adulthood period.[11,22] Differences in incidence between races are largely due to differences in the prevalence of infection. Also, the risk of disease following infection is significantly higher in virgin population, i.e. groups that have not been previously exposed to contact with TB cases.

A proportion of cases get naturally cured even without treatment. In a longitudinal study carried by the National Tuberculosis Institute, Bengaluru (NTI), during early 1960s, about 31% of smear-positive cases with X-ray shadows suggestive of TB had become culture negative after 1.5 years.[23] However, a higher risk of recurrence of TB in such naturally cured patients has been demonstrated in some studies.[24]

Smoking is one of the major risk factors inviting TB infection and disease.[12,25] Smoking has also been found to be related to severity of TB disease. A high prevalence of smoking in the economically most productive age group, which also bears most of the TB burden highlights its public health importance. Alcohol consumption has also been observed in a few studies to increase the risk of TB disease.[26] The risk is compounded in the presence of both smoking and alcohol.[12] HIV infection imposes a high risk of TB among people infected with HIV, as well as *M. tuberculosis*. High prevalence of HIV infection in certain population groups further increases the risk.[27]

About 15% of total incidence cases of TB and one-fourth of TB deaths worldwide in the year 2008 were estimated to be among HIV positive persons.[27] Similarly, one-fourth of the persons who died with HIV infection were also suffering from TB.[27]

Other Medical Conditions

Diabetes Mellitus (DM) is associated with an increased risk of TB, as demonstrated by a recent meta-analysis.[28] Persons with silicosis are at a significantly high risk of developing TB. A relative risk* of 2.8 was observed among men suffering from silicosis compared to those without silicosis in a prospective cohort study among gold miners in South Africa.[29] People with lower biomass index generally have a higher risk of TB.[30] The incidence of TB has been demonstrated to increase during the periods of food shortage implying the role of under-nutrition as a risk factor for TB. Certain malignancies have been identified to be associated with increased morbidity due to TB.[31]

Social Conditions

Poor socioeconomic conditions are associated with higher incidence of TB.[32, 33] There is higher level of infection transmission due to poor living conditions. In addition, poor nutritional levels enhance the risk of contracting TB. Homeless people experience a particularly high risk of both TB and HIV.[34]

Death Due to TB

Reduction in the risk of death from TB is dependent on the timely diagnosis and treatment. From public health point of view, pulmonary TB accounts for a majority of the TB deaths. The case fatality rates are much higher among smear-positive cases when compared to smear-negative cases.[35,36] If untreated, about one-third of patients with smear-positive pulmonary TB have been observed to die within one year of diagnosis.[37] About two-thirds die within five years. Inefficient case finding program, delay in diagnosis and poor quality of treatment not only increase the TB mortality, but also contribute to unchecked transmission of infection in the community.

THE EPIDEMIC CURVE OF TB

Temporal epidemic curves depict the time trends of morbidity and mortality of communicable diseases, in given communities. They usually show an ascending and a descending limb separated by a peak or an extended peak, which almost looks like a plateau (Fig. 36.1). The ascending limb of the curve called the "Epidemic Phase" represents the phase of rapid spread and increasing incidence with time. The peak/plateau aspect denotes the "Transitional Phase" when the disease incidence stabilizes. The descending limb represents the "Phase of decline". The time span of this phase is much longer than the epidemic phase since the rate of decline in disease incidence is much lower than the rate of increase during the epidemic phase. Thus, the ascending limb is steeper and shorter than the decelerating descending limb. The declining phase is often followed by a "Low Endemic Phase" when the cases continue to emerge at lower and lower incidence rates for varying periods of time. In the case of acute diseases, the duration of an epidemic curve is usually a few days, weeks or even months. In case of TB, under natural conditions without interference of control measures, the epidemic curve spans a century or more and is therefore called "Secular Curve".[38]

TB epidemic starts when infection is sown for the first time in a virgin community hitherto unexposed to TB infection. At the beginning, spread of infection is rapid and almost everybody gets infected. Most infected individuals develop disease since a large proportion of population is susceptible due to lack of immunity. Case Fatality Rates (CFRs) are high since most of the diseased die due to poor host resistance. Thus, there are high rates of morbidity and mortality. The steepness of the ascending limb is determined by the speed of spread, which depends upon the number of contacts per case per unit of time. The disease is common across all age-groups, childhood TB is common. During the early period of this

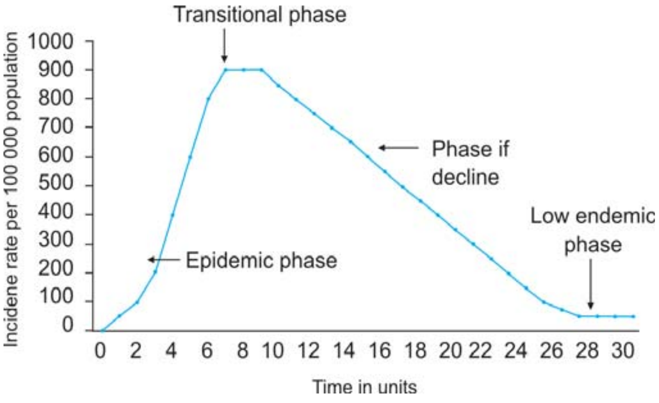

Fig. 36.1: A hypothetical epidemical curve

Note: The curve is imaginary. Incidence rates presented here cannot be extrapolated to any disease in a given community and depend upon local conditions taking different time periods for each phase

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**Relative risk is the ratio of incidence of disease in persons exposed to a known risk factor to the incidence among the unexposed, over a given time period.*

phase, the disease is more concentrated in urban areas, increase in urbanization speeds up the epidemic. As the wave advances, infection and disease spread to rural areas. The disease is more of exudative and disseminative type.

During the transitional phase, incidence rates are still high, but remain stable over years without any significant increase. Morbidity and mortality are highest in middle ages. The disease is of mixed type, tending to become chronic and less generalized. Mortality diminishes slightly. During the phase of decline, prevalence of infection decelerates and TB incidence rates decline naturally. Because, the rate of decline is slower than the rate of increase during the epidemic phase, the phase of decline lasts for a much longer duration than the epidemic phase. The disease is more of localized variety resulting in an increase in the proportion of cases with cavitations. Even though the transmission rates continue to be high, there comes a moment when the numbers of susceptible contacts begin to decline due to the higher levels of resistance than before. The age at first infection gets shifted to adolescence and adulthood. Thus childhood TB becomes less common in the terms of absolute numbers and as a proportion of total cases. Majority of the disease gets localized to older age group, and the disease rates are similar in urban and rural areas. Case fatality and mortality rates decline in the community.

With time, the number of susceptible contacts is reduced to an extent that TB ceases as a public health problem. However, the descending limb of the epidemic curve does not touch the baseline and continues in the same mode indefinitely. This underlies the difficulty in eradication and the disease continues as a low endemic for prolonged periods of time. In primitive societies where there were limited transportation facilities, the epidemic wave of TB might run its course on a local scale. In countries with large population, different geographical areas may simultaneously experience different phases of the epidemic, depending upon the period of its introduction. Communities may also experience temporary fluctuations like in the case of social upheavals, wars and emergence of new risk factors. In modern times, immigration from high prevalence countries has lead to temporary upheavals in the "Phase of decline" in many developed countries.

The duration of each of the limbs of the secular curve of TB can be reduced by effective control programs.

METHODS TO MEASURE EPIDEMIOLOGY OF TB AND ITS TRENDS

The study of epidemiological situation of any disease provides insight into the disease burden shared by the community. Such information is vital for planning control strategies by harnessing required resources for their implementation. It is also imperative to measure the changes in incidence and prevalence of TB disease and mortality in order to monitor the epidemiological trends of the disease and the impact of control measures.

Measuring Prevalence of TB Disease

Prevalence is defined as the proportion of people suffering from TB disease at a given point of time, commonly expressed as a proportion per 100,000 population. Prevalence is the product of incidence and duration of illness. A good chemotherapy program reduces the average duration of illness. Therefore, in the presence of an efficient TB control program, the prevalence of disease declines more rapidly. Incidence takes longer to decline since new cases continue to emerge from amongst the pool of already infected people. Prevalence is generally estimated directly by community based cross-sectional surveys. Indirect estimates can also be made by using the above equation, provided reliable estimates of incidence and duration are available.

Surveys to estimate the prevalence of Pulmonary Tuberculosis (PTB) involve the following steps:

i. *Sampling:* Selecting a representative sample of the population by using appropriate statistical techniques of sample size estimation and the sampling process[β].
ii. *Screening:* To identify the individuals likely to suffer from TB, in the study population, one or both of the following screening tools are used: (a) Mass Miniature Radiography (MMR) of the chest, (b) personal interview to elicit the presence of one or more of the following pulmonary symptoms:
    - Persistent cough for $\geq$ two weeks
    - Fever for $\geq$ one month
    - Chest pain for $\geq$ one month
    - Hemoptysis: At least one episode during the last six months.

    Ideally, radiography, as well as symptom elicitation should both be used for screening. Radiography of

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[β] *The sample size of about 1,80,000 is required to estimate prevalence within 15% of the true value for a cluster sampling design, if the expected prevalence is about 200 per 100,000 population. A similar sample size would be required if the objective is to estimate trends between two surveys five years apart with 90% power at 5% level of significance, expecting the prevalence as above at the first survey and change in prevalence at the rate of 5% per year. Much higher sample sizes would be required for more precise estimates of prevalence at any of the surveys.*

the chest has a higher sensitivity[Ω] than symptom screening for detecting active TB, but its application is cumbersome; whereas in symptomatic screening, which has lower sensitivity, there is likelihood of missing mildly symptomatic or asymptomatic cases.

iii. *Procedures to identify individuals for sputum examination:* X-ray films are read independently by two readers having vast experience in reading MMR films. Each independent reader classifies the X-ray films into one of the three categories—normal, nontuberculous lesion, tuberculous lesion. Individuals found to have abnormal shadow (tuberculous/nontuberculous), by any of the two independent readers are eligible for sputum collection. Similarly, individuals suffering from one or more of the symptoms are eligible for sputum examination.

iv. *Collecting sputum specimen:* Two sputum specimens (one spot and one overnight) are collected from each eligible individual.

v. *Bacteriological examination:* The sputum specimens are subjected to both smear microscopy, as well as culture for Acid-fast Bacilli (AFB).

vi. *Estimating prevalence:* Analysis is undertaken to estimate prevalence and the confidence intervals while taking into account the sampling strategy.

It is extremely important to estimate prevalence of bacteriologically positive PTB[©] efficiently because these cases are responsible for spreading infection in the community. For estimating prevalence of radiologically active PTB, those individuals whose X-ray films are labeled normal by both the independent readers are considered as such. In case of disagreement between the two readers, the film is referred to an umpire reader. Any individual with a lesion classified as tuberculous in nature, by at least two of the three readers is considered to suffer from radiologically active PTB. Often, there is a tendency to over estimate the prevalence of abacillary[μ] PTB, due to low specificity of chest X-ray. Some of the strengths and limitations of prevalence as an epidemiological indicator are summarized as under:

Strengths	*Limitations*
Prevalence changes quickly in response to efficient TB control activities	Large sample size needed to estimate prevalence
Reflects on the efficiency of case finding and treatment under TB control program	Prevalence surveys require huge resources in terms of skilled manpower, equipment, funds and organizational infrastructure
Surveys to estimate prevalence provide opportunity to include subsidiary objectives, for examples, to obtain information on risk factors, health seeking behavior. However, care should be taken so that the primary objective is not compromised.	A significant proportion (30 to 50%) of prevalent cases is missed if screening is based only on symptoms elicitation; if screening includes chest radiography, it is needed to transport radiology equipment to the field
	Not suitable to estimate the prevalence of childhood TB and extrapulmonary TB due to impracticability of required investigations under field conditions.

Measuring Incidence of TB Disease

Incidence of TB is defined as the number of new cases arising in a given period of time (usually one year) in a given community, expressed as a rate per unit population, usually 100,000. Ideally, the incidence should include new, as well as relapse[¥] cases. Estimating the trends in rates of incidence is the most important epidemiological indicator to measure the progress towards disease control and elimination, since it reflects the number of people afflicted with the disease.

The commonly used approaches to estimate incidence are as under:

Cohort Studies

Meticulously carried out prospective cohort studies facilitate the direct measurement of incidence of PTB. Such studies involve repeat prevalence surveys within a reasonable period of time. New cases detected at the later

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[Ω] *Sensitivity is the ability of test to detect disease among those who actually have the disease.*

[©] *Bacteriologically positive case of PTB: A person whose sputum is found to be positive for acid-fast bacilli, either on microscopy or culture, irrespective of the report of X-ray chest.*

[μ] *Abacillary case of PTB: A person whose sputum is found to be negative for acid-fast bacilli on microscopy, as well as on culture, but X-ray is suggestive of PTB.*

[¥] *A relapse case is the one who was declared cured on previous treatment for TB and gets a new episode of TB disease, which could be either a true relapse of the earlier episode or it could be an entirely new episode due to re-infection.*

Strengths	*Limitations*
Provide a direct measure of incidence.	Methodologically cumbersome. Costlier than surveys to estimate prevalence, because of the requirement of a larger sample size and the need to undertake repeat surveys. Need for intensive follow-up of the study population to diagnose all incidence cases that occur in between the follow-up examinations, some of these cases may be diagnosed outside the specific geographical area.

survey among persons not found to be suffering from TB disease at the time of the previous survey represent the incidence cases arising during the intervening period. Nevertheless, many new cases occurring in the intervening period may be missed by the virtue of cure or death. Therefore, information should also be obtained from the records of health centers in the area on additional new cases registered for anti-TB treatment during the period intervening between the two surveys.

Indirect Measurement from the Prevalence

Incidence can be estimated by dividing prevalence with the duration. For the purpose of estimating duration of bacteriological cases, the average delay in initiating treatment after the onset of pulmonary symptoms and the average duration of infectiousness after initiating treatment are considered. Delay on the part of the patient in seeking health care may be estimated through behavioral studies, which may be carried out along with prevalence surveys. However, care should be taken in estimating patient delay because patients usually under estimate the duration of their illness. The delay on the part of the health services in initiating treatment may be estimated through specially commissioned studies to find out the practices of health providers.

It has been estimated that the mean duration for which a bacteriological case remains culture positive after initiating treatment is three months. The disease durations are estimated separately for cases treated under DOTS, non-DOTS and those who remain untreated, by HIV status and then pooled to find out the mean duration.

Indirect Estimation from the Annual Risk of Tuberculosis Infection (ARTI)

ARTI is defined as the probability of acquiring new infection with tubercle bacilli over a period of one year. It is computed from the prevalence of infection estimated through a cross-sectional tuberculin survey among young children. A parametric relationship was proposed by Styblo during early 1980s, according to which every one percent of ARTI among children corresponded to 50 smear-positive incidence cases per 100,000 population per year.[39] This was derived from observations of six studies. However, only two of these studies measured the incidence directly through prospective cohort studies. It was derived indirectly from the prevalence of smear-positive PTB in two studies and from mortality due to TB in the other two studies.

In many countries, including in India, the incidence of smear-positive PTB has been estimated by applying Styblo's hypothesis. There is ample evidence that shows that this proposition may no longer be valid.[40] In a well performing DOTS program, the mean duration of infectiousness of the cases would be reduced and thus a larger number of incidence cases would be needed to infect one percent of the population. Similarly, in situations where significant proportions of TB cases are also infected with Human Immunodeficiency Virus (HIV), a shorter survival reduces the average duration of infectiousness for *M. tuberculosis.*[41,42] Therefore, in the present epidemiological environment, each one percent of ARTI should correspond to larger number of incidence cases.

Estimating Incidence from TB Notification Data

As conveyed above, estimating incidence from community-based surveys has its limitations. Presence of an efficient routine surveillance system, which fulfills the following minimum criteria offers an alternative for deriving incidence rates from case notification data.

- TB control activities well integrated with the general health system
- Universal access to TB diagnostic and treatment facilities, so that there is minimum diagnostic and treatment delay
- Quality assured laboratory procedures with adequate and timely supply of lab reagents
- Adequate and timely supply of anti-TB drugs
- Operational mechanism to trace initial defaulters
- Effective staffing in terms of vacancies, training and retaining the trained staff

- Correct classification of new and retreatment cases
- Efficient collaborative activities between HIV and TB control programs
- Effective coverage of health providers, including the private sector and NGOs, with respect to quality of the diagnosis, treatment and recording and reporting
- Efficient data management practices.

Since the implementation of DOTS, standardized case definitions and routine surveillance procedures under NTPs are now in place in most countries. In situations, where almost entire population have access to health services and most of the incidence TB cases are detected and reported to NTPs, the annual case notification rates could be equated with incidence rates. In such a scene, the trends in annual case notification rates reflect the trends in incidence provided that the efficiency of case finding does not vary with time. However, the surveillance data should be examined for completeness in the terms of reporting units, duplications and misclassifications, if any and whether the data are consistent with known epidemiology of the disease, i.e. the proportion of smear-positive cases out of all cases, proportion of pediatric cases, etc.

In majority of the developing countries, only cases having access to health services are included in the notification data of NTPs. In such situations, the notification data does not directly provide a fair assessment of the incidence rates. Also, there has been an intensification of case finding efforts in the recent years with the result that the present trends of increase in case notification rates cannot be equated to the trends in the incidence.

The following approaches may be used for deriving more reliable estimates of incidence, using the case notification data.

a. *Estimating missing cases:* Many cases are usually missed from notification under routine surveillance, due to various reasons:

i. A proportion of cases may not have any access to health care.

ii. A proportion may not seek care despite having access to health services, due to various reasons, such as non-perception of symptoms or the felt-need to seek care, home remedies or belief in traditional medicines.

iii. Some cases remain undiagnosed inspite of contact with health providers, due to failure on the part of the providers to diagnose TB owing to various reasons like technical skills and shortage of resources like laboratory reagents, etc.

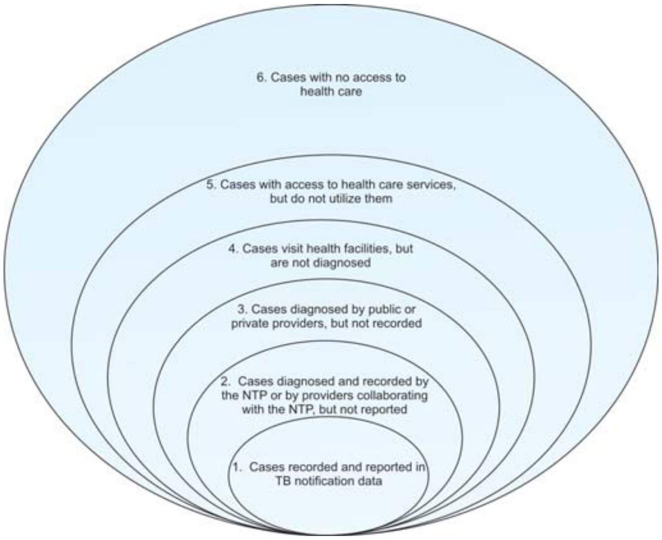
6. Cases with no access to health care
5. Cases with access to health care services, but do not utilize them
4. Cases visit health facilities, but are not diagnosed
3. Cases diagnosed by public or private providers, but not recorded
2. Cases diagnosed and recorded by the NTP or by providers collaborating with the NTP, but not reported
1. Cases recorded and reported in TB notification data

Fig. 36.2: A schematic presentation of TB cases missed in notification data[43]

Note: The areas of the respective rings are arbitrary and do not imply the proportions of cases missed in each ring.

iv. Some cases may be diagnosed (and treated), but may not be recorded in the TB registers, due to administrative errors on the part of health staff.

v. Some cases inspite of having been registered and recorded may not be notified in case finding reports due to administrative errors.

Therefore, only a proportion of the incidence cases are ultimately included in the surveillance data. If we estimate the proportion of cases missed at each of the stages as above, the incidence in the community can be estimated on dividing the number of cases notified by the total proportion of cases that are missed through an "*Onion Model*" approach (Fig. 36.2). The information on the proportion of cases missed in each of the rings 2-5 can be estimated by conducting special investigations and studies besides using the available information.

This exercise assists to formulate appropriate strategy to improve the efficiency of the routine surveillance system and thus reduce the proportion of cases missed. It should be undertaken in each tuberculosis unit responsible for implementing control services in a given area.

b. *Inventory method:* In this method, data is collected from all possible sources and the total numbers of TB cases recorded are counted after checking for duplications. However, cases undiagnosed or not recorded will be missed.

c. *Capture-recapture technique:* This technique was originally developed by zoologists to count wildlife population. Such studies can be used to derive a better estimate of the real numbers of TB cases by finding out the proportion of under or overestimation of the case notifications by two independent sources.[44,45]

This method is based on several assumptions, importantly that there are no births, deaths or migrations in the area, i.e. it is a closed population, and that case definitions are correctly applied by both the sources.

There can be a degree of overestimation, if cases captured by both sources are not recognized as being the same (negative dependence). On the other hand, a positive dependence between the two sources would lead to underestimation. Nevertheless, the number estimated by capture-recapture study is likely to be closer to the truth than the numbers reported by NTP alone. Such studies also provide opportunities to find out the efficiency of the surveillance system of NTP. It is desirable to include a minimum of three sources of data for such a study. More the number of sources of data used for such exercises, more accurate are the number of estimated new TB cases. Capture-recapture studies may be utilized to estimate the number of TB cases that are diagnosed, but not reported (Rings 2 and 3 of Fig. 36.2).

Deriving Trends in Incidence from Age Distribution of Notified Cases

The age distribution of incidence cases and TB deaths throws light on trends. For example, at present, a majority of cases in the indigenous European population occur in the elderly people who were probably infected in the remote past when TB transmission rates were relatively higher.[38,46] Similarly, trends in mean age of notified cases can provide a clue to the direction of the epidemic.

A worsening of TB situation accompanied by increase in the TB incidence, for example in high HIV prevalence areas, leads to increase in the transmission of infection. This is accompanied by an increase in the proportion of cases emerging among the younger age group leading to reduction in the mean age of notified TB cases.[47] Conversely, implementation of effective TB control activities leads to a higher proportion of cases belonging to the older age group since the majority of cases in older people are caused by the reactivation of infection acquired in the remote past. This is accompanied by an increase in the mean age of incidence cases.[48,49] This must be interpreted cautiously since there are other factors, which may influence the age distribution of cases—increase in life-expectancy of the general population, increase in accessibility to health care resulting in the higher proportion of elderly cases seeking anti-TB services, errors in population projection in different age groups.

Measuring TB Mortality

TB mortality rate is defined as the proportion of individuals in the community who die of TB in a given period of time (usually one year), an important indicator to measure progress towards MDGs [*Deaths among HIV positive TB cases are not counted as TB deaths, and are classified under HIV deaths as per International Classification of Diseases (ICD-10)*].

Of the total burden of TB measured in "Disability-Adjusted Life Years (DALYs§)" lost, more than 80% is accounted by premature deaths rather than illness per se.[50] As an effective treatment drastically reduces the risk of death, efficient case finding and treatment activities have a faster impact on TB mortality than on incidence.

Direct estimation of TB mortality rate through prospective cohort studies is operationally difficult. Further, routine TB surveillance systems in most high burden countries do not provide accurate information on TB mortality rates due to a combination of multiple reasons, viz. less than 100% case detection rate, non-ascertainment of the Cause of Death (COD) among cases who died during treatment, deaths occurring due to TB after completion of treatment period not captured by surveillance data. Thus, recording and reporting data at best throws light on case fatality rates during the period of treatment. In such situations, the commonly used practical approaches to measure TB mortality are as under:

Using Vital Registration Data

The most cost-effective approach would be to have an efficient system of vital registration in place wherein the underlying cause for every death occurring in the community is identified, coded as per ICD, and reported. As of now, only a third of the deaths occurring worldwide are reported by the vital registration systems.[51] Especially, in most high burden TB countries, vital registration system is plagued by the lack of universal population coverage, inaccuracy in assigning COD and poor reporting.[51] Concerted efforts are being

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§DALYs is a unit for measuring disease burden in time and is expressed as the number of healthy years of life lost due to disability or premature death.

made by individual countries to improve the functioning of vital registration systems.

Verbal Autopsy Studies

Verbal autopsy (VA) method is now increasingly used to find out the COD.[52-54] In this method, the information on events of deaths having taken place in a community is obtained from various sources such as hospital data, religious places, crematoria and community-based volunteers. The workers trained in verbal autopsy methods visit the houses of the diseased and conduct interviews with the close relative of the deceased. Pre-structured set of questions are put to the family members of the diseased, for each death occurring in the past one year, using a standardized questionnaire. Information is obtained on symptoms, duration of disease, anatomical site and COD as known to family members. The information from available hospital and other records is also obtained. The interviewer is required to write a narrative of events starting from the onset of illness till death. Later, each filled-in questionnaire is scrutinized by a medical officer and COD is assigned. The COD is subsequently coded as per ICD, by trained coders.

Verbal autopsy studies are especially useful for assigning COD in countries where the well functioning death registration systems are not in place, the methods need further standardization to reduce the mis-classifications. Before undertaking these studies in a given area, validation studies to find out sensitivity and specificity of COD should be carried out.

Indirect Derivation from Incidence Rate

This can be obtained by applying the formula: Mortality rate = incidence rate × case fatality rate.

Different rates of case fatality are applied for cases treated by DOTS programs, non-DOTS programs and untreated cases, by HIV status and pooled to estimate the average mortality rate. The limitations of this method are:

i. Deaths occurring during treatment are not always caused by TB, but are always attributed to TB in the DOTS surveillance system.
ii. Fate of TB cases who default from treatment or are transferred out is usually not known.
iii. Some cases may die due to TB even after having completed treatment.[55]

Measuring ARTI

Incidence rate of new tuberculous infections depends upon the load of infectious TB cases in the community, efficiency of TB control programs and socio-environmental factors that determine the extent of interaction between TB cases and susceptible individuals. Ideally, the incidence of infection can be measured through prospective follow-up studies of noninfected people. But there are major impediments to this approach, due to the possibility of reversion of tuberculin sensitivity with time and of boosting, which results from recall of waned cell-mediated immunity due to repeated tuberculin testing. To circumvent this problem, epidemiologists first estimate the prevalence of infection in the community by carrying out cross-sectional tuberculin surveys. It is assumed that a person once infected remains infected for the rest of his/her life. Prevalence of infection thus represents the cumulative effect of the incidence rates of infections experienced by the study sample during each of the individual years since birth.

The annual risk of tuberculosis infection (termed so, to distinguish it from incidence of infection) is computed from estimated prevalence of infection, using an appropriate formula. ARTI represents the average of the risks of tuberculous infection experienced by a group of individuals during each of the individual years from their birth to the time of the survey. The trends in ARTI have been observed to run in parallel with trends in prevalence of TB.[35,56-60] Thus, ARTI is an important epidemiological indicator to monitor the progress towards MDGs.

Prevalence of infection is generally measured through tuberculin surveys generally carried out among children since the ARTI rates estimated among them reflect on relatively recent disease situation. On the other hand, surveys, if carried out among older individuals would represent the average of the risks of infection over a longer period in the past. Also, a higher prevalence of infection with Nontuberculous Mycobacteria (NTM) in older age groups may interfere with the interpretation of the survey data.[61]

In most countries, e.g. in India, the BCG vaccination coverage is high. Thus, the small proportion of children without BCG scar is not adequately representative of the target population. Even though a majority of children vaccinated at birth elicit low levels of tuberculin sensitivity, inclusion of vaccinated children in the 0-4 years age group may interfere with the interpretation of the survey results. On the other hand, in the 5-9 years age group, inclusion of BCG vaccinated children has not been found to significantly influence the survey results.[62] Therefore, children between 5 and 9 years of age, including those with and without BCG scar, comprise the most appropriate study population for tuberculin surveys. Younger children may be included in a particular country if there is past evidence of BCG vaccination not influencing significantly the estimates of ARTI.

School-based surveys are operationally more convenient than house-based surveys. However, house-based surveys may be preferred in communities with low (<80%) school attendance since children not attending schools may be at a different risk of tuberculous infection. Tuberculin surveys require meticulous designing, planning, implementation, quality control of data collection and careful interpretation.[63,64] To study the trends, repeat tuberculin surveys may be carried out with an optimum interval of 5-8 years.

First step in analyzing the tuberculin survey data is to decide on the criteria for estimating the prevalence of infection.[65] For this purpose, frequency distribution graph is generated with reaction size on X-axis and percentage of reactors on Y-axis. A classical graph of tuberculin survey data is bimodal showing two distinct modes and an easily identifiable anti-mode (Fig. 36.3). The reactions to the left of the anti-mode most probably represent cross reactions due to infection with NTM or BCG vaccination. The reactions to the right of the anti-mode most probably represent the subgroup of children who are infected with tubercle bacilli. In a situation, where the anti-mode is clearly discernible, prevalence of infection may be estimated as the proportion of children having reactions equal to or larger than the anti-mode.

The anti-mode is usually not clearly identifiable in areas with moderate-to-high prevalence of NTM infections or when BCG vaccinated children are included in the study sample. In these situations, the prevalence of infection is estimated using "mirror–image technique". In this technique, the proportions of reactions larger than the second mode is doubled and added to the frequency at the second mode. The rationale of this approach is that tuberculin reactions due to infection with tubercle bacilli are distributed more or less similarly in the both sides of mode, as seen in a normal frequency curve. The influence of BCG-induced tuberculin sensitivity on estimate of prevalence of infection is minimal if the estimation is done using mirror–image technique, since tuberculin sensitivity induced by BCG vaccination rarely elicits reactions larger than the second mode.

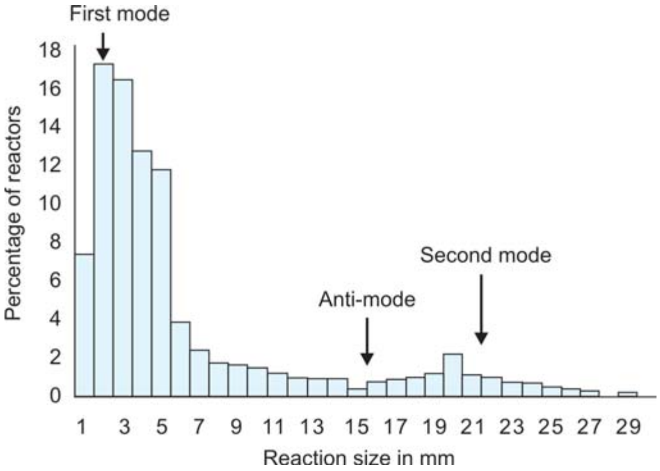

Fig. 36.3: An example of frequency distribution of tuberculin reaction sizes obtained in a survey

Sometimes, it is possible that neither the anti-mode nor the mode is clearly discernible on the frequency distribution graph. Such situations are quite likely in communities with the low prevalence of infection. In such a scenario, the mode observed in smear-positive cases may be used to select a cut-off point for estimating the prevalence of infection among children (distribution of reaction sizes among TB cases is characteristically unimodal). The rationale for the latter approach is that the position and shape of tuberculous reactions among apparently healthy, but infected individuals ought to be similar to the distribution of reactions among TB cases. Many tuberculin readers have a tendency of "digit preference" whereby reaction sizes ending with zero or five are recorded more often. Therefore, survey data may be corrected for digit preference before estimating prevalence.

Another method of analyzing tuberculin survey data is the "mixture model" approach based on Bayesian statistics.[66] This method operates by estimating the probability of true tuberculous infection at each mm of reaction size. Analysis using this model is undertaken separately for children with and without BCG scar. For analysis among those without scar, two component distributions are assumed; one for tuberculous infections and the other, for cross-reactions to infection with NTM. A third component attributable to BCG is assumed among children with BCG scar. This analysis can be undertaken using R software (version 2.4.1, http:/lib.stat.cmu.edu/R/CRAN) and ready scripts available at www.tbrieder.org.

ARTI can be computed from the estimated prevalence of infection and the trends, i.e. the average per annum change in the ARTI (α) between two surveys can be estimated.[67, 68]

The estimated ARTI[Φ] rates represent the overall effect of incidence of infectious TB cases, their average duration

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[Φ] *Interferon GAMA Release Assay (IGRA) based tests for detecting tuberculous infection are not suitable for surveys to estimate ARTI, due to the difficulty of drawing blood by venepuncture among children in field conditions and its rapid transportation from peripheral areas, besides the high cost.*

of infectiousness and interactions between infectious cases and susceptible individuals. The average duration of infectiousness depends upon several factors, chiefly the efficiency of TB control program in term of case detection rate, treatment success and delay in diagnosis. Since, the extent of transmission of infection determines the total pool of infected people in the community, ARTI estimates give a fairly predictable estimate of new cases likely to emerge in the years to come.

In communities where efficiently functioning TB control programs are run with the high levels of case-detection and cure of smear-positive cases, the risk of infection declines. Therefore, the extent of per year decline in ARTI rates observed from repeat tuberculin surveys becomes a good gauge of program efficiency. It has been estimated that if at least 70% of incidence cases of smear-positive pulmonary TB are detected every year and 85% of them are cured, ARTI rates would decline by 7 to 11% per year.[40] In contrast, an increasing trend in ARTI points towards poor performance of control programs and/or several other epidemiological factors, such as an increase in HIV sero-prevalence in the community. It should be kept in mind that ARTI, which is estimated from the prevalence of infection among children might not be applicable to all age groups as the risk of tuberculous infection in different age groups may vary even if slightly and, is observed to be age dependent.

There are factors which may generate a bias in the estimates of prevalence of infection- boosting due to previous tuberculin testing, waning of tuberculin sensitivity with time, cross-reactivity to NTM, missing data on the risk of infection experienced by the children hospitalized at the time of survey or those who had died in the past. With a greater efficiency of DOTS programs, prevalence of infection among children falls faster.[56,69] These factors might lead to the absence of bimodality on the frequency distribution of reaction sizes contributing to ambiguities in deciding the anti-mode or mode. Such data from tuberculin surveys create difficulties in analysis. Tuberculin surveys may therefore primarily be useful for the study of trend in ARTI. There is a word of caution here too. Significant levels of migration in certain areas may also render the data on trends difficult to interpret.

INDIA—A CASE STUDY FOR MEASURING EPIDEMIOLOGICAL SITUATION AND TRENDS

A significant amount of community-based data has been generated over the years in India, even though such studies are operationally difficult due to the requirement of large sample sizes and huge amount of required resources in the terms of finances, time and highly skilled manpower. The data on prevalence, incidence and mortality obtained from such studies and other sources besides the WHO estimates and their trends are presented in this section.

Prevalence Surveys

The Indian Council of Medical Research (ICMR) conducted a nation-wide survey during 1955-58 to estimate the prevalence of PTB.[70] The study population was screened using MMR and one sputum sample and one laryngeal swab were collected from each of those showing any abnormal shadow. Findings of this large scale survey revealed that the average national level prevalence of bacteriologically positive PTB was similar in the rural and the urban areas of the country at 400 per 100,000 population, 80% of the cases lived in rural areas. Hitherto, TB was believed to be predominantly urban disease. This information was useful for planning the strategy and resources required for NTP, which was implemented across the country from 1962. Though the survey was not aimed at study of differences in prevalence between different areas, significant difference could still be observed, for example, between different cities.

A number of surveys have been carried out subsequently in different geographical locations. (Tables 36.2 and 36.3). There were some variations across the surveys in the definition of pulmonary symptoms. While two sputum specimens were collected from each eligible individual, some investigators examined sputum specimens either by culture or smear, others performed both. Similarly, there were variations in the methods used for smear microscopy—Ziehl-Nelson technique, fluorescent microscopy. Consequently, there was variation in definition of a bacillary case of PTB. Even though, the methods were not uniform across the surveys, the results had given reliable indicators on the magnitude of TB burden, which seemingly varied.

The trends in the prevalence of TB are available from some of these areas. Prior to the demarcation year of 1990, serial surveys were carried out in Tumkur, Madanapalle, rural Bengaluru, Chingleput and a defined area of Delhi.[20,21,71-77] Significant decline in the prevalence of TB was not observed over the years except in Madanapalle, which was the site of an intensified chemotherapy program. The progress towards MDGs from the base year of 1990 is thus far available only from Tiruvallur where three rounds of surveys carried out between 1999–2006 revealed a decline of about 12% per year in the prevalence of smear-positive, as well as culture-positive

TABLE 36.2: Prevalence of PTB per 100,000 population—surveys carried out during 1955-1989

State and district	*Study period*	*Age (yr)*	*Sample size*	*Screening method*	*Prevalence / 100,000 population*		
					Cul +ve	*Sm* +ve	*cul and/or* sm +ve
National Sample Survey[70]	1955-58	>4	290 758	MMR	-	-	400
Tumkur (Kar) [71]	1960-61	>9	21 021	MMR	314	281	410
	1979		24 785		399	262	444
Madanapalle (AP) [72]	1960-61	>14	46 888	MMR	-	-	681
	1962-64		46 296				501
	1965-68		84 486				483
Bengaluru rural (Kar.)[21,73-75]	1960-61	>4	43 889	MMR	406	-	-
	1962-63		40 633		372		
	1964-65		40 405		337		
	1966-68		41 213		393		
	1974-75		15 243		320		
	1984-86		21 924		438		
Srinagar, Baramulla and Anantnag (J and K) [76]	1978	>4	14 226	MMR	-	-	280
Delhi[77]	1962	>4	21 344	MMR	-	-	400
	1964		22 621				700
	1967		24 803				700
	1969		24 808				210
	1972		26 132				280
	1976		26 686				320
	1981		25 583				360
Wardha (Mah.) [78]	1982-88	>4	687 401	Symptoms	71	80	182
North Arcot—KV Kuppam Block (TN) [79]	1981	>9	18 688	Symptoms	-	241	-
North Arcot—plains (TN) [80]	1989	>14	(a) 64 077 (b) 25 485	(a) Symptoms (b) MMR +symptoms	-	-	(a) 430 (b) 790
North Arcot—tribal (TN) [81]	1889	>14	16 017	MMR +symptoms	520	470	840
Raichur (Kar.) [82]	1988-89	>14	40 496	Symptoms	-	760	1090
[$]Chingleput (TN) [20,83]	1968-70	>9	206 609	MMR	800	570	
	1971-73		101 331		819	476	1070
	1973-75		104 789		868	496	
	1976-78		112 142		815	406	
	1979-81		115 164		759	436	-
	1981-83		120 118		767	471	
	1984-86		121 877		689	423	
Car Nicobar (A and N)[84]	1986	>14	9514	Symptoms	-	410	-

Cul: Culture, Sm: Smear, J and K: Jammu and Kashmir, TN: Tamil Nadu, Mah.: Maharashtra, Kar.: Karnataka, AP: Andhra Pradesh, A and N: Andaman and Nicobar: Not available, [$]prevalence surveys from 1971 onwards were carried out in a subset of the study sample surveyed in 1968-70

TABLE 36.3: Prevalence of PTB per 100,000 population – surveys, carried out during 1990-2009

State and district	*Study period*	*Age (yr)*	*Sample size*	*Screening method*	*Prevalence of PTB cases/100,000 population*		
					Cul + ve	*Sm* + ve	*cul and/or* sm + ve
Delhi[77]	1991	>4	27 838	MMR	-	-	330
Car Nicobar (A and N)[84]	2000-2001	>14	10 570	Symptoms	-	729	-
Thiruvallur (TN)[85]	1999-2001	>14	83 425	MMR + symptoms	609	326	
	2001-2003		85 474		451	257	
	2004-2006		89 413		311	169	
Morena (MP)[86]	1991-1992	>14	11 097	Symptoms	-	-	1270
Tribal areas (MP)[87]	2006-07	≥15	20 000	Symptoms		387	-
Wardha (Maharashtra)[88]	2007-09	≥15	55 036	MMR + symptoms			
Nelamangala Rural Bengaluru[88] (Kar.)	2007-09	≥15	70 000$^{@}$	MMR + symptoms			
Faridabad (Haryana)[88]	2008-09	≥15	105 202	Symptoms	Final Result Awaited$^{@}$		
Mohali (Punjab)[88]	2008-09	≥15	91 030	Symptoms			
Jabalpur (MP)[88]	2008-09	≥15	99 595	Symptoms			
Kanpur and Banda (UP)[88]	2008-09	≥15	110 680	Symptoms			

Cul: Culture, Sm: Smear, Kar.: Karnataka, MP: Madhya Pradesh, TN: Tamil Nadu, A and N: Andaman and Nicobar; MP: Madhya Pradesh; UP: Uttar Pradesh, Not available, $^{@}$survey still in progress

PTB.[85] Whereas results from a survey carried out in Car Nicobar during 2001-02 showed an increase in prevalence when compared to a survey carried out there during 1986.[84] Considering the shortcomings in the availability of trends in the different parts of the country, baseline surveys have been carried out during 2007-2010 in six other sites (rural Bengaluru, Wardha, Faridabad, Mohali, Banda and Jabalpur). The preliminary results from these sites show large variation in the prevalence of disease across different sites.[88]

Although, the above mentioned surveys were not specifically designed to compare prevalence by age group and sex, the prevalence was generally found to be significantly higher among males with a male to female ratio from 2:1 to 5:1 in different surveys. This difference by sex was more pronounced after 35 years of age. More than half of the disease burden in females was concentrated in the reproductive age group of 20-44 years. The prevalence was also observed to increase with age, more so among males. Nearly half of the prevalence cases were concentrated in ≥ 40 plus years age group. The national level survey (1955-58) and the survey in the Wardha district (1982-88) also revealed an association between disease prevalence and socioeconomic conditions, as the prevalence was higher among those living in *kaccha* (mud) houses compared to *pucca* (concrete) houses.[70,78]

The estimates of prevalence of abacillary PTB and their time trends are not presented, there has been a greater variation in the techniques of interpretation of X-ray films across the surveys in different areas and during the different rounds of surveys in the same areas. Often, there is a tendency to overestimate the prevalence of abacillary TB during the surveys. Moreover, the standard procedure of giving a course of antibiotics to abacillary case before deciding on the nature of the X-ray lesion has never been followed during the surveys.

TABLE 36.4: Annual incidence rate of culture/smear-positive PTB per 100,000 population in selected areas

Study area	*Study period*	*Age group (in years)*	*Sample size*	*Incidence rate /100,000 population*	
				Culture +ve PTB	*Smear +ve PTB*
Bengaluru Rural[21]	1961-62	>4	34 476	132	-
	1962-64		32 194	79	
	1964-68		31 381	99	
Chingleput[20,83]	1971-73	>9	213 307	352	157
	1973-75		38 461	250	142
	1976-78		44 091	251	106
	1979-81		50 794	207	104
	1981-83		56 067	209	127
	1984-86		65 826	189	113
North Arcot[79]	1981-82	>9	19 129	-	110
	1982-83		19 570		
Tiruvallur[85]	2001-03	>14	60 009	-	126

-: Not available

Cohort Studies for Measuring Incidence

A limited number of community-based studies on the incidence of PTB are available from India (Table 36.4). In rural Bengaluru, South India, the annual incidence of culture-positive PTB ranged between 79-132 per 100,000 population.

In Chingleput, the incidence of culture-positive PTB varied from 189 to 352 per 100,000 population. The incidence of smear-positive PTB varied from 113 to 157 per 100,000 population. Overall, there was an average decline of 4.3% per year in incidence of culture-positive PTB and 2.3% per year in the incidence of smear-positive PTB. In North Arcot, incidence of smear-positive TB was estimated at 1.1 per 1,000 population during 1981-83.[79] In Thiruvallur, incidence of smear-positive cases among adults between three surveys carried out between 1999 and 2003 was 126 per 100,000 population.[85] Passive case finding at the health centers was also included in this estimation, but there was no selective case finding as in Chingleput.

Incidentally, the above mentioned serial surveys in Chingleput were carried out as a component of a Randomized Control Trial (RCT), to estimate the protective efficacy of Bacille Calmette-Guérin (BCG) vaccine against bacteriologically positive PTB.[83,89] It was observed over the 15-year period of follow-up that BCG offered no protection against bacteriologically positive PTB among adults. Even though, a protective efficacy 27% against bacteriologically positive PTB was observed among children 1-9 years of age, it was not significant statistically.

Ratio Between Prevalence and Incidence

The ratio of incidence to prevalence of TB reflects the efficiency of TB control activities. During the pre-chemotherapy era, the average duration of infectiousness of a smear-positive case was found to be about 2 years, therefore, the ratio of incidence to prevalence was observed as 1:2. However, in Chingleput, this ratio was observed to increase from 2.5 to 4.2 between 1968 and 86.[20] This increase signified further accumulation of old cases attributable to increases in the duration of illness, diagnostic delays and poor treatment success rates. An effective implementation of DOTS strategy should decrease this ratio by decreasing the average duration of disease.

Annual Risk of Tuberculous Infection

A number of surveys were carried out in the country during the second-half of 20th century, to estimate ARTI among children. The estimated ARTI during most of the surveys varied between 1 to 2%. (Fig. 36.4).

However, except for two, the rest of these surveys were carried out in limited geographic areas of South India. Thereafter, four zonal level surveys were carried out in 2000-2003.[96] For this purpose, the country was divided into four zones, each zone consisted of contiguous states combined to encompass one-fourth of the country's population. Each zonal survey was carried out in 6-8 districts selected by Population Proportion to Size (PPS) method. The purpose of the surveys was to estimate ARTI among children without BCG scar and

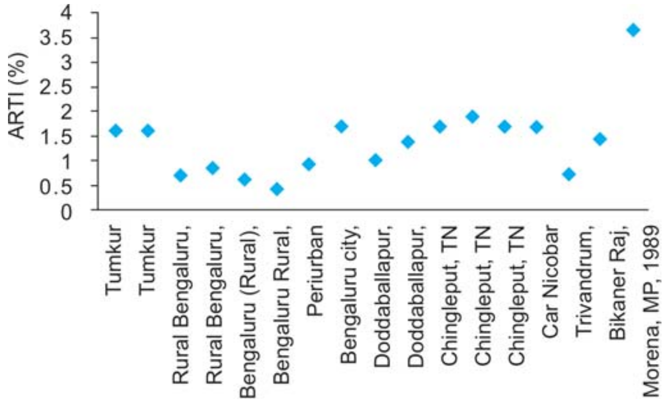

Fig. 36.4: ARTI in different parts of India, 1960-2000

1-9 years of age, in each of the zones. The estimated ARTI varied between 1% in Southern zone to 1.9% in Northern zone[96] (Fig. 36.5).

Survey findings also revealed higher rates of infection transmission in urban areas compared to rural areas.

Though the first zonal level surveys were designed to estimate ARTI among children without BCG scar, children with scar were also tuberculin tested. Data revealed that there was no statistical significant difference in the estimates of ARTI rates between children with and without BCG scar in 5-9 years age group.[63] A significant difference was however seen in 1-4 years age group. Earlier, tuberculin surveys were traditionally conducted among children with BCG scar, based on the observations of influence of BCG-induced tuberculin sensitivity, when BCG was given under research conditions or as special campaigns. Several tuberculin surveys have been carried out after the turn of the millennium (Table 36.5).[69,84,96,98-103] The results of no influence by BCG in later surveys could be attributed to low dose vaccine given immediately after birth under program conditions. These findings, however, should not be construed as indicating that BCG is not protective against childhood forms of TB, as no relationship has been found between tuberculin sensitivity induced by BCG vaccination and the protective effect of BCG.[97]

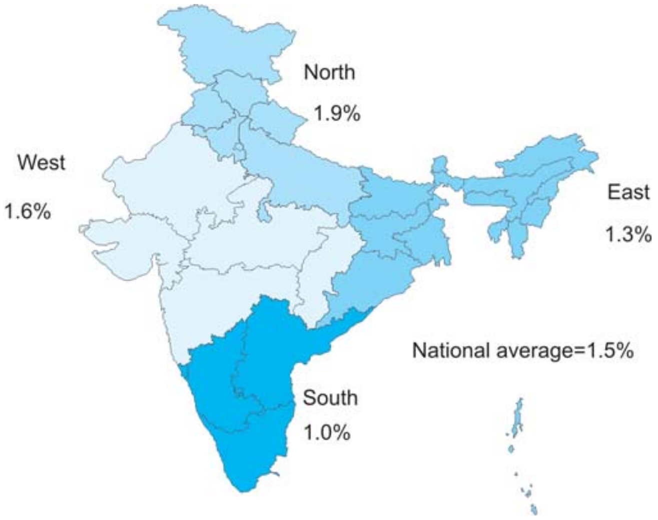

Fig. 36.5: First zonal level ARTI surveys, 2000-03

Note: The percentages quoted in the figure are best estimates of ARTI in respective zones demarcated here by different colors

Trends in ARTI are available from six defined geographical areas. During the pre-DOTS period, there was no decline in Chingleput and Doddaballapur while a small decline of 3% per year attributed to natural phenomena was observed in rural Bengaluru.[20,90,92] Trends available in the recent past from Tiruvallur district and Bengaluru city revealed a decline of 6% and 4% per year respectively (Table 36.6).[56,69,104]

TB-specific Mortality Rates

Direct estimate of TB mortality is available from a prospective cohort study carried out in rural Bengaluru during 1960-68 when annual TB-specific mortality rate was estimated at 80 per 100,000 population.[105] An estimated 50% of the annual deaths are presently notified under the vital registration system in the country.[106] However, a Sample Registration System (SRS) was initiated in 1969 to count the births and deaths in a nationally representative sample of villages and urban blocks.[107] The sampling frame for the selection of areas to be included in SRS and the numbers of sampling units to be selected is revised every ten years after the completion of each census. The SRS data provides useful information on crude birth and death rates and the infant and maternal mortality rates. The data on the causes of death is published as a separate report. TB accounted for about 6% of all deaths during 2001-03.[108] A verbal autopsy-based study in Chennai revealed TB mortality rate at 152 per 100,000 population among males and 43 per 100,000 among females.[109] A national level study to find out the COD for 1 million deaths is currently in progress.[54]

WHO Estimates

In the year 2008, there occurred about 2 million TB cases in India, which amount to 20% of the incidence cases worldwide.[1] There has been a significant decline in the prevalence of TB from 340 per 100,000 population during

TABLE 36.5: ARTI surveys carried out in India, since 1990

Area	*Year of survey*	*Sample size*	*Age group*	*ARTI (%)*
Bengaluru city[69]	1998	4936	5-8	2.2
	2006	3354	5-8	1.5
Rural areas, Tiruvallur district, Tamil Nadu[56]	1999-01	12854	0-9	1.6
	2004-05	8668	0-9	1.4
	2001-03	8329	0-9	1.2
Orissa- state level survey[98]	2002	10626	1-9	1.7
Andhra Pradesh-state level survey[99]	2005-06	3636	5-9	1.4
Khammam, Andhra Pradesh[100]	2001-02		5-7	1.5
Zonal level surveys (4 zones)[96]	2000-03	N. Zone-51380 W. zone-51733 E. Zone-42836 S. Zone-52300	0-9	N. Zone-1.9 W. Zone-1.6 E. Zone-1.3 S. Zone-1.0
Kerala--state level survey[101]	2006	4821	5-9	Not available*
Chennai city[102]	2006	7008	1-9	2.0
Tribal areas, Madhya Pradesh[103]	2006	4802	1-9	1.3
Car Nicobar[84]	2001-02	2708	0-9	2.1

*Due to absence of a cut-off point on frequency distribution of tuberculin reactions.

TABLE 36.6: ARTI trends in India

Area	*Study period*	*Per year decline in ARTI*
Rural Bengaluru[21]	1962-1984	3%
Chingleput[20]	1969-1984	0%
Bengaluru city[69]	1998-2006	4%
Thiruvallur[56]	1999-2005	6%
Peri-urban Bengaluru villages[104]	1992-2006	3%

1990 to 190 during 2008.[3] The TB mortality rates declined from 40 per 100,000 population in 1990 to 23 in 2008.[3] These trends may be related to a combination of improvements in living conditions on an average and the implementation of Revised National TB Control Programme (RNTCP) based on DOTS, and now the Stop TB Strategy. Treatment success of 80% and above has been consistently achieved among the cases treated by DOTS and there has been continuous improvement in case detection rates. During 2008, the overall case detection rate was 69% and the treatment success rate for the cohort of new smear-positive cases registered for treatment during 2007 was 87%.[3] However, the incidence has remained stable during this period at 170 per 100,000 population per year.[3]

Multidrug-Resistant TB

The study of proportion of MDR-TB cases and the proportion of all TB cases attributable to HIV infection is an integral part of the description of epidemiological situation of TB. Several drug resistance surveys conducted in India recently have revealed that about 2 to 3% of new PTB cases and 12 to 17% of retreatment cases are MDR-TB (defined as resistance to at least INH and rifampicin).[110,111] This amounts to 1,11,000 MDR cases emerging every year in India, which comprise about 30% of all MDR-TB cases globally.[111] In a study among patients from tertiary care centers, 4.6% of MDR cases were found to be Extremely Drug Resistant (XDR) defined as resistance to both rifampicin and isoniazid, as well as to any one member of the quinolone family and at least one of the parenteral second-line anti-TB injectable drugs, i.e. kanamycin, capreomycin or amikacin.[112] The sentinel surveillance of HIV seroprevalence among TB cases showed that about 6.7% of the incidence TB cases during the year in India were HIV positive.[3]

Prospects for TB Control in India

If changes in prevalence and mortality between 2001 and 2006 estimated as per WHO model continue in future, then MDG targets for India for these two parameters are likely to be met by 2015.[111] The average ARTI of 1.5% in the county computed during the nationwide survey in 2000-2003 implies that about 1,500 individuals for every 100,000 population acquire new tuberculous infection every year.[113] This adds to the total pool of infected people potentially at the risk of developing TB in future. Thus, new TB cases shall continue to emerge in large numbers for several years to come. However, there is reasonable evidence from tuberculin surveys in limited geographical areas about the declines in the transmission of infection as a result of DOTS. Therefore, it is possible that the incidence would start falling once the cohort of older people with the higher prevalence of infection is replaced by cohort of younger people with lower prevalence of infection.

Achievement of targets for case finding and treatment success consistently over next 10-12 years would lead to significant reduction in the disease burden. However, an increase in seroprevalence of HIV and multidrug-resistance TB is likely to have opposing influence on epidemiological trends of TB.

GLOBAL TRENDS OF TUBERCULOSIS

During the first half of the 18th century, TB mortality rates as high as 900 per 100,000 population per year were recorded in England. The TB mortality rates peaked in most Western European countries around the beginning of the 19th century and a few decades later in Eastern Europe.[38] In the 20th century, the morbidity and mortality rates declined considerably in most of the developed countries of North America and West Europe.[38,114] For example, the incidence fell by 58% in Denmark within a time period of 20 years from 1921 to 1940.[115] The trends were accompanied by a parallel decline in the risk of infection and consequently in TB among children. The ARTI rates fell at the rate of 5% or more per year in the most European countries.[116-118]

The decline was attributed to improvements in socio-economic and living conditions. The little information that is available from the developing countries revealed no downward trend during the first-half of 20th century.[118] For example, TB mortality in Alaska, accounting for about 35% all deaths remained constant at 65 per 100,000 population from 1920-1950.[119]

From the middle of the 20th century, the rate of decline in the North American and Western European countries hastened when chemotherapy for tuberculosis became increasingly available.[118] Some of these countries recorded declines of 10 to 15% per year in case notification rates and ARTI up to 1980s, underline the potential of success in TB control.[90,115, 116,118,119] There was more rapid decline among children and young adults. In contrast, the TB situation remained stable in most developing countries despite the introduction of chemotherapy.[118] This was primarily due to the poor implementation of anti-TB activities. The ARTI rates during this period were 50-100 times of that in developed countries.[118]

The declining trend of TB in the industrialized countries and in some of the middle-income countries witnessed a reversal after mid-eighties, as a result of the advent of HIV epidemic and other sociodemographic factors. These trends can be most appropriately illustrated by the TB situation in USA where, after a dramatic decline in the incidence of TB during most of the 20th century, there occurred a 20% increase in notification rates from 1985 to 1992.[120] Most of the increase occurred in the heavily populated urban areas, which had the highest numbers of immigrants from countries with high prevalence of TB. Significantly, the median age of persons with TB decreased from 49 years in 1985 to 43 years in 1992.[120] Additional factors responsible for the rising trend of TB were increase in cases of MDR-TB mainly in the urban and minority population, rising numbers of intravenous drug users with high prevalence of HIV infection, and non-adherence to chemotherapy by homeless persons.

Increase in the TB incidence was also observed in Eastern Europe primarily due to civil strife accompanied by economic difficulties and breakdown of health care and drug supply system.[115] While resurgence took place in the developed world after the years of continuous decline, there was further worsening of the TB problem in developing countries. The advent of HIV/AIDS epidemic in many countries was strongly associated with increasing TB incidence with maximum impact in countries with high HIV prevalence rates. There were 3-4 fold increases in case notifications in countries most affected by HIV, such as in sub-Saharan Africa over a period of 1-2 decades.[121, 122] HIV seroprevalence rates of more than 40% among TB cases are now common in some of these countries.[121, 122] TB became the most common opportunistic disease associated with HIV.[123] In most countries with high HIV prevalence, e.g. Zambia, there has been a decline in life-expectancy with concomitant increase in TB incidence.[124] High rates of HIV prevalence and TB reported from Northern Thailand and Southern American countries.[125,126] An increasing trend of HIV seropositivity rates among TB cases has also been observed in India.[127]

Fortunately, with the introduction of DOTS, under sustained control program, the TB rates have started declining again from the mid-1990s in the developed countries which had witnessed resurgence only about a decade earlier.[128] The decline in MDR-TB was in fact faster than in the drug-sensitive TB. Of late, the community-based studies in India and Indonesia have demonstrated significant declines in the prevalence of TB.[56,129] In China, which is the second highest TB burden country after India, a decline of 32% in prevalence of bacteriologically positive pulmonary TB has been observed between the two surveys carried out in 1990 and 2000.[59] A similar decline of about 30% in prevalence of bacteriologically positive pulmonary TB was observed between two surveys carried out in 1997 and 2007 in Philippines, another high burden country.[130] The annual WHO estimates also demonstrate a drastic reduction in prevalence in most countries of the world, after implementation of DOTS. Trends in Americas have been strongly correlated with coverage of prevalence with DOTS.[128]

Based on detailed analysis of notification data, the incidence of smear-positive TB in Peru is estimated to have declined at the rate of 6% per year between 1991 and 2000.[131] There are signs of decline in TB incidence in some of the areas where a reversal of HIV epidemic has been witnessed in the recent period. The declining trend in China and Peru is attributed to not only TB control programs, but also improvements in general health and socioeconomic status of their population.[128] The declining trends in TB incidence in some countries are related to life-expectancy, under-five child mortality rate (both are indicators of general health status) and measles vaccination coverage (indicator of health services).[128]

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37

Risk Factors for Tuberculosis

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INTRODUCTION

Tuberculosis (TB) develops as a result of the progression of primary infection, exogenous reinfection or endogenous reactivation. Risk of active disease is highest immediately (within 24 hours) after infection is acquired, the accepted principle being that the risk of disease is greatest within first 2 years following infection, which starts to level off after about 7 years, remaining low and unchanged over the following decade and usually during lifetime. Also, if the infection is acquired during childhood, the lifetime risk of progression from infection to disease is around 10%.[1] The development of tuberculosis in man is essentially a two-stage process in which a susceptible person exposed to an infectious TB case becomes infected and may later develop the disease. In individuals infected with *Mycobacterium tuberculosis*, any condition modifying the balance established in the body between the host's immune defences and the tubercle bacilli can have an impact on the risk of developing the disease. Different factors both "intrinsic" and "extrinsic" to the host can variously affect an individual's susceptibility to develop TB (Table 37.1).[2,3]

TABLE 37.1: Risk factors for tuberculosis

A. Underlying Medical Illness
  a. HIV infection
  b. Diabetes
  c. Transplantation
  d. Silicosis
  e. Malignancy
  f. Gastrectomy
  g. Jejunoileal bypass surgery
  h. Chronic renal failure
  i. Malnutrition
  j. Immunosuppressant/corticosteroid treatment

B. Sociodemographic Factors
  a. Age
  b. Overcrowding
  c. Homelessness
  d. Correctional facilities and prisons
  e. Intravenous drug abuse
  f. Alcohol abuse
  g. Immigration from endemic areas
  h. Smoking
  i. Poverty
  j. Malnutrition

C. Host Genetic Factors
  a. Polymorphism in NRAMP1 gene
  b. Vitamin D receptor gene
  c. Gamma interferon signaling
  d. TNF receptor gene

RISK FACTORS OF DEVELOPING TUBERCULOSIS

Some of the known important risk factors are discussed below:

Underlying Medical Illnesses

Human Immunodeficiency Virus (HIV) Infection

Worldwide, tuberculosis is the commonest HIV associated disease of public health importance and HIV infection is the strongest risk factor for the reactivation of tuberculosis infection and progression to active disease. The effect of the HIV epidemic on TB has been well-documented, with incident rates of TB, particularly in Africa, rising rapidly as a result of HIV.[4] Among

9.27 million incident cases of TB in 2007, an estimated 1.37 million (14.8%) were HIV-positive. This number, although double the estimate of 0.7 million cases in 2006, that WHO published in 2008[5] does not mean that the number of HIV-positive cases of TB doubled between 2006 and 2007; rather, new data that became available during 2008 have been used to estimate both the number of HIV-positive TB cases in 2007 and to revise the estimates of the number of such cases that occurred in previous years. The global number of incident HIV-positive TB cases is estimated to have peaked in 2005, at 1.39 million. In 2007, as in previous years, the African Region accounted for most (79%) HIV-positive TB cases, followed by the South-East Asian Region (mainly India) with 11% of total cases, South Africa accounted for 31% of cases in the African Region.[4] Around 0.45 million patients co-infected with HIV died of TB in 2007; tuberculosis is also the leading cause of death in patients living with HIV, even in those receiving antiretroviral therapy.[4,6]

Direct estimates of the prevalence of HIV in TB provide strong evidence that the risk of developing TB in HIV-positive compared with HIV-negative (the incidence rate ratio or IRR) is higher than previously estimated. The IRR was estimated as 20.6 (95% Confidence Interval (CI) 15.4–27.5) in 2007 in countries with a generalized HIV epidemic (i.e. countries where the prevalence of HIV was above 1% in the general population), and 26.7 (95% CI 20.4–34.9) in countries where the prevalence of HIV in the general population was between 0.1% and 1%; and 36.7 (95% CI 11.6–116) in countries where the prevalence of HIV in the general population was less than 0.1%. These IRR estimates compare with previous estimates of 6, 6 and 30, respectively.[4]

The impact of HIV infection on tuberculosis pandemic is multifold. The risk of active TB doubles in the first year of HIV coinfection while the risk of developing active disease in those who have Latent TB Infection (LTBI) is 10% per year.[7,8] However, the impact of HIV infection on TB is not limited to the reactivation of LTBI. It has been shown in several studies that HIV-infected patients, who at any point of time, become infected or reinfected with *M. tuberculosis,* progress faster to full-blown disease than HIV-negative individuals who develop tuberculosis.[9-12] Thankfully, however, HIV-infected tuberculosis patients do not appear to be potent transmitters of *M. tuberculosis*, the fact being substantiated by numerous household contact studies which have consistently shown that HIV-infected patients with tuberculosis are less likely to transmit tubercle bacilli to their close contacts than HIV uninfected individuals with tuberculosis.[13-16] HIV-TB coinfected individuals have reduced survival[17] and are at higher risk for subsequent opportunistic infections.[18] In overcrowded and poor living conditions, the combined effect of the two epidemics is magnified as evidenced by more than 2,000 per 1,00,000 population prevalence rates in certain South African communities.[19,20] Added complications in coinfected individuals include drug-resistant TB and immune reconstitution inflammatory syndrome.[21] The emergence of drug-resistant TB in countries with a high HIV prevalence poses an additional public health threat, not only to people with HIV, but also to the broader community.[8]

Tuberculosis is the prototype of infections that require a cellular immune response for their control.[22] All persons have a native population of lymphocytes, mostly $CD4^+$ cells bearing αβ T-cell receptors, capable of recognizing mycobacterial antigens, processed and presented by macrophages. In tuberculin-positive patients (those who have been infected with *M. tuberculosis*), endogenous foci may reactivate repeatedly and active CD4 surveillance is mandatory to maintain quiescence. As the CD4 levels fall in HIV-infected patients, both in early (CD4 > 300 cells/mm^3) and late (< 200 cells/mm^3) stage of the disease, the chances of both endogenous reactivation and exogenous reinfection increase substantially. The earliest description of tuberculosis in Acquired Immunodeficiency Syndrome (AIDS) patients emphasized the increased risk of reactivation of remote infection due to progressively compromised immunity. Studies carried out in Haitians, all of whom were likely to be infected with *M. tuberculosis* in childhood, showed that AIDS was associated with development of active tuberculosis in 60%.[23] Subsequent studies in methadone clinic patients in the New York City who were HIV-positive and tuberculin-positive revealed, that tuberculosis developed in 8% of the clinic patients per year.[8] These studies thus suggest that nearly all tuberculin-positive patients with HIV infection eventually develop active tuberculosis unless either HIV or tuberculous infection or both are effectively treated or some other fatal complication of AIDS occur.

The clinical picture of tuberculosis in HIV infection is defined by the degree of immunocompromise.[24] The clinical spectrum ranges from a negative tuberculin sensitivity test result, greater incidence of extra-pulmonary disease (>50%), middle and lower lung zone involvement and absence of cavitation to positive tuberculin test result, cavitatory disease (less than 10% to 15%), predominant extra-pulmonary involvement and a diffuse rapidly progressive disease, which is often fatal. Management of these patients may be further complicated by concomitant intravenous drug use and homelessness. Failure to isolate and treat these patients under supervision is a major contributor to the outbreak of Multidrug-Resistant Tuberculosis (MDR-TB) in this population. Directly Observed Treatment Short-Course (DOTS) is especially important in coinfected individuals to ensure drug compliance, which is otherwise poor.

Diabetes

Physicians have noted the relationship between diabetes and tuberculosis since ancient times; perhaps the earliest was by Susruta, the Indian physician in 600 AD. Avicenna too had noticed phthisis complicated diabetes and that the presence of diabetes resulted in an increased risk of developing TB.[25] However, it has gone unnoticed and in the most recent national guidelines, has only been mentioned as something needing more research.[26] If not acknowledged appropriately, the association is believed to pose a threat, both to the successful TB control and to the treatment of diabetes.[27] Several large studies have demonstrated the increased risk of tuberculosis in patients with diabetes. In Korea, a 3-year longitudinal study involving 8,00,000 civil servants showed that the risk-ratio of TB in diabetic patients versus non-diabetic controls was 3.47 (95% CI 2.98–4.03).[28] From the UK General Practice Research Database, which included records from over 2 million patients, Jick and colleagues[29] identified all cases of TB reported between 1990 and 2001 and found that the adjusted odds ratio (adjusted for age, sex and practice) for TB was 3.8 (95% CI 2.3–6.1) for diabetic patients compared with those without diabetes. In Hong Kong[30], in a 5-year study of 42,000 elderly individuals, the adjusted hazard of active TB was higher in diabetic patients than in individuals without diabetes (1.77; 95% CI 1.41–2.24), but this increased risk was only present in those with hemoglobin A1c concentrations greater than 7%. Indeed, a recent large meta-analysis[31] showed that diabetic patients were 3.1 times (95% CI 2.27–4.26) more likely to have TB than controls with higher effect sizes in non-North American population. The presence of diabetes was found to increase the risk of contracting tuberculosis by 1.5 to 7.8 fold in various studies, being highest in the younger age group without any influence of gender.[32,33] Stevenson et al.[34] estimated that the population attributable risk for tuberculosis from diabetes was 14.8% of incident tuberculosis cases and about 20% of sputum-positive cases in India. Insulin dependence suggestive of a severe diabetes and a higher HbA1c as a marker of poor glycemic control have been found to be associated with a higher risk of tuberculosis.[32,35] In the setting of the increasing overlap of population at risk for both diseases, the combination of TB and diabetes mellitus represents a worldwide health threat.[36]

TABLE 37.2: Possible mechanisms underlying increased risk to tuberculosis in diabetics

1. Impaired phagocytic activity of monocytes/macrophages
   - Impaired chemotaxis
   - Impaired phagocytosis
   - Impaired activation
   - Impaired antigen presentation by phagocytes in response to *M. tuberculosis*
2. Altered polymorphonuclear cell function
3. Impairment in T-cell production of gamma interferon
4. Impaired T-cell growth, proliferation and function
5. Diabetic microangiopathy induced alteration of local response.

Several mechanisms have been put forward to explain the phenomenon of increased risk of TB in diabetes (Table 37.2). Alterations in pulmonary immune cell function reduced activity of monocytes/macrophages; impaired activation, chemotaxis and antigen presentation leading to ineffective phagocytosis of intracellular organisms, reduced lymphocyte function and impaired T-cell growth, proliferation and function may all be responsible. The varied effects of diabetic microangiopathy on the capillaries of alveolar septa and arterioles may also affect the local response to infection.[37-39]

Evolution of the symptoms and signs of tuberculosis in diabetic patients are same as that in non-diabetic patients. The coexistence is expectedly known to result in greater complications. The mortality of tuberculosis has been reported to be higher when complicated by diabetes and the disease tends to have increased severity characterized by cavitations, lower lobe involvement and smear positivity.[40,41] A higher risk of multidrug-resistant tuberculosis has also been reported in diabetics even as some other studies have shown no significant risk of drug resistance.[42-48]

It is unclear, whether the aggressive management of Diabetes Mellitus (DM) would improve treatment response. Since the causes of death are not reported in most studies, we do not know whether excess mortality is explained by increased severity of TB in diabetic or by the existence of comorbidities attributable to diabetes mellitus compounded by more advanced age.[36] People with DM may also be important targets for interventions such as active case finding and the treatment of latent TB. [27]

Organ Transplantation

Procedures employed to minimize the risk of rejection in transplant recipients produce an alteration of immune status in them, predisposing such patients to infections caused by both common and rare organisms. Tuberculosis associated with organ transplantation, occurs in an estimated 0.35 to 6.5% of organ recipients post-transplantation in the United States and Europe, the risk of TB in transplant recipients is estimated to be 20 to 50 times higher than in general population and mortality rates vary from 20 to 40%.[49] Nearly 49% of the US transplant recipients with TB have disseminated disease and 38% of them die.[49]

Risk factors for the development of TB in transplant recipients include previous TB infection, immunosuppressive treatment with OKT3 or anti-T cell antibodies, diabetes mellitus, chronic liver disease and coexisting infections.[49-52] Tuberculosis is rare after Hematopoietic Stem Cell Transplantation (HSCT) and ten times less frequent than in Solid Organ Transplantation (SOT), as HSCT recipients do not receive lifelong immunosuppression. Undergoing transplant in a country with a high endemic rate of TB is also an important risk factor.[53] Unrelated or mismatched related transplants, Graft-Versus-Host Disease (GVHD) and total body irradiation increase the risk of TB reactivation after HSCT.[54] The majority of TB cases among organ transplant recipients are caused by the activation of LTBI in the recipient. Once immunosuppressive medications are started to prevent organ rejection; a minority are attributed to donor transmission. In one international study, 4% of TB infections in recipients were considered donor derived.[49]

Clinical aspects of the disease includes a high incidence of extrapulmonary or disseminated tuberculosis (49%).[49] Among extrapulmonary cases presentations include gastrointestinal, hepatic, skin, muscle, osteoarticular, genitourinary, ganglia, central nervous system and other more uncommon sites of disease such as the larynx, tonsils or eyes.[49,55] In transplant patients, TB should be considered in the differential diagnosis of persistent fever, pneumonia, meningitis, septic arthritis, pyelonephritis, septicemia, graft rejection or bone marrow suppression. Clinicians should recognize that the presence of an unusual constellation of symptoms, particularly during the first few weeks after transplantation, raises the possibility of donor-transmitted infection or activation of LTBI. Even with a high index of suspicion, TB in an organ recipient can be challenging to diagnose 75 to 80% of organ recipients who developed TB, had a false-negative pretransplantation Tuberculin Skin Test (TST).[56] It is important to recognize that in this immunosuppressed population, symptoms of TB might be attributed to other potential complications, including organ rejection or other infectious diseases. Diagnosis of TB in an organ recipient, in the absence of clear risk factors or other evidence from pretransplantation screening, should prompt the investigation of possible transmission from the donor. Other recipients from a common donor might be at risk and should be evaluated for TB.

Investigation of epidemiological risk for LTBI is mandatory in transplant recipients. LTBI can be evaluated through TST. The sensitivity of TST is lower in immunocompromised hosts, induration of ≥ 5 mm, is considered positive.[57] In SOT, around 20% of the recipients test positive, the positivity being greater in liver transplant recipients (around 70%).[49] Positivity of 23% was observed among HSCT recipients.[58] It is important to highlight that the specificity of TST may be impaired in transplant patients from developing countries since a positive test may indicate infection with nontuberculous mycobacteria or previous vaccination with the Bacille Calmette-Guérin (BCG).[59] The role of TST, as well as of the new Interferon-Gamma Release Assays (IGRAs), such as the QuantiFERON test, in the evaluation of LTBI in transplant recipients has not been fully investigated. A recent meta-analysis suggests that IGRAs may be more sensitive than TST in immunocompromised patients suspected of having TB.[60]

Pretransplant evaluation of epidemiological risk of TB should be made for donors and recipients. Previous TB infection or contact with infected persons should be particularly investigated, as well as careful radiological evaluation should be done to check for images suggestive of previous healed TB.[61] Tuberculin skin test with 5 tuberculin units of purified protein derivative is recommended for transplant candidates, a negative test should not exclude the possibility of LTBI. If LTBI is suspected, treatment with Isoniazid (INH) should be started. A full 9-month course is recommended. Alternative schedules may be considered on individual basis. In HSCT recipients, the combination of pyrazinamide and rifampicin has shown significant liver toxicity and its use is not recommended.[62]

Silicosis

Silicosis, a fibrosing lung disease caused by the inhalation and deposition of crystalline silica particles, is the most prevalent pneumoconiosis.[63] The risk of developing pulmonary tuberculosis is reported to be 2.8 to 3.9 times higher for patients with silicosis than for healthy controls.[64-66] Patients with silicosis are also at a higher risk for extrapulmonary tuberculosis, the estimated risk being about 3.7 times higher.[65,67]

Local alterations in the lungs together with unfavorable conditions in the mines, inability to diagnose the disease rapidly and the high prevalence of TB in the population, are some of the factors responsible for the high incidence of this disease in this group of people. Important local alterations include the impairment of macrophage function (which plays a major role in the pathogenesis of the disease). Sublethal doses of silica dust also affect the ability of macrophages to inhibit the growth of *M. tuberculosis*.[68] Silica is reported to modify the immune response of the lungs, impair the metabolism/function of pulmonary macrophages and with frequent exposure, cause macrophage apoptosis.[67,68] These findings are consistent with observations that the incidence of tuberculosis is higher in dust-exposed workers, even in those without established silicosis, than in workers not so exposed. Surfactant protein A is also found to be high in BAL fluid of patients with silicosis. An excess of this protein seems to be associated with higher susceptibility to tuberculosis, possibly because it allows mycobacteria to enter the alveolar macrophages without triggering cytotoxicity and inhibits the formation of reactive nitrogen species by the activated macrophages.[69,70] The tubercle bacilli are also believed to remain encapsulated within the silicotic nodules, which would be responsible for the reactivation of tuberculosis in such patients.

Diagnosis of tuberculosis in silicotic patients is difficult since the symptoms are nonspecific. Moreover acid-fast stains of sputa of these patients are usually negative, probably because the tubercle bacilli do not reach the bronchial tree due to fibrotic changes. Chest roentgenogram can be of great value in the diagnosis. Radiographic criteria strongly suggestive of tuberculosis include the appearance of new infiltrates, cavities, pleural effusion, coalescence of nodules and development of bronchial stenosis.[68] Patterns suggestive of silicotuberculosis have also been recognized on chest CT scans. The principal findings consistent with active tuberculosis superimposed on silicosis are thick-walled cavities, consolidations, images presenting a tree-in-bud pattern, nodular image asymmetry and rapid disease progression.[71-73]

Longer therapeutic regimens with conventional antitubercular drugs are employed for the treatment of tuberculosis in these patients; the longer duration is necessitated because of the low penetration of the drugs into silicotic nodules. A study conducted in Hong Kong showed that 22% of the patients in the 6-month therapy group had bacteriological relapse in comparison to 7% relapses seen in patients in the 8-month therapy group, thus suggesting that the standard 6-month short course therapy is inadequate for these patients.[74] As a general recommendation, the sterilizing phase in these patients should be prolonged and they should be treated for at least 9 months. Moreover, therapy with rifampicin and isoniazid must be given for a minimum of 12 months, if pyrazinamide is not incorporated in the regimen.[68] Preventive chemoprophylaxis with INH has also been considered of great value in reducing the rates of active disease. One such study compared the treatment of 825 silicotic patients with 2,408 untreated silicotic patients. It was shown that preventive therapy with INH decreased the risk of developing active tuberculosis from 2.66 to 0.32%.[68]

The American Thoracic Society recommends that tuberculin skin tests should be performed in patients with silicosis. In cases of positive results (induration $\geq$10 mm) and after excluding active tuberculosis, the Society recommends that chemoprophylaxis should be instituted, using one of the four possible regimens: Isoniazid for nine months; isoniazid for six months; rifampicin and pyrazinamide for two to three months; or rifampicin for four months. The determination of bilirubin and hepatic enzyme levels in the initial evaluation is indicated only for individuals considered to be at high-risk for liver disease such as alcoholics, pregnant women and HIV-infected individuals.[57]

Malignant Disease

The synchronous occurrence of tuberculosis and carcinoma is unusual and the association of the two has baffled surgeons and physicians for over two centuries. Bayle first described the association of tuberculosis and carcinoma in 1810. He described “cavitation cancereuse” as one of the six types of tuberculosis, which appears to be the first published description of coexistence of the two.[75] The association of tuberculosis and cancer has been recorded in most of the organs. Kaplan et al. (1974)[76] reviewed 58,245 patients with cancer and identified 201 cases of coexisting tuberculosis. The highest prevalence was seen in patients with Hodgkin’s disease (96/10,000 cases) followed by lung cancer (92/10,000), lymphosarcoma (88/10,000) and reticulum cell sarcoma (78/10,000). Hematological malignancies have a higher incidence of tuberculosis than solid organ cancers.[77,78] Patients with hematological malignancies have impaired immunity, partly due to the disease process itself and partly due to cancer treatment, including chemotherapy, radiotherapy, long-term corticosteroid regimes, etc. Patients with leukemia are more prone to develop disseminated or extrapulmonary disease as compared to those with other hematological tumors.[77,79] Patients suffering from hairy cell leukemia have increased chances of developing tuberculosis, with incidences as high as 50%.[80] Lymphomas, notably Hodgkin lymphoma also placed an individual at greater risk of having these manifestations, although extrapulmonary tuberculosis in these patients is usually a focal disease.[81]

Tuberculosis in solid organ malignancies is mainly pulmonary, extrapulmonary/disseminated disease being less common.[77] Highest incidence has been seen in head and neck cancers, lung cancers and gastrointestinal malignancies.[77,81] In a recent case control study from Korea, the incidence of active tuberculosis was 3.07 per 1,000 persons per year against 0.7 amongst controls, showing an increased risk of developing tuberculosis (incidence ratio of 4.46).[82] The authors concluded that immune suppression by cancer or by anticancer chemotherapy increased vulnerability to reactivation of TB, especially in cancer patients with old healed TB. Lung cancer and pulmonary TB have been known to coexist. In some series, the relationship between these two entities was found to be more frequent than other associations.[77] The location of tuberculosis and lung cancer can either be same or different. Interestingly, if HIV infection is associated with lung cancer and tuberculosis, a normal radiographic pattern can be seen. Except for the increased incidence of the disease, TB in cancer patients does not seem to have different characteristics as compared to the general population.[77] A more severe pattern of disease is noted if cancer and tuberculosis appear in a sequential pattern, the reason being a greater debilitation of the patient during cancer.[77]

Gastrectomy and Jejunoileal Bypass Surgery

Subtotal gastrectomy and other gastric surgical procedures have been reported to be associated with an increased risk for tuberculosis since 1920s. The association was initially recognized at a time when gastric resection was widely performed for the treatment of refractory peptic ulcer disease. In recent decades, following the introduction of histamine type 2 blockers and proton pump inhibitors, gastric surgery has come to play a minor role in treating peptic ulcer disease. However, evidence that gastrectomy predisposes to the increased incidence of tuberculosis is highly suggestive, but not conclusive. Recent data suggest that gastrectomy patients are more predisposed to develop tuberculosis with an estimated two-to five-fold relative risk.[83-86]

Jejunoileal bypass surgery has been used increasingly in the recent decades to cause weight loss in patients of morbid obesity who do not respond to less drastic weight reduction measures. The average annual incidence of tuberculosis among bypass patients has been reported to be 27- and 63-fold higher than the incidence in comparison population.[87,88] Presumably, patients who are at greatest risk of developing tuberculosis are those who are already infected with tuberculosis at the time of the operation. However, none of the published reports provides data on the incidence or prevalence of disease among those infected or those uninfected, preoperatively. Nonpulmonary tuberculosis accounts for only 15% of the total cases in the general population, but 82% of cases in bypass patients have involved nonpulmonary sites. The reason for the increased risk of tuberculosis after bypass operation is unknown. Many patients become protein and zinc deficient postoperatively; both conditions are reported to adversely affect the cell-mediated immune responses.[89] The pathogenesis of the increased risk for tuberculosis after gastrectomy and bariatric surgery remains speculative. Confounding, attributed to factors, such as age, poverty, crowded living conditions, heavy ethanol consumption, nosocomial infection after surgery, severe weight loss caused by malabsorption and alkaline reflux gastritis, has been proposed.[83,84] The most widely cited hypothesis is that the increased risk of tuberculosis is attributed to rapid weight loss, malnutrition, and in some individuals, malabsorption. Tuberculosis occurs frequently in persons with protein-calorie malnutrition and resultant impaired cell-mediated immunity.[90]

As per the ATS/CDC guidelines,[57] individuals with weight loss of more than 10% of ideal body weight and those with gastrectomy or jejunoileal bypass surgery are considered at increased risk and should be offered treatment for latent tuberculosis infection if they have a PPD skin test reaction of 10 mm or more induration. Nine months of INH is now the preferred regimen for treatment of latent tuberculosis infection for most persons. Clinicians caring for patients, who have had gastric bypass surgery, need to be aware of the increased risk of tuberculosis in this patient population. Prompt diagnostic evaluation with chest roentgenogram, sputum examination, tissue biopsy and other appropriate studies should be initiated in patients with unexplained malaise, fever, cough and lymphadenopathy. In particular, a high level of clinical suspicion is needed for the diagnosis of extrapulmonary tuberculosis. Finally, because of potential problems with the malabsorption of oral drugs in patients after weight-reduction surgery, treatment should be coordinated with experienced tuberculosis control staff and monitoring of serum drug concentrations should be considered.

Sociodemographic Factors

Overcrowding

The most important determinant of infection is the closeness and the infectiousness of the source. *M. tuberculosis* infection is usually airborne; almost all infections are due to the inhalation of droplet nuclei that are infectious particles aerosolized by coughing, sneezing or talking. These particles are dry while airborne, remain suspended for long periods, get inhaled and reach terminal air passages. A sneeze can generate up to 40,000 droplets, which can evaporate to produce droplets of 0.5–12 mm in diameter. A cough can generate about 3,000 droplet nuclei, the same number as talking for five minutes (from Elsevier journal). A single cough, talking for five minutes and sneezing can generate equal number of droplet nuclei, which may be equal to 3,000 infectious droplet nuclei, or more.[91] The air in a room, occupied by a person with pulmonary tuberculosis, may remain infectious even after his/her absence.

Pulmonary tuberculosis fortunately is a disease with low infectiousness. Generally, prolonged contact and multiple aerosol inocula are required to establish infection. However, *M. tuberculosis* strains may vary widely in their transmissibility. In an outbreak in Kentucky, it was seen that people were infected in spite of the brief casual contact with the index case.[92] Closed spaces with little or no air circulation at all, favors the spread of tuberculosis. In USA, around 27% of household contacts of smear positive cases became infected, whereas rates as high as 80% were seen to occur in closed environments.[93]

Homelessness

With estimated prevalence of 1.6% to 6.8%, homelessness is regarded as one of the important risk factors for the development of tuberculosis.[94] The factors that contribute to an increased risk for tuberculosis among homeless persons include insufficient access to preventive services and health care as a result of financial, geographical and cultural barriers. Point prevalence of active TB as high as 968/1,00,000 homeless adults has been reported, nearly 100–300 times the nation wide prevalence.[95] Among homeless persons, the increased prevalence of conditions, which can suppress the immune system (like HIV infection, poor nutrition, untreated diabetes, COPD, alcoholism, illicit drug use and psychological stress) may increase the risk for active tuberculosis if infected.[96-99] Homeless persons also lack access to good health care and are highly mobile, they do not complete TB therapy and the likelihood of relapse, drug resistance and further transmission of tuberculosis among shelter residents thus increased. [97,99-101]

Clinical characteristics of TB in this group are similar to those in the general population and variations, if any, are due to the presence of concomitant factors such as HIV infection. Treatment of tuberculosis in this group of people should be using common therapeutic regimes.[94] Measures to curtail the spread of infection in these settings should be directed at rapid diagnosis and treatment of infectious cases, since establishing an effective prevention program is difficult in shelters.[102,103] Structural measures in shelters have also been considered as useful to prevent transmission of the disease; use of ultraviolet lamps to disinfect air and enhanced ventilation systems to reduce airborne transmission of the disease in some of them.[94] As seen with drug abusers, outcome of these homeless is dependent on compliance of therapy, which as expected is very low. DOTS is indicated for these difficult cases. Several incentives have been recommended, aimed at increasing the adherence to therapy, such as travel tickets, food, clothes or even money and have proven to be effective in increasing the compliance to drug therapy amongst these patients.[94]

Correctional Facilities and Prisons

Tuberculosis is a problem in correctional facilities and prisons; 3.7% of all the cases of tuberculosis in the United States in 1996 occurred amongst the residents of correctional facilities, with incidence rates of new cases in prison systems as high as 200 per 1,00,000 against the general population incidence of 8.0 per 1,00,000.[104-109]

Transmission of tuberculosis from prisons into surrounding communities has also been documented and therefore, correctional facilities may be important reservoirs of infection.[106] A prison was potentially linked to 9% of a state's tuberculosis cases during a 5-year period.[106] Incarcerated inmates have high rates of substance abuse, HIV infection, latent tuberculous infection, low socioeconomic status and other risk factors associated with active tuberculosis and hence have multiple factors operating for a higher risk of developing TB.

Drug Abuse

In recent years, drug abuse has emerged as a significant risk factor for the development of TB. Close association between HIV infection and intravenous drug abuse makes it difficult to differentiate between the independent roles of the two risk factors in the progression of TB. Apart from HIV infection, other factors that put drug abusers at increased risk include malnutrition, bad hygienic practices, antisocial behavior (e.g. criminality, auto-medication, and trading of pills to obtain money or drugs). Relation between tuberculosis and intravenous drug abuse has been well-known for many years.[104-113] A positive TST has been reported in up to 44% of HIV negative IV drug users and tuberculous disease has been reported in 6.8%.[104,105] On the other hand, several studies have shown drug abuse to be a statistically significant risk factor for tuberculosis in the general population.[106,107]

In HIV-infected drug abusers, the effects of HIV infection on the immune system often over-shadow other possible defects, which are contributory to increased risk of tuberculous disease. Nonetheless, immune defects can be found in HIV non-infected patients too. Due to the presence of concomitant HIV infection and several other infections, a high index of suspicion is required to diagnose tuberculosis in intravenous drug abusers. It should be a dictum to rule out tuberculosis in any such patient who presents with fever.[114] Screening of these patients for TB is also difficult owing to their anergy status because of HIV infection. A single skin test has previously been reported to be an unreliable predictor of development of TB and as such is not advocated in this patient population.[115] Instituting chemoprophylaxis in infected patients has been proved to prevent the development of active disease.[116-118] However, the same does not hold true for HIV anergic patients, in whom chemoprophylaxis does not reduce the incidence of disease; hence it is not indicated in these cases.[110,118]

Treatment of active disease has also been shown to be effective with some modifications in HIV patients keeping in view the possible drug interactions among the antiretroviral drugs and the anti-tubercular drugs.[16,44] Another major issue in treatment is that of non-compliance, which leads to increased chances of therapeutic failure among them with prolonged infectivity, increased rates of transmission and development of drug-resistant strains.[119] Measures for ensuring compliance in this group of patients have included forced confinement during treatment, but by far is the most effective and promising strategy.[119]

Alcohol Abuse

Alcoholism and alcohol intake are closely associated with tuberculosis.[120,121] In one hospital-based study, 49% prevalence of alcoholism was seen in patients with newly diagnosed tuberculosis.[122] The rate of active TB among alcoholics and drug abusers was 28 times higher than in general New York City population.[120] Alcohol intake was found to be associated with increased risk as well as poor compliance to treatment. These facts call for alcohol intervention campaigns along with tuberculosis control programs.[123]

Age

Among persons with tuberculous infection, rates of occurrence of diseases vary markedly with age. The case-rates are considerably increased amongst infants, young adults and elderly subjects. The reasons for the variations in age are as yet undetermined, but may relate to influences on the effectiveness of the immune response. Infection acquired early in life can progress to typical disease as the age advances. In the past, almost all patients were adolescents and young adults, but the recent years have witnessed a marked change in the clinical pattern of disease.

Infection in infants often results in disease; the younger the patient, the greater is the risk of progressive disease, until the age of 5 years. From this age onwards until puberty, there is relative resistance to the development of progressive disease, but not to infection. Disease confined to lungs in this age group usually heals spontaneously. Nonetheless, lymph nodes and bones may be involved. Short-term prognosis in these patients is good, although the frequency of relapse with chronic cavitary TB is high, especially during the more disease prone periods of adolescence and young adulthood.[118] Clinical disease that develops in adolescence and young adulthood may resemble childhood infection, but with less parenchymal and hilar calcification, this being particularly the case in dark-skinned races and immunocompromised patients, including those with AIDS.[24] Disease in this age group appears as chronic upper lobe tuberculosis with no clinical features of childhood disease. Tendency towards apical cavitation immediately after childhood infection appears after puberty and is marked in young adults.[57] Mostly, pulmonary TB in this age group is due to recent new infection rather than due to the progression of childhood infection, which is being substantiated by the fact that most young people in industrialized countries are tuberculin negative.

Infection acquired during the middle years of life has a much better prognosis, both long and short-term, than infection acquired in teens and in early 20s, presumably because of a reduced tendency to tissue necrosis.[118]

The incidence among women peaks at 25 to 34 years of age, rates being usually higher in women in this age group, while in older age groups, the opposite is true.

Immigration

Prevalence of tuberculosis is higher in the African and the Asian countries. Migratory movements of people between countries have become more frequent, favoring the transmission of infectious diseases from one place to another. These unrestricted movements from high prevalence areas can affect the control programs of other countries. As a matter of fact, immigration has been considered as a major cause of resurgence of tuberculosis in the Western countries.

Illegal immigration poses more threats to the control of potentially infected population. A study conducted in Spain showed that 78% were amongst illegal immigrants with active disease. Other factors that complicate the management of TB in this population include the language barriers, overcrowding, poverty, fear to seek professional advice and frequent imprisonment. All these factors affected compliance since adherence to therapy was even lower in infected patients without active disease.[124] However, strict follow-up and other complementary measures (e.g. use of patient's language for examination) increased the compliance of tuberculous patients to 78%.[124,125]

The potential transmission of tuberculosis from immigrants to local population is a theoretical risk. A molecular epidemiology analysis, making use of Restriction Fragment Length Polymorphism (RFLP) and spoligotyping, found only nine minor clusters in both Danish and immigrant patients, thus depicting only minor transmission between these population.[126] However, many other clusters were found suggesting the existence of predominant strains between immigrants and transmission between them.[125,126] A possible explanation is the low social contact between these two communities. Several other reports suggest that tuberculosis in immigrants is the result of reactivation and not of primary disease due to recent infection.[113,126-128] Drug resistance is an additional problem in infected immigrants on account of the multidrug resistance in their native countries. Antimicrobial testing may hence be indicated in such patients for appropriate therapy.

Others Risk Factors

There are numerous other factors that favor the progression of infection to active disease, notable among them being smoking, poverty and malnutrition, renal failure, immunosuppression and host genetic factors. Each of these factors places an individual at an increased risk of developing tuberculosis; nonetheless even in the same person, interplay of all or some of the above mentioned factors are seen on occasion.

Tobacco Smoking

An association between tobacco smoking and tuberculosis has been debated for over a hundred years and there is considerable evidence confirming the presence, strength and consistency of this association and the different levels at which it operates. Recent research demonstrates a direct connection between smoking and TB. Smoking increases the risk of latent TB infection by nearly two times, as well as increasing the risk of active TB by around two and a half times.[129] The basis of these findings was a large-scale meta-analysis, in which studies from 14 different countries were assessed.[129] Other research has produced similar results, with smokers having a relative risk of around twice that of nonsmokers for acquiring TB.[129-131] Smoking has also been found to lead to increased severity of the disease, longer hospital stays and decreased survival rates.[132,133]

Many physical and social factors associated with cigarette smoking are also known to contribute in the development of tuberculosis;[130] immunosuppression, old-healed fibrotic lesions, unemployment, and lower socioeconomic and education status being some of them. It has been shown that tobacco smoking causes pulmonary impairment and smoking would be expected to increase the risk of pulmonary impairment due to tuberculosis.[134] Indoor air pollution from passive smoking is another strong factor in causing tuberculosis. Chronic exposures to smoke from biomass fuels is another contributory risk for tuberculosis, as well as other lung diseases particularly in immigrants.[135-139] A history of such biomass smoke exposure may be an important risk factor for pulmonary tuberculosis and abnormal pulmonary function following its microbiological cure. However, these possibilities need to be substantiated with further research.

Poverty

Growing poverty is an important variable that globally prevents the decline in the number of cases due to tuberculosis. Poverty has always been associated with tuberculosis.[140] A decline in the incidence of tuberculosis seen in the European countries in 19th century was parallel to the reduction of poverty. Economic downfall in Russia in the last decades has been linked to the increased incidence of tuberculosis in that country.[141] Along with HIV/AIDS and malaria, tuberculosis is implicated as one of the three major diseases associated with poverty.

Malnutrition and Immunosuppression

Immunosuppression and malnutrition form the basis for many, if not all, the factors to produce the varied effects of this disease. The population of patients whose host defences are compromised by the underlying diseases or by the medical treatments continue to increase; posing new and complex threats to the ongoing control measures. Both these factors play a pivotal role, not only in the reactivation of latent infection, but also in acquiring primary infection. Contributions of these variables in the development and progression of tuberculosis have already been described under the relevant headings.

Chronic Renal Failure

Chronic renal failure impairs immune function and is associated with an increased incidence of TB. Rates of tuberculosis are 10- to 25-fold amongst patients of renal failure on renal replacement therapy (hemodialysis or continuous ambulatory peritoneal dialysis), equating to incidence rates of approximately 250 per 1,00,000 per year.[142-145]

Ethnic and Genetic Factors

It has long been recognized that certain population appears to have a high degree of vulnerability to tuberculosis. Extreme susceptibility to the disease has been observed in Eskimo population in North America, Yanomami Indians in the Brazilian Amazon and black population in the United States.[146-148] Host genetic factors also influence disease expression, with reports from India suggesting a clear association between HLA-DR2 and increased risk of progression to advanced disease.[149] It has also been shown that DRB1*1501 allele correlates with advanced disease and treatment failure and that DRB1*1502 correlates with decreased risk.[150] A clue to the genetic basis of resistance was provided by the studies of Gros and colleagues who identified a strain of mice with exquisite vulnerability to overwhelming infection with certain bacteria and some strains of mycobacteria , particularly *Mycobacterium bovis*.[151,152] Eventually, the genetic basis of this susceptibility was mapped to a locus encoding a gene on murine chromosome 1, initially called *Bcg,* then renamed *Nramp1*, responsible for the production of a so-called natural resistance-associated macrophage protein.[152]

Several polymorphisms of the human *Nramp1* gene have been identified and population-based studies in several regions have been conducted, which have identified increased relative risk for moving from latent infection to active disease associated with certain polymorphisms.[153] However, the risk attributable to these polymorphisms is relatively small, and it is clear that *Nramp* alone explains only a portion of genetic susceptibility to tuberculosis. Several other genes and gene families, including those for vitamin D receptors and the components of IFN-γ–signalling pathways, have also been studied for their role in susceptibility to tuberculosis.[154-155] A recent study has concluded that a variation in the 3' untranslated region of the tumor necrosis factor receptor superfamily member 1B gene, which has been shown to be implicated in messenger ribonucleic acid destabilization, contributes to tuberculosis susceptibility.[156] These investigation clearly suggests that resistance or susceptibility to tuberculosis is a complex genetic trait and it is highly unlikely that there is a single dominant genetic factor involved.

In conclusion, the mere fact that more than a quarter of the world's population is infected with *M. tuberculosis* and the active disease remains a worldwide pandemic in spite of the availability of effective antitubercular drugs, bears testimony to the fact that risk factors of TB continue to pose a big challenge. The presence of a large number of these variables is an important determinant of the occurrence of TB, as well as of its clinical spectrum and course.

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Mycobacteria: An Overview

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INTRODUCTION

Mycobacterium tuberculosis (*M. tb*) is a gram-positive, nonmotile acid-fast bacillus **(**retention of carbol fuchsin dye even after treatment with acidic alcohol due to the presence of waxy mycolipids in its cell wall), which occur in the form of pleomorphic non-sporulated rods.[1] It belongs to the actinomycetes group with a length of approximately 1–4 µm and diameter of 0.3–0.6 µm. In smears stained with carbol fuchsin and examined under light microscope, the tubercle bacilli typically appear as pink colored straight or slightly curved rods.[2] *M. tuberculosis*, like any other bacteria, has a life cycle consisting of lag, log, stationary and death phases. It is an obligate intracellular, slow growing aerobe that divides every 16–20 hours and has DNA with a high Guanine-Cytosine (GC)-content (60 to 70%).

Cell Wall Structure

Mycobacterium has an extremely uncommon cell wall structure; up to 60% of the mycobacterial cell wall is composed of lipids that consist basically of uncommonly long-chain fatty acids with 60 to 90 carbons, denominated as mycolic acids.[3] A far more distinctive feature is that mycolic acids are branched fatty acids that have a short and a long branch, with 22 to 24 and 40 to 64 carbons, respectively; they are covalently linked to the polysaccharide that composes the cell wall, the arabinogalactan, which in turn is attached to peptidoglycan by a phosphodiester link.[3] This unusually impermeable cell wall of mycobacterium is thought to be advantageous in withstanding weak disinfectants and surviving in a dry state for weeks,[2] in stressful conditions of osmotic shock or desiccation, as well as contributing to its considerable resistance to many drugs.[1]

Mycobacterial Groups

The most important of mycobacterial group is *Mycobacterium tuberculosis* complex (MTC), which includes *M. tb*, *M. leprae, M. bovis* and *M. africanum*. *M. tuberculosis* and *M. leprae* cause tuberculosis and leprosy, respectively, in humans. *M. bovis* causes tuberculosis in cattle and in humans. Some mycobacteria are saprophytes (i.e. they live on decaying organic matter), and others are obligate parasites. Most are found in the soil and water in a free-living form or in the diseased tissues of animals. The other group “atypical mycobacteria” that is different from typical MTC on the basis of their *in vitro* characteristics is the Nontuberculous Mycobacteria (NTM). In 1950s, it was divided into four categories on the basis of Runyon classification: Photochromogens, that produced pigment only when exposed to light, e.g. *M. kansasii, M. marinum*; Scotochromogens, produced pigment irrespective of light exposure, e.g. *M. scrofulaceum, M. xenopi*; Nonchromogens, that did not produce any pigment, e.g. MAC, *M. terrae* complex; and rapidly growing mycobacteria, e.g. *M. chelonae, M. fortuitum*.

Mycobacterium avium and *Mycobacterium intracellulare* are closely related and commonly grouped to form the *Mycobacterium avium* complex (MAC) that is implicated as a potential pathogen for both animals and humans. In patients with HIV infection and/or AIDS, opportunistic infections, caused by the atypical mycobacteria, include the *M. avium* complex, *M. kansasii*, *M. fortuitum* and *M. chelonae*, although these species are essentially saprophytic. *Mycobacterium avium,* however, is the most clinically significant of the environmental mycobacteria that opportunistically infects susceptible humans having systemic immunosuppression.[4]

Mycobacterial Identification

The identification of different mycobacterial species is based on their phenotypic characteristics such as the growth rate, colony morphology and pigmentation. It is possible to distinguish *M. tuberculosis* and *M. avium* using culture and a battery of biochemical tests, but these are complicated and time consuming. The biochemical tests, which are specific for *M. tb* are niacin reduction test, nitrate test and urease test. Niacin test is considered a confirmatory test for *M. tb* identification as nearly all strains of *M. tb* are unable to metabolize niacin that is produced during mycobacterial growth. This excess niacin is then secreted into the surrounding medium where it can be detected. On the other hand, tellurite reduction and catalase tests are given positive specifically by MAC species.

Route and Spread of Infection

After inhalation of infectious droplets from an infected individual, mycobacterium normally enters the host via mucosal surface of the lung rich in oxygen supply, which provides a suitable environment for this slow replicating pathogen. The infection is established in the alveolar spaces, where phagocytic cells take up the bacteria. Ingestion of bacteria includes a rapid inflammatory response, which results in the recognition of the pathogen by adaptive immune response and thus leads to the accumulation of a variety of immune cells followed by the formation of granuloma, characterized by a relatively small number of infected phagocytes surrounded by activated monocytes/macrophages and activated lymphocytes.[5]

The complex immune responses mounted against *Mycobacterium tuberculosis* are well defined at cellular level and involve both innate and adaptive immune responses. One of the most remarkable features of the nonsporulating *M. tuberculosis* is its ability to remain dormant within an individual for decades before reactivating into active tuberculosis.[6] Latent TB is a clinical syndrome caused by exposure to *M. tuberculosis*, followed by the establishment of infection and host's immune response to control bacillary growth, forcing it into a quiescent state in the infected tissue. It is a state of mycobacteria surviving in closed necrotic lesions, characterized by a reduction of bacterial metabolism, as a consequence of the action of cellular immune response, and which can, to a certain point, contain, but not eradicate the infection.

Mycobacterial Genome

Sequencing of *M. tuberculosis* H37Rv (a virulent laboratory strain) by Cole and co-workers in 1998 revealed it to possess 4,411,532 bp, the second largest microbial genome sequenced at that time.[7] Mycobacterial genome is comprised of approximately 4,000 genes and around 4% of the genome is composed of Insertion Sequences (IS) and phages. Specificity of these IS elements act as a fundamental tool for the identification of different mycobacterial species. For example, IS6110 is the IS that is most abundantly present in *Mycobacterium tuberculosis* whereas IS1110 and IS1245 are specific to *Mycobacterium avium*. The sequencing of mycobacterial genome has provided an invaluable insight into the biological functions of this organism. The most important fact about *M. tb* genome is that approximately 8% of the total genome is involved in encoding the enzymes of lipid metabolism that indicates the significance of lipids in *M. tb* life cycle. On contrary, the genome surprisingly encodes a number of lipolytic proteins that may be important in host pathogen interactions.

Another important finding of *M. tuberculosis* genome project was the identification of large novel gene families PE and PPE, which have a conserved N-terminal region with the characteristic motifs ProGlu and ProProGlu respectively. Another such class of novel mycobacterial proteins is PE proteins that belong to Polymorphic GC-Rich Sequence (PGRS) family that has glycine as half of its amino acid content. These genes are considered to be important as a source of genetic diversity in *M. tb.*

Mycobacterium pathogenicity is attributed to the various genes and the cellular components they encode, which are known as virulence factors and the most important of these are the transcription regulators. Among transcriptional regulatory proteins, there are 13 sigma factors (e.g. Sigma A, F, E, H, etc.) that confer the transcriptional specificity to RNA polymerases. They basically control the mycobacterial response to external stimuli and are induced after the exposure of the organism to various environmental stresses such as high temperatures, detergents etc.[8] Other regulatory proteins include two component response regulators (e.g. PhoP, PrrA, mprA) that are activated by the environmental signals and also serve as transducer of these signals. These genes constitute approximately 0.6% of the total mycobacterial genome.

In addition to these proteins, a number of genes have been identified in mycobacterial genome that encode for various cell surface components that are particularly unique to pathogenic mycobacteria and are speculated to be *M. tb* virulence factors. In this category, those genes are included that code for the proteins expected to be exposed to the environment in which *M. tb* grows, e.g. surrounding culture medium during *in vitro* conditions and mycophagosome under *in vivo* conditions. These proteins are either secreted proteins or the enzymes that have an important role in the synthesis of various cell surface components. The secreted proteins are also called as Culture Filtrate Proteins (CFPs) due to their release in the culture media in which *M. tb* is grown. There are ~ 200 CFPs and these proteins are considered to be an early target of host immune system for the generation of anti-mycobacterial immune responses. Due to these facts, live attenuated *M. tb* vaccines are considered to be better than heat killed bacilli. Some immunodominant culture filtrate proteins include Antigen 85 complex, ESAT6, CFP10, HspX, etc.

Genomic Analysis

Comparative genomic analysis has revealed the existence of several *M. tuberculosis*-specific regions that have been deleted from Bacillus Calmette-Guérin (BCG). The *in vitro* attenuation of BCG was accompanied by the loss of several major deleted regions, which presumably contained virulence factors that would not be primed by a BCG vaccination. These antigens may include important protective T-cell antigens and are thus attractive vaccine candidates to supplement BCG vaccination or for the T-cell based diagnostic assays such as Interferon Gamma Release Assays (IGRAs). In total these major deletions include 129 Open Reading Frames (ORFs), which are missing in some or all strains of BCG.[9,10] The RD1 region, responsible for the initial attenuation of BCG[9] contains eight ORFs and is present in all clinical isolates of *M. tuberculosis* and *M. bovis*. These genes play an important role in virulence, demonstrated by the attenuation of *M. bovis* and *M. tuberculosis* strains that carry knockout mutations in the RD1 region.[11-13] Four highly reactive T-cell antigens, ESAT-6, CFP-10, TB27.4 and TB37.6, are encoded by neighboring genes in this region.[14-17]

To sum up, considerable information is now available in the literature regarding the chemical structure and immunological properties of *M. tb* unique cell envelope. Further, decoding of *M. tb* genome has provided us a wealth of information that can be important for the understanding of the molecular basis of *M. tb* pathogencity. This in turn can be translated into the development of new drugs, diagnostic tests and vaccines to combat tuberculosis and for the development of novel control strategies for tuberculosis.

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Immunology and Pathogenesis

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INTRODUCTION

Mycobacterium tuberculosis (*M. tb*), the causative agent of tuberculosis (TB) is one of the most successful human pathogens, which continues to kill more people than ever before worldwide. In approximately 5 to 10% of the individuals who get infected with *M. tb*, the bacteria continue to replicate, resulting into clinical TB. In the remaining 90 to 95% of the infected individuals, effective immune responses are elicited, which contain the bacteria in granulomas where they persist latently for several years. It is estimated that the one third of the world population is latently infected with *M. tb* and only 5 to 10% of these individuals develop TB some time in their lifetime when their immune system is compromised due to ageing, malnutrition, physical stress, immnuosupressive drugs and Human Immunodeficiency Virus (HIV) infection. Thus, it is clear that immune responses elicited in majority of *M. tb* infected individuals are sufficient for inhibiting the development of TB. This chapter is focused on providing the current understanding of the role of immune responses in pathogenesis of TB.

MYCOBACTERIUM TUBERCULOSIS INFECTION AND OVERVIEW OF IMMUNOPATHOGENESIS

Despite several recent advancements, the pathogenesis of TB is still not clearly defined. The current view of TB pathogenesis in human can still be pictured as a multiple-stage process, which was described over a decade ago using the rabbit model of TB.[1] Overall, it is a kind of tug of war between host immune system and tubercle bacillus (Fig. 39.1).

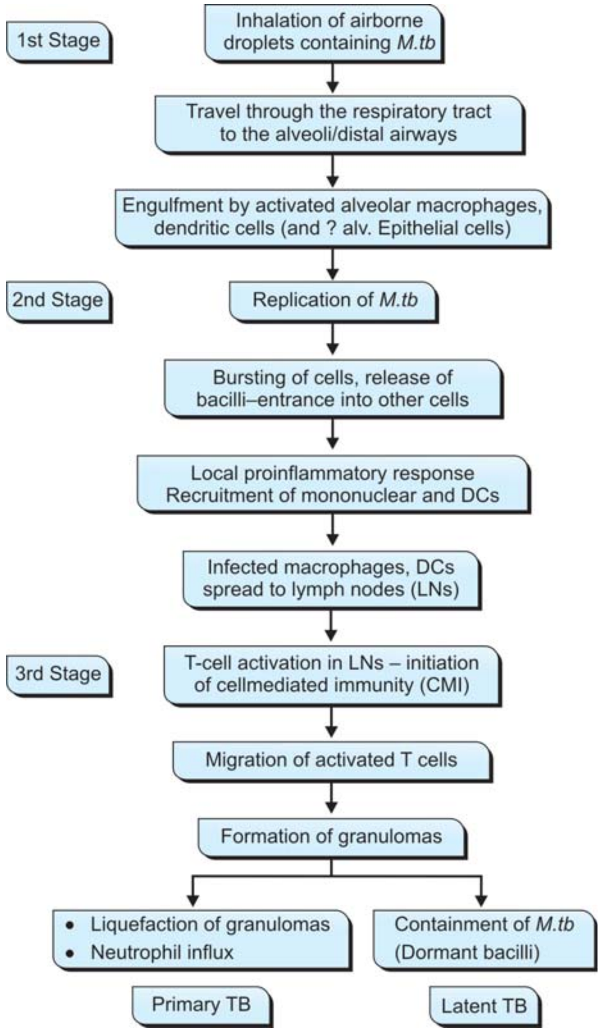
1st Stage
Inhalation of airborne droplets containing M.tb
Travel through the respiratory tract to the alveoli/distal airways
Engulfment by activated alveolar macrophages, dendritic cells (and ? alv. Epithelial cells)
2nd Stage
Replication of M.tb
Bursting of cells, release of bacilli–entrance into other cells
Local proinflammatory response Recruitment of mononuclear and DCs
Infected macrophages, DCs spread to lymph nodes (LNs)
3rd Stage
T-cell activation in LNs – initiation of cellmediated immunity (CMI)
Migration of activated T cells
Formation of granulomas
• Liquefaction of granulomas
• Neutrophil influx
Containment of M.tb (Dormant bacilli)
Primary TB
Latent TB

Fig. 39.1: Various stages in the pathogenesis of tuberculosis

The first stage starts with the inhalation of small airborne droplet (1–5 μm) containing *M. tb* expectorated by an individual with pulmonary or laryngeal tuberculosis while coughing, sneezing or talking.[2] These droplets can remain in the environment for several hours. Various factors that affect the likelihood and intensity of aerogenic transmission of *M. tb* from a TB index case to a contact person include (i) duration and intensity of the exposure; (ii) cough and sputum-related host factors; and (iii) virulence of *M. tb* strain.[3] The infectious droplets pass through the upper parts of the airways where the majority of bacilli are trapped in mucus and removed by cilia. The remaining droplets containing bacteria settle in the alveoli of distal airways where they are engulfed non-specifically by activated alveolar macrophages, Dendritic Cells (DCs) and probably by alveolar epithelial cells also.[4,5]

Being a successful human pathogen, *M. tb* has developed various strategies to avoid the intracellular killing mechanisms of host cells. Thus, the second stage begins with the replication of bacilli in alveolar macrophages, to some extent in DCs and possibly in alveolar epithelial cells. The bacilli multiply in these cells until they burst, the released bacilli are ingested by other alveolar macrophages. It is followed by a localized proinflammatory response, which directs the recruitment of mononuclear and DCs from neighboring blood vessels, providing fresh host cells for expanding the bacterial population and also induces alveolar macrophages to invade the lung epithelium.[6-9] The accumulation of these cells at the site of infection initiates the early lesion formation in the lung.[1,7,8] Simultaneously, the bacilli ingested macrophages and DCs disseminate to lymph nodes via the lymphatic system[2,7] or probably by the direct breaching of alveolar wall.[10]

The arrival of bacilli containing macrophages and DCs to the lymph nodes initiates the cell-mediated immunity (CMI), which is the beginning of the third stage of the pathogenesis. Recent studies have shown that T-cell activation starts in lymph nodes draining the lung and the development of CMI occurs between two to eight weeks postinfection in the majority of individuals.[2,11] The activated T-cells expand and migrate to the site of infection in the lung where they activate macrophages and induce the formation of granulomas. Initially, the granuloma is an amorphous mass of various cells, which becomes more organized and stratified structure with the development of acquired immune response.[6] In human, the granuloma is the hallmark of pulmonary TB, characterized by a central acellular eosinophilic region of caseous necrosis surrounded by the concentric layers of macrophages, large epitheloid cells, multinucleated giant langhans cells and lymphocytes.[12,13] The central necrotic core of the granuloma with sparse mycobacteria is surrounded by the two layers of cells.[13] The inner layer consists of mycobacteria containing CD68$^+$ Antigen Presenting Cells (APCs), epitheloid cells and giant langhans cells. This layer is also rich in CD4$^+$ T-cells and CD45RO$^+$ memory cells, but CD8$^+$ T-cells are rarely present.[13] The outer layer is found to contain mycobacteria infected APCs, numerous CD4$^+$ and CD8$^+$ T-cells and different types of B-cells (CD23$^+$ naïve, CD27$^+$ memory and plasma B-cells).[13]

Foamy macrophages (macrophages filled with lipid containing bodies) infected with mycobacteria have been demonstrated in the interface region flanking the necrotic core in the granulomas of TB patients.[14] It is suggested that these cells might act as a nutrient reservoir for persistent mycobacteria in the granuloma.[14] During the early phase of granuloma formation, the structure is highly vascularized. However, as granuloma matures, blood vessels start disappearing and a fibrous sheath of collagen and other extracellular matrix components form around macrophage rich layer leaving majority of lymphocyte outside.[15] At these "late" stages, the caseous portion of the granuloma becomes hypoxic; bacilli stop replicating and enter into a dormant phase.[16] Successful granuloma formation and maintenance leads to the containment of the pathogen.[12,17] The infected individuals at this stage show no overt sign of disease and categorized as individuals with latent TB.

In the majority of latently infected individuals, the bacilli remain dormant for their entire life and never cause TB. Unfortunately in some of these individuals, at the time when their immune system becomes weak, the tubercle bacilli out—compete the host immune response and start undergoing intracellular replication. This results into the extensive macrophage death and necrosis and the granuloma starts liquefying to form cavity, which permits the spill of numerous viable bacilli into airways.[12,15] Recent immunohistochemical analysis of the human tuberculous cavities showed that during liquefaction, the bacilli replicate rapidly in macrophages lining the surface of the cavities rather than in the extracellular acellular necrotic material, which was thought previously.[12,18]

In late-stage disease, neutrophil influx has also been implicated in the tissue damage and the dissemination of infectious bacteria into the airways in TB patients.[19] Despite evidence of T-cell responses in granulomatous layer of cavity to control bacillary growth, rapid replication of bacilli occurs in the cavity resulting huge load of bacilli in the respiratory tree.[18] This final stage of the TB pathogenesis completes with development of productive cough, which promotes the spread of viable bacilli in the aerosol droplets to other individuals. This process is an important step in the life cycle of *M. tb* for maintaining itself in human population.

IMMUNE RESPONSES TO TUBERCULOSIS

As described above, during the entire life cycle of the *M. tb* from the inhalation of a few bacteria in the lung to the generation of large number of bacilli in the airway by liquefaction of granuloma, there is a constant battle between *M. tb* and immune system. Although immune system is able to control infection in the majority of infected individuals, a small proportion of these individuals loose this battle and develop TB. Currently, the mechanism of immune defense against mycobacteria is not clearly known, however, our understanding has considerably increased due to elegant studies performed in the past decade. These studies have demonstrated that both innate and adaptive immune systems are involved in providing immunity against *M. tb* (Table 39.1). The following sections are aimed to describe current knowledge about innate and adaptive immunity to TB.

Innate Immunity

In general, innate immune system recognizes microbes immediately after infection by using receptors and induces secretion of a range of chemokines and cytokines, which direct the recruitment of various immune cells, including the phagocytic cells to the site of infection to kill the microbes. Although the mechanism of innate immunity during *M. tb* infection is poorly understood, the contribution of different components of innate immune system is discussed.

TABLE 39.1: Role of different immune responses in tuberculosis

A. Innate immunity
  i. Role of receptors
  ii. Role of macrophages and dendritic cells (DCs)
  iii. Role of Natural killer (NK) cells
  iv. Role of Neutrophils
B. Cytokines and chemokines bridging the innate and adaptive immunity
C. Adaptive immunity
  a. Cell-mediated immunity
    i. Role of $CD4^+$/$CD8^+$ T-cells
    ii. Role of regulatory T (T_{reg}) cells
    iii. Role of $\gamma\delta$ T-cells
    iv. Role of memory T (T_M) cells
    v. Role of unconventional T-cells
  b. Humoral immunity – Role of B-cell

Role of Receptors

Upon entry into the host lungs by aerosol inhalation, *M. tb* interacts with various receptors, such as the Pattern Recognition Receptors (PRRs), which include toll-like receptors (TLRs), Nucleotide-Binding and Oligomerization Domain (NOD)-like Receptors (NLRs) and dectin-1.[7,20] Other receptors involved in this interaction include Complement Receptor 3 (CR3), Mannose Receptor (MR), scavenger receptor, DC-Specific Intercellular-Adhesion-Molecule-3-Grabbing Non-integrin (DC-SIGN) on the surface of macrophages and DCs.

TLRs are transmembrane receptors present on macrophages, DCs, B-cells, specific types of T-cells, as well as on fibroblasts and epithelial cells.[21] The role of various TLRs in *M. tb* infection is not clearly understood, but it is likely that TLR2, TLR4 and TLR9 are involved in signaling innate immune responses against *M. tb* infection.[7] Several mycobacterial proteins, such as 19 kDa lipoprotein (LpqH), LprA, LprG, 38 kDa, PE-PGRS33, HSP65, HSP70, and lipids like Phosphatidyl-Myo-Inositol (PIM), lipomannan (LM), Mannose-Capped Lipoarabinomannan (ManLAM), Glycopeptidolipids (GPL) have been identified as ligands for TLR2 and TLR4.[7,22] The interaction of these mycobacterial ligands with TLR2 and/or TLR4 have been shown to induce the production of proinflammatory (TNF-α, IL-6, IL-12) and anti-inflammatory (IL-10) cytokines, DC maturation, cell apoptosis and mycobacterial killing.[7,22] TLR9 is found to recognize mycobacterial DNA and signals synthesis of proinflammatory cytokines.[7]

Activation of TLRs also leads to upregulated expression of the vitamin D receptor (VDR) and the vitamin D-1-hydroxylase genes resulting in to the conversion of provitamin D into the active form 1,25(OH)2D3. This leads to the induction of the antimicrobial peptides cathelicidin and β-defensin to kill intracellular mycobacteria.[23,24] In a recent study, when TLR2/4/9 triple-deficient mice and adaptor protein myeloid differentiation primary response protein 88 (MyD88) deficient mice were infected with *M. tb*, while growth of *M. tb* in the lung of TLR2/4/9 triple-deficient mice was observed to be similar to the wild type mice, bacterial load in MyD88 deficient mice was found significantly higher compared to wild type.[25] These results suggest that TLR 2, 4 and 9 are not critical for restricting *M. tb* growth, but MyD88, which is involved in TLRs signaling, plays an essential role in protection against TB.

Another transmembrane PRR; dectin-1 is found on macrophages and DCs and binds to β-glucan.[21] Although, dectin-1 plays an important role in antimicrobial response in fungal infections, involvement of dectin-1 in mycobacterial infection is not well studied[21] except that it is shown to be involved in eliciting proinflammatory response to *M. tb* infection.[26] It has also been demonstrated that NOD2, which belongs to NLRs family of cytosolic receptor proteins recognizes muramyl dipeptide and induces the production of proinflammatory cytokines following interaction with *M. tb*.[20] In addition, NOD2 and dectin-1 cooperate with TLR-2 during interaction with *M. tb* to activate NF-κB and induce proinammatory cytokines, including TNF-α, IL-1, IL-12, IL-18 and chemokines, which attract neutrophils, NK cells, T-cells, DCs and macrophages to the infection site.[20,27]

The interaction of receptors with *M. tb* results in not only the induction of proinflammatory cytokine response, but also serves as a mechanism for bacilli to avoid killing by innate immune cells. Amongst complement receptors, the phagocytosis of *M. tb* via CR3 has been found to prevent respiratory burst leading to phagosomal arrest of early endosomes and no inflammatory response.[7] Mannose receptor mediates phagocytosis by binding to ManLAM of *M. tb*, which results in the inhibition of phagosome-lysosome fusion leading to increased survival of *M. tb* in macrophages.[7] Number of host components, such as Surfactant Protein -A (SP-A) and -D (SP-D) also affect the uptake and survival of *M. tb* in macrophages.[7] Recent studies have shown that plasma membrane cholesterol is essential for the phagocytosis of *M. tb* by macrophages and it aids in preventing phagosome-lysosome fusion by mediating the phagosomal association with Tryptophan Aspartate-Containing Coat Protein (TACO), which avoid lysosomal degradation of *M. tb*.[28]

Role of Macrophages and Dendritic Cells (DCs)

The uptake of *M. tb* by alveolar macrophages represents the first step in the innate host defense against TB. Following mycobacterial infection, macrophages can differentiate either in IL-23-producing type 1 macrophages that promote Th1 immunity to mycobacteria or IL-10-producing type 2 macrophages that suppress immunity to myco-bacteria.[29] IL-10 producing type 2 macrophages can also induce $CD4^+$ T-cells to adopt regulatory T-cells (Treg) phenotype.[30] IFN-γ is key activating agent that triggers the antimycobacterial effects of macrophages.[31,32] A major effector mechanism responsible for the antimycobacterial activity of IFN-γ is the induction of nitric oxide and related reactive nitrogen intermediates by macrophages via the action of inducible form of nitric oxide synthase.[33,34] Along with IFN-α, TNF-α and IL-1α also stimulate the production of nitric oxide in macrophages. The precise mechanism(s) by which nitric oxide and other reactive nitrogen species antagonize *M. tb* is not known. It is suggested that it may involve the disruption of bacterial DNA, proteins, signaling, and/or induction of apoptosis of macrophages that harbor mycobacteria.

In spite of the potent bactericidal activity of macrophages, *M. tb is* able to survive and replicate in these cells by avoiding the killing mechanisms. It has been shown that *M. tb* survive inside macrophage by avoiding the fusion of phagosomes with lysosomes.[7,35] Retention of early endosomal markers by *M. tb* vacuole longer than normal maturing phagosomes suggested a defect in maturation of *M. tb* phagosome.[36] *M. tb* phagosomes are shown to be deficient in lysosomal hydrolases and Vesicular Proton-Adenosine Triphosphatase (v-ATPase) required for the acidification of phagosomes.[7,36] Also, *M. tb* phagosome fails to replace the small GTP-binding Rab family protein Rab5 with Rab7, which is a critical step during phagolysosome formation.[37] Furthermore, *M. tb* is observed to prevent the accumulation of Phosphatidylinositol 3-Phosphate (PI3P) on phagosome, which is a host membrane protein and essential for the biosynthesis of phagolysosome.[36]

Recently, LAM from *M. tb* has been demonstrated to inhibit phagosome maturation via blocking cytosolic Ca^{2+} increase, which is required for Ca^{2+}/calmodulin PI3 kinase responsible for PI3P production on phagosomes.[37,38] *M. tb* SapM, a eukaryotic-like acid phosphatase has been found to interfere with phagosome maturation by hydrolyzing PIP3 on phagosomal membrane.[39,40] The eukaryotic-like serine/threonine Protein Kinase G (PknG) of *M. tb* has also been demonstrated to inhibit phagosome-lysosome fusion.[41] Most recently, it is suggested that *M. tb* Protein Tyrosine Phosphatases (PtpA and PtpB) are involved in blocking the phgosome-lysosome fusion by interfering with host trafficking process.[40] Although, these studies provide a glimpse of the *M. tb* components involved in the blocking of phagosome-lysosome fusion, more research is needed to completely understand the role of *M. tb* molecules in its survival inside the macrophages.

Unlike macrophages, the interaction of DCs with *M. tb* is not well studied, but they have been shown to have a significant role in mounting protective immune responses against *M. tb* infection.[42] It has been shown that *M. tb* enters DCs via binding with DC-SIGN receptors.[5] Mycobacterial ManLAM has been found to be ligand for DC-SIGN and binding of ManLAM with DC-SIGN inhibits the maturation of DCs.[43] *In vivo*, it seems that similar to *M. tb* receptor, DC-SIGN is also utilized by HIV for its entry in these cells.[44] It is suggested that DC-SIGN might account for several pathological and immunological aspects of *M. tb* infection in subjects co-infected with HIV. Although *M. tb* is able to survive and persist in DCs, conflicting results have been obtained regarding its replication.[45,46]

Both macrophages and DCs can inhibit mycobacterial growth in nitric oxide dependent manner; however, *in vitro* studies have demonstrated that macrophages are more efficient in killing *M. tb* than DCs.[46] Similar to macrophages, mycobacterial vacuoles in infected DCs are also known to lack acidification and fusion with lysosomes, which suggest similar mechanism for survival of *M. tb* in DCs.[45] However, in contrast to macrophages, the finding of impaired communication between *M. tb* phagosomes and host recycling and biosynthetic pathways leading to the absence of essential nutrients needed for *M. tb* survival in the phagosomes of infected DCs indicates the different mechanism of survival and persistence of *M. tb* in DCs.[45]

Role of Natural Killer (NK) Cells

Natural killer cells are one of the major components of innate immune system and provide the first line of defense against infection.[47] The recognition of the target cells by NK cells is performed with a variety of cell surface activating receptors (NKp46, NKp44, CD16 and NKG2D) and inhibitory receptors (killer immunoglobulin-like receptors; KIRs and the NKG2A:CD94 dimer), which regulate the cytolytic activities of these cells.[47] In addition to cytotoxic activity, NK cells have also been found to be a potent early source of cytokines particularly IFN-γ, IL-5, IL-13 and IL-10.[47] Role of human NK cells in protection against *M. tb* infection is demonstrated by *in vitro* studies, which showed that NK cells can directly lead to lysis or apoptosis of *M. tb* infected monocytes and macrophages.[20] A recent study showed that NK cells restrict the growth of *M. tb* in macrophages via production of IL-22, which increases the phagosome-lysosome fusion.[48] NK cells can also regulate the expansion and cytotoxicity of $CD8^+$ T-cells for lysis of *M. tb* infected monocytes, which depend on the production of IFN-γ by NK cells, direct contact of NK cells with monocytes and secretion of IL-12, IL-15 and IL-18 by monocytes.[47]

Role of Neutrophils

The influx of Polymorphonuclear Neutrophils (PMNs) to the lung is one of the first events in the pathogenesis of pulmonary tuberculosis, which play a significant role in the acute phase of the disease.[49] In addition, protective role of neutrophils in systemic *M. tb* infection of mice has been demonstrated.[50] Moreover, studies with human neutrophils suggest that these cells restrict the growth of *M. tb* and secrete several cytokines and chemokines on interaction with *M. tb*.[20] The risk of development of TB is inversely associated with the neutrophil count in the blood from contacts of TB patients further supporting the protective role of neutrophils in TB.[51] The fact that IL-17 is important in the early phase of host defense against TB by attracting the neutrophils at the site of infection further confirms the role of these cells in antimycobacterial immunity.[20] However, massive production of IL18, another neutrophil attracting chemokine in the lung of active TB patients indicates a pathological rather than protective role of neutrophils at late stages of the disease.[20] It is also observed that the ingestion of apoptotic neutrophils by macrophages enhances *M. tb* killing.[20,52] Thus, majority of studies indicate that neutrophils contribute to protective immunity against TB during early stages.

Cytokines and Chemokines Bridging the Innate and Adaptive Immunity

The majority of immunocompetent individuals control mycobacterial infection efficiently. This is mainly owing to an efficient coordination of both innate and adaptive immune responses by the cytokine and chemokine network. The control of *M. tb* infection depends on the appropriate development of inflammatory responses because improper responses can cause chronic infection and associated pathology.

Infected macrophages and dendritic cells produce Interleukin-12 (IL-12), the crucial cytokine in controlling early *M. tb* infection.[53,54] IL-12 induces the secretion of IFN-γ and down modulation of IL-10 and IL-4 that results in the differentiation of naïve T-cells to Th1 cells. IL-12 therefore provides an important link between innate and adaptive immune system.[54] Increased susceptibility to *M. tb* infection observed in IL-12 deficient mice indicates its role in protective immunity to TB.[55]

IFN-γ, secreted from activated T-cells and NK cells can further activate macrophages resulting into phagosomal maturation and production of antimicrobial reactive nitrogen intermediates and reactive oxygen intermediates to promote bacterial killing.[56,57] IFN-γ production is controlled by cytokines released by Antigen Presenting Cells (APCs) mainly IL-12 and IL-18.[58] IFN-γ signaling pathways can also induce autophagy in macrophages that further increases their bactericidal capacity.[59,60] Role of IFN-γ in human TB has been demonstrated by studies which show that individuals defective in either IFN-γ or IFN-γ receptor genes are susceptible to mycobacterial infections.[55] Besides IFN-γ, TNF-α, a proinflammatory cytokine secreted by macrophages, DCs and T-cells also plays an important role in killing intracellular *M. tb* through reactive nitrogen intermediates together with IFN-γ and are involved in granuloma formation.[53,61] The role of TNF-α in protective immunity against *M. tb* in human is suggested by studies showing increased susceptibility to develop TB in Crohn's disease and rheumatoid arthritis patients using anti-TNF-α antibodies.[55] Furthermore, variations in TNF-α receptor 1 (*TNFR1*) gene are found to be associated with TNF-α production and progression of active TB.[55]

IL-10, an anti-inflammatory cytokine produced by macrophages, DCs, B-cells and T-cells plays an important regulatory role in bacterial and viral infections by the inhibiting synthesis of proinflammatory cytokines like IFN-γ, TNF-α and IL-12.[55,62] In *in vitro* studies, IL-10 is shown to be upregulated in TB and inhibition of IL-10 has been shown to partially restore the suppression of T-cell proliferation.[55] In anergic TB patients, increased production of IL-10 also suggests its role in effective suppression of host immune response.[7] Polymorphisms in the promoter region of IL-10 are found to be associated with altered IL-10 level and susceptibilities to TB in human, however, inconsistent results of some studies raises question on role of IL-10 promoter polymorphism in TB susceptibilities.[55] IL-4 is another anti-inflammatory cytokine that has been implicated in various intracellular infections including *M. tb* for its harmful effects by suppressing IFN-γ production and macrophage activation.[62] In human, progressive TB, mainly in developing countries is found to be associated with increased IL-4 expression.[53,62,63]

Another anti-inflammatory cytokine that is implicated in suppressing protective immunity to *M. tb* is Transforming Growth Factor (TGF)-β.[64] Production of TGF-β by monocytes and DCs is induced by mycobacterial components specifically by ManLAM.[62,64] An increased production of TGF-β is observed in blood mononuclear cells and lung lesion of TB patients.[64] *In vitro* studies showed that suppressive effect of TGF-β on mononuclear cells from TB patients and *M. tb* infected macrophages is neutralized by its natural inhibitors.[62] TGF-β is also found to promote production and deposition of macrophage collagenases and collagen matrix suggesting its role in tissue damage and fibrosis during TB.[62] Inhibition of IFN-γ induced NOS2 production is shown to be responsible for deactivation of macrophages by TGF-β.[53] Also, TGF-β induces secretion of another anti-inflammatory cytokine IL-10 and both the cytokines have been observed to act in synergy for suppression of IFN-γ production.[62]

In addition to above mentioned cytokines, several investigators have shown that *M. tb* or its components induce chemokines from monocytes, macrophages, multinucleated giant cells, DCs, granulocytes, etc.[7,65,66] Evidence for *in vivo* production of chemokines in humans during *M. tb* infection is provided by studies showing the increased levels of CCL2, CCL5, CCL7, CCL12, CXCL8 and CXCL10 in Bronchoalveolar Lavage (BAL) fluid from TB patients.[66] Recently, expression of CXCL8 by mononuclear cells and fibroblasts in human tuberculous granuloma has also been observed.[65] *In vitro* studies have also demonstrated the influence of chemokines on intracellular growth of *M. tb*.[65] Neutralization of CCL4 and CCL5 is found to enhance the growth of mycobacteria in alveolar macrophages. Also, growth of *M. tb* is significantly reduced in macrophages stimulated with CXCL7. Furthermore, CXCL8 has been found to enhance the killing of mycobacteria by human granulocytes.

Various *in vitro* and *in vivo* studies suggest that cytokine TNF-α regulate the expression of chemokines during *M. tb* infection.[65,66] Neutralization of TNF-α production by LAM stimulated PBMCs and *M. tb* infected murine macrophages alter the secretion of various chemokines.[65,66] Expression of chemokine receptors CCR2 and CCR5 has also shown to be affected by TNF-α. Since, TNF-α is shown to play a crucial role in granuloma formation, whether chemokines are also involved in granuloma formation is not known.

Adaptive Immunity

Although, *M. tb* infection elicits both humoral and cell-mediated immune responses, due to intracellular residence of *M. tb*, it is well accepted that only cell-mediate immunity provides protection against TB.[53,67] However, in recent years it has been shown that humoral immune responses also play important role in protection to TB.[68,69]

Cell-Mediated Immunity

The T-cells which comprise of $CD4^+$ T Helper Cells (Th), $CD8^+$ Cytotoxic T-cells (CTLs), γδ T-cells, regulatory T-cells (T_{reg} cells), memory T-cells and unconventional CD1 restricted T-cells play main role in providing cell-mediated immunity. $CD4^+$ Th cells can be differentiated into Th1, Th2, Th17 and Treg cells. The Th1 cells produce cytokines, notably IFN-γ, TNF-α, IL-2, lymphotoxin etc., which further prompt the stimulation of Th1 cells, CTL, and macrophages maturation and activation. The cytokines, such as IL-12, IL-18 and costimulatory molecules have been found to facilitate the differentiation of $CD4^+$ T-cells into Th1 type.[56] The Th2 cells produce B cell-stimulation factors, such as IL-4, IL-5, IL-10 and IL-13, which promote antibody production, but suppress the Th1 type immune response. IL-4, IL-5 and IL-13 induce Th2 cell development. The Th17 cells produce unique cytokines IL-17, IL-17F, IL-21 and IL-22, which stimulate defensin production and recruit neutrophils and monocytes to the site of inflammation, and are involved in the early phase of host defense. IL-23, IL-6, IL-21 and low concentration of TGF-β could induce Th17 differentiation. $CD4^+CD25^+FoxP3^+$ Treg cells can affect the differentiation of Th1, Th2 and Th17 subsets by releasing TGF-β and IL-10.

Role of $CD4^+$/$CD8^+$ T-cells: The direct evidence for the involvement of $CD4^+$ T-cells in protective immunity against *M. tb* infection has been provided by several murine studies using $CD4^+$ T-cells depletion or adoptive transfer or genetically deficient mice.[53] In human, the protective role of $CD4^+$ T-cells during *M. tb* infection has been suggested by enhanced occurrence of both primary and reactivated TB in HIV-infected individuals showing loss of these cells.[53,67] Although, the mechanism of protection by $CD4^+$ T-cells is not clear, so far studies suggest that during *M. tb* infection, $CD4^+$ T-cells of Th1 type activate macrophages primarily through IFN-γ production, which results in the induction of enzymes Inducible Nitric Oxide Synthase or Nitric Oxide Synthase 2 (iNOS or NOS2) and phagocyte oxidase (NOX2/gp91^{phox}) to produce mycobactericidal Reactive Nitrogen Intermediates (RNI) and Reactive Oxygen Intermediates (ROI) respectively.[56,70] Although, these studies suggested that $CD4^+$ T-cells controls *M. tb* infection via IFN-γ production, other antimycobacterial mechanisms suggested for these cells include apoptosis of infected macrophages, release of ATP and Lymphotoxin α_3 ($LT\alpha_3$) or TNF-β for control of *M. tb* infection.[56,71]

Despite potent abilities of $CD4^+$ T-cells to control *M. tb* infection, existence of persistent infection in the majority of *M. tb* infected individuals suggests that these cells are ineffective in eliminating the *M. tb* infection. Although, reasons are not clearly known, it has been shown that *M. tb* infection reduces the antigen presentation by macrophages to $CD4^+$ T-cells by the down regulation of surface expression of MHC class II molecules.[53] Moreover, delayed appearance of *M. tb* specific $CD4^+$ T-cells during *M. tb* infection compared to infection caused by other pulmonary pathogens can also contribute to the inabilities of these cells to clear infection.[72]

M. tb infection of mice with either β2-microglobulin or Transporter Associated with Antigen Processing (TAP) gene disruption, which results in the lack of both MHC class I (class Ia- and class Ib) molecules and $CD8^+$ T-cells has demonstrated that $CD8^+$ T-cells are also required for control of *M. tb* infection.[53,72,73] Since *M. tb* resides in phagosomes, it is still unclear how *M. tb* antigens gain access to the MHC class I processing system. It has been suggested that *M. tb* perforates the membrane of phagosome by which its antigens translocate to MHC class I pathway.[53,56] However, other studies have provided evidence against the translocation of molecules from phagosomes to cytoplasm.[56] Although, the main function of the $CD8^+$ T-cells is the lysis of infected cells, it is also most likely that IFN-γ from $CD8^+$ T-cells activates macrophages and participates in the killing of *M. tb* as described above for $CD4^+$ T-cells. However, unlike $CD4^+$ T-cells, very low spontaneous IFN-γ production by $CD8^+$ T-cells is observed.[53] The $CD8^+$ T-cells can lyse the infected cells by using perforin and granulysin or Fas/FasL pathway.[53] Perforin forms pore and granulysin is required to kill the intracellular organism.[56] It has also been suggested that the lysis of infected cells by $CD8^+$ T-cells promotes the control of *M. tb* infection by the release of *M. tb* from incapacitated cells and their subsequent phagocytosis by activated macrophages.[56]

Role of regulatory T (T_{reg}) cells: T_{reg} cells express CD4, CD25 and Foxp3 and produce IL-10, TGF-β and IFN-γ.[75,76,82] In addition to $CD4^+CD25^+FoxP3^+$ T_{reg} cell subsets, $CD8^+$ T_{reg} cells inhibiting the T-cell proliferation and cytokine production are also described.[74] IL-2 and high concentration of TGF-β could induce T_{reg} differentiation[75,76] whereas IL-6 inhibits the generation of T_{reg} cells. T_{reg} cells are found to suppress the proliferation and function of $CD4^+CD25^-$ cells and inhibit the production of IFN-γ by secreting IL-10 and TGF-β.[77,78] During *M. tb* infection in mice, T_{reg} cells proliferate and accumulate at the site of infection and prevent efficient clearance of infection.[78]

Recent study also showed that TB patients have more T$_{reg}$ cells than healthy tuberculin responders and these cells inhibit BCG induced IFN-γ production by CD4$^+$ T–cells.[78,79] It has been observed that IFN-γ production by *M. tb* stimulated PBMCs is increased by depleting T$_{reg}$ cells.[78] Furthermore, expansion of T$_{reg}$ cells in response to *M. tb* infection is shown to be dependent on ManLAM and production of prostaglandin E2 by monocytes.[78] So far studies suggest that *M. tb* infection promotes the expansion of T$_{reg}$ cells that are able to suppress the protective immune responses developed against its own infection.

Role of γδ T-cells: During mycobacterial infection, γδ T-cell are rapidly recruited to lung, secrete IFN-γ and kill *M. tb* infected cells.[80,81] In humans, γδ T-cells recognize mycobacterial nonpeptidic phosphoantigens without any requirement for MHC molecules leading to the secretion of Th1 cytokines primarily IFN-γ and killing of *M. tb* infected cells.[80] The occurrence of increase size of granuloma and enhanced numbers of neutrophils in granuloma of *M. tb* infected γδ TCR-KO mice suggested that γδ T-cells are involved in the regulation of granuloma formation.[81] The involvement of γδ T-cells in providing protection against *M. tb* infection in human has been demonstrated by studies, which showed decreased number of Vγ9Vδ2 T-cells in the blood and lung of pulmonary TB patients, as well as diminished ability of Vγ9Vδ2 T-cells from TB patients to expand in response to *M. tb* or its antigens.[81] Together these studies suggest that γδ T-cells contribute to protective immunity against *M. tb* infection.

Role of memory T (T$_M$) cells: Although, role of T$_M$ cells in providing protection against *M. tb* infection is poorly defined, persistence of latent *M. tb* infection in majority of infected individuals suggest the involvement of these cells in controlling *M. tb* infection during latency. In humans, there are two types of T$_M$ cells; Effector memory T (T$_{EM}$) cells with CCR7^{lo}, CD62L^{lo}, CD69^{hi} and central memory T (T$_{CM}$) cells with CCR7^{hi}, CD62L^{hi}, CD69^{lo}[82]. *M. tb* infection in mice induces antigen specific T$_M$ cells; however, these memory responses provide only short-term protection.[67,72] Similarly, occurrence of *M. tb* reinfection in cured TB patients suggests that either no T$_M$ cells are induced or these cells are unable to provide protection. It has been proposed that efficient activation of effector T-cells for long time by persistent antigens can exhaust memory and cause no memory in extreme cases like in TB patients.[82] Recently, vaccination with BCG and MVA85A has been shown to induce long lasting poly-functional *M. tb* specific CD4$^+$ T$_M$ cells.[83]

Role of unconventional T-cells: In addition to MHC class I restricted CD8$^+$ T-cells, presence of non-classically restricted CD8$^+$ T-cells have also been observed during *M. tb* infection in humans.[53,56] Group I CD 1 molecules, which are structurally similar to MHC class I molecules have been found to present several lipids and glycolipid antigens of mycobacterial cell wall to non-classically restricted CD8$^+$ T-cells resulting into release of IFN-γ and expression of cytolytic activity.[53,56] Group I CD1a and CD1c can easily have access to mycobacterial antigens in phagosomes whereas group I CD1b molecules can primarily interact with those mycobacterial antigens that are shed inside the phagosomes and enter into late endosomes/lysosomes.[53,56] As group1 CD1 molecules are primarily found on DCs and almost absent on macrophages, the CD1 presentation therefore requires transfer of mycobacterial antigens from infected macrophages to bystander DCs.[56]

The natural killer T (NKT) cells are also unconventional T-cells that are group 2 CD1d restricted and stimulated by glycolipid antigens of mycobacterial cell-wall. *In vitro* studies showed that human activated NKT cells express granulysin and can kill the *M. tb*.[84] Another non-classical antigen presenting molecules H2-M3, a type of murine MHC class Ib molecules have been reported in mouse TB model and shown to present N-formylated peptides to CD8$^+$ T-cells.[53,56] The CD8$^+$ and CD4$^-$8$^-$ T-cells specific for mycobacterial N-formylated peptides are shown to produce IFN-γ and lyse *M. tb* infected macrophages.[53] Since homologues of H2-M3 molecules in humans are not identified, their role in human TB is not known.[56] However, CD8$^+$ T-cells restricted by non-classical molecules, but not CD1 restricted have been found in *M. tb* infected humans.[53]

Humoral Immunity

Historically, it is accepted that B cells play no significant role in providing protection against *M. tb* infection.[68,69,85,86] Although, studies of *M. tb* infection in B-cell-deficient mice have yielded variable results, recent data from *M. tb* infected B-cell-deficient mice and polymeric Ig receptor knockout mice deficient in secretory IgA have convincingly demonstrated a role of B cells and antibodies in protection against *M. tb* infection.[68,69] Moreover, protection observed by the administration of Intravenous Immunoglobulin (IVIg) against *M. tb* infection in mice and by passive serum therapy with anti-*M. tb* polyclonal antibodies to reactivation of TB in SCID mice further support the role of humoral components in host defense to TB.[68,69]

Monoclonal antibodies against several mycobacterial antigens, such as arabinomannan, LAM, 16-kDa α-crystallin, Heparin-Binding Hemagglutinin (HBHA) and MPB83 have been demonstrated to provide protection against TB in mice.[68,86] Following *M. tb* infection, B cells have also been found to influence the T-cell activation by regulating antigen presentation, as well as the modulation of cytokine profile thereby influencing the disease outcome.[69,87] Interestingly, a *M. tb* arabinomannan-Ag85B conjugated vaccine that induce both humoral and cellular immune responses has been observed to provide protection against *M. tb* infection in mice, rabbits and guinea pigs similar to BCG.[68,69]

Although, in humans, evidence for the role of B cells in immunity against *M. tb* infection is not available, presence of follicle-like B cell aggregates in the periphery of granuloma in the lung of TB patients suggest their role for maintaining the granuloma during *M. tb* infection.[13,69] The demonstration of significantly enhanced internalization and growth inhibition of BCG by neutrophil and monocyte/macrophages in the presence of serum from BCG vaccinated individuals and reversal of these effects by the depletion of IgG from serum suggest the involvement of anti-mycobacterial antibodies in protection against *M. tb* infection in humans.[68] Together, studies conducted in recent years support the role of humoral immune responses in defense against *M. tb* infection.

CONCLUSION

A complex interaction of multiple cell types of host immune system is important for optimal immunity against mycobacteria. The cross talk between *M. tb* and the host immune system determines the outcome of infection. After uptake of *M. tb* in alveolar macrophages and possibly other cells too, if infection is established, a focal nonspecific inflammatory response regulated by a network of proinflammatory and anti-inflammatory cytokines and chemokines derived from macrophages or DCs, NK cells and T-cells is elicited. This initial response determines the fate of infection either leading to local outgrowth of *M. tb* (sometimes dissemination) or containment of infection. At many stages in the host response, *M. tb* has developed mechanisms to circumvent or antagonize protective immunity. A clear picture of the network of host immune responses to this pathogen is essential to the design and implementation of effective vaccines and treatment strategies for tuberculosis. The combination of studies in animal models and human subjects, as well as technical advances in genetic manipulation of the organism, will help in enhancing our understanding of this immensely successful pathogen in the future.

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40

Pulmonary Tuberculosis: Clinical Features and Diagnosis

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INTRODUCTION

The clinical features of tuberculosis (TB) depend upon the site and the type of involvement. They are rarely diagnostic. Nonetheless, diagnosis in most of the patients is first suspected on the basis of clinical symptoms and signs. The primary site of implantation of bacilli in the lung parenchyma is called Ghon focus, which, together with the draining lymphatics and enlarged draining lymph nodes constitute the primary complex, also known as the Ranke or Ghon complex. In an immunocompetent host, development of specific immunity is usually able to arrest the bacillary proliferation within the primary lesion with little or no signs of illness, the initial lesion eventually resolves or calcifies. These healed lesions may contain dormant and viable bacilli, maintaining continuous hypersensitivity to tuberculous antigen, producing a state of latent TB infection. In a minority of infected individuals (10%), the disease progresses during the initial weeks or months after infection, and the patient develops the typical symptoms of progressive primary TB. In patients with little or no host response and overwhelming infection, disseminated/miliary TB may develop.

POST PRIMARY PULMONARY TUBERCULOSIS

Most common cause of post primary TB is the endogenous reactivation of dormant bacilli lying in residual foci. Coinfection with HIV is the strongest known risk factor for progression from latent infection to active TB.[1] Other known risk factors are malnutrition, drug and alcohol abuse, coexistent medical conditions, corticosteroid or other immunosuppressive and biological therapies.[1]

Exogenous reinfection can also be responsible for post primary TB, although less frequently. In endemic countries, using molecular genotyping methods, it has been demonstrated that reinfection with novel *Mycobacterium tuberculosis* strains may occur in 40% of relapsing cases of TB.[2] Reactivation can occur at any site; however, lung is the most common site of reactivation.[3] Post primary disease differs from primary TB in its preferential apical localization, a strong immune response, marked presence of caseation necrosis and cavities.[4] Traditionally, primary and post primary TB are described in children and adults respectively. Due to the presence of large number of immunocompromised patients and aging populations, atypical and “mixed” radioclinical patterns are frequently observed in adults, with the consequent fading of the age-related distinction between primary and post primary TB.

SYMPTOMS AND SIGNS

Pulmonary Tuberculosis (PTB) is a disease with protean manifestations, often associated with nonspecific constitutional and specific respiratory signs and symptoms. Constitutional symptoms include tiredness, malaise, weight loss, fever, night sweats, anorexia and headache. They are generally attributed to the release of various cytokines in the systemic circulation. Symptoms are minimal or absent until the disease is in an advanced stage. Complete absence of symptoms has been reported in 4.9% of active adult PTB cases, majority of patients are from countries with endemic TB.[5,6] Most patients develop symptoms insidiously; although, acute manifestations have been also reported.

Fever

Fever is an inconsistent symptom in pulmonary tuberculosis. Cowie et al.[7] reported fever in only 40% of 300 admitted patients. Similarly, Wang et al.[8] in a recent study reported fever in 33.3 and 15.4% of sputum positive and sputum negative pulmonary tuberculosis cases respectively. Absence of fever does not exclude the diagnosis of tuberculosis. Fever in pulmonary TB historically has been described by the typical evening rise of temperature. The evening spike of fever may be due to increase in the bacillary multiplication related to the diurnal pattern of adrenal gland steroid release. However, in miliary tuberculosis, fever can have morning spikes.[9] The other two conditions associated with morning temperature elevations are typhoid fever and periarteritis nodosa.[10] Initially, fever in PTB is of low grade, but it becomes high grade with the progression of disease. Tuberculosis is also an important cause of Fever of Unknown Origin (FUO) in several studies.[11,12] In a combined (prospective and retrospective) study of 150 cases of FUO, infections, particularly tuberculosis, were the most common (50%) cause.[12] Extrapulmonary tuberculosis is more common in such a situation.

Cough

Cough is the most predominant symptom in tuberculosis.[13] In the initial stages, cough is dry, but subsequently there occurs the production of mucoid or mucopurulent sputum, generally in small amounts. Sometimes, sputum may also be streaked with blood. At the onset, it is more in the early morning; with progressions of disease, it becomes persistent throughout day and night. Cough is less frequent in tubercular pleural effusion. A typical harsh, barking cough is often present in endobronchial TB, which responds to steroids and antituberculosis treatment, has poor response to antitussive medication.[14] As per ACCP guidelines, in the high prevalence areas of tuberculosis, chronic cough should be defined as cough of two to three weeks duration similar to that recommended by the World Health Organization (WHO).[15]

Hemoptysis

Hemoptysis is usually mild in TB, but occasionally it can be massive. When massive, it is mostly of bronchial artery or nonpulmonary systemic artery origin. Rarely, hemoptysis can also be the presenting symptom. Both active and inactive tuberculosis can produce hemoptysis. Tuberculosis is the most common cause of hemoptysis in endemic countries.[16] It was reported in 79.2% of 476 admitted patients of a chest department.[17] Similarly, in another report, approximately one-third of the patients of tuberculosis had hemoptysis of various grade at different stages of their disease.[18] However, the incidence of significant hemoptysis was 8% and fatal hemoptysis was reported in 1 to 5% cases.[18]

There are several mechanisms, which can cause hemoptysis in pulmonary tuberculosis (Table 40.1). Usually, massive bleeding is seen in inactive TB with cavitary and bronchiectatic sequelae. Bleeding occurs less commonly in patients of active cavitary disease with associated granulomatous vasculitis, since vascular thrombosis within necrotic areas causes the obliteration of pulmonary vessels.[19] However, it can be seen in active tuberculosis if adequate chemotherapy is not given and radiograph shows thick walled cavities.[20] After achieving cure, if the patient complains of recurrent hemoptysis, evaluation for bronchiectasis and/or mycetoma should be done.

Pulmonary mycetoma is the fungal colonization, mainly by aspergillus species, in a preexisting pulmonary cavity and without the evidence of invasion into the surrounding structures. Mycetomas have also been reported in other pulmonary conditions such as sarcoidosis, bronchiectasis, lung abscess, neoplasms, pulmonary infarcts, nontuberculous mycobacteria and various mycoses.[21-24] Severe hemoptysis may occur in up to one-third of the cases of mycetoma.[23] In HIV-infected patient with pulmonary mycetoma, significant hemoptysis is less likely observed as compared to immunocompetent patient, but these patients have a high risk of disease progression to more invasive disease.[24] Rasmussen's aneurysm is a rare complication of cavitary pulmonary tuberculosis caused by granulomatous weakening of a pulmonary arterial wall. It can present as the repeated episodes of minor hemoptysis or occasionally as major hemoptysis. Incidence of Rasmussen's aneurysm is 4% in patients with advanced cavitary disease.

TABLE 40.1: Mechanisms of hemoptysis in tuberculosis

- Necrosis of pulmonary venules and capillaries in early stages
- Rupture of *Rasmussen's aneurysm*
- Post-tubercular bronchiectasis
- Mycetoma in tubercular cavity
- Broncholiths
- Scar carcinoma–very rarely

Breathlessness

Breathlessness, which is a late symptom in pulmonary TB may result from extensive pulmonary involvement, bronchial obstruction, pneumothorax and pleural effusion. Rarely, patients with miliary TB or TB bronchopneumonia may present with the symptoms of respiratory failure. The incidence of respiratory failure secondary to pulmonary TB is 1.5 to 1.9%.[25-27] Diagnosis of TB is more likely delayed or missed in patients presenting with acute respiratory failure.[28] Destroyed lung due to tuberculosis is also a common cause of respiratory failure in endemic area.[29] The prognosis of TB presenting with respiratory failure is dismal with hospital mortality of 60%.[30]

Chest Pain

Involvement of pleural surface can cause pleuritic chest pain. Pain is referred to ipsilateral shoulder in diaphragmatic pleurisy and to upper abdomen in costal pleural involvement. Pneumothorax due to tuberculosis can also cause acute pleuritic chest pain. Sometimes, chest pain can be dull and poorly localized. Chest pain is an early and relatively frequent symptom and it disappears within two or three weeks after effective treatment is started.

Hoarseness

The most common cause of hoarseness of voice in pulmonary TB is due to the associated laryngeal tuberculosis. Rarely, inflamed TB nodes or the retraction of left upper lobe bronchus by cicatrization atelectasis can cause recurrent laryngeal nerve palsy and hoarseness of voice.[31]

In TB endemic countries, *M. tuberculosis* can have Community-Acquired Pneumonia (CAP) like presentation. Empirical therapy with fluoroquinolones in this condition, misdiagnosed as acute bacterial pneumonia, can suppress the early symptoms of TB and often delay the diagnosis of TB. Therefore, in endemic area for TB, fluoroquinolones should be judiciously used. In a multivariate analysis involving patients presenting with CAP like manifestations, features, such as the longer duration of symptoms (more than two weeks before hospital admission), history of night sweats, upper lobe involvement, cavitary infiltrates, lower total white blood cell count and lymphopenia, have been reported as more predictive of pulmonary TB.[32]

Primary TB in children is mostly asymptomatic and recognized solely through contact investigation. Some children may experience a symptomatic pneumonia like presentation. Progressive primary tuberculosis patients may present with cough, hemoptysis and weight loss. Because of smaller diameter airways, younger children are more prone to airway compression.[33]

TUBERCULOSIS IN THE ELDERLY

The elderly population is particularly susceptible to TB because of the age induced decline in cell mediated immunity.[34] More specifically, impairment of helper T-lymphocyte functions and subsequently defects in secretion and response to different cytokines are particularly important in increasing the susceptibility of TB in elderly subjects.[35] Elderly individuals are also more likely to suffer from various immunosuppressive conditions. There are several characteristics features of TB in the elderly.[36] After exposure, elderly subjects are more likely to become infected with *M. tuberculosis* than younger subjects, they also develop tuberculous diseases more easily after contracting infection. Mortality from TB is also high in this population.

Delayed diagnosis is not uncommon as the clinico-radiological presentations of TB are often atypical in the elderly.[37] Some patients may present with only non-pulmonary symptoms such as unexplained weight loss, weakness or change in cognitive status.[38] Classical symptoms, such as night sweats, fever and hemoptysis, are less frequently observed in the elderly.[5] Fever is infrequent because of age associated decrease in pyrogenic response. There is decreased responsiveness of the hypothalamic thermoregulatory center to prostaglandin E2 (released by interleukin-1) and an increased sensitivity to natural occurring antipyretics such as alfa melanocyte stimulating hormone.[39] Cavitation is less common in elderly age group, which can explain the lower frequency of hemoptysis. Potential of adverse drug reactions is also high in elderly subjects.

MILIARY TB

Miliary tuberculosis contributes 1 to 2% of all cases of tuberculosis and about 8% of all the forms of extrapulmonary tuberculosis in the immunocompetent individuals.[40] However, it is more common in immunosuppressed individuals. Clinical manifestations are nonspecific and the typical chest radiographic finding of miliary nodules may not be apparent till late in the course of the disease. Atypical presentations are more common and often delay the diagnosis. Associated tuberculosis meningitis has been described in 10 to 30% of adult patients with miliary tuberculosis.[41] Choroidal tubercles and cutaneous findings (tuberculosis cutis acuta generalizata) are highly specific, but insensitive for miliary TB.[41] Cutaneous manifestations are more commonly seen in HIV infected patients with advanced immunosuppression ($CD4^+$ cell counts <100 cells/cmm).[42]

TB through hematogenous dissemination can occasionally lead to sepsis and septic shock, it was known as Landouzy septicemia or sepsis tuberculosa acutissima in the past.[43] It is most commonly noted in immunocompromised patients, especially in patients with HIV, but may also occur in immunocompetent patients.[44]

HIV AND TB

Tuberculosis can involve HIV infected patients at all the levels of CD4 T-lymphocyte counts, but clinical and radiological manifestations depend on the severity of immunosuppression.[45] Majority of patients with CD4 counts >200 cells/cmm have disease limited to the lungs with common chest radiographic findings, such as upper lobe infiltrates with or without cavitation, not substantially different from HIV-negative patients. On the other hand, patients with advanced HIV disease (CD4 T-lymphocyte count<200/cmm) are more likely to have atypical presentation such as the lower lobe predominance, adenopathy and absence of cavities. Extrapulmonary and disseminated disease is common in advanced HIV infection, occurring in 63% of patients.[46] Severely immunocompromised patients can have sepsis like syndrome with high fevers[47] (See Chapter 51 for details).

PLEURAL EFFUSION

In primary TB, effusions typically develop three to six months after infection, are due to hypersensitivity response to a small amount of tuberculoprotein released into the pleural space.[48] Pleural effusion is less commonly seen in post primary TB, it is due to the rupture of a cavity or adjacent parenchymal focus into pleural space, releasing large number of bacteria in contrast to primary TB. In patients of pulmonary tuberculosis, pleural involvement appears to be more common in HIV coinfected individuals. Tuberculous pleuritis often presents acutely, shows significantly higher frequency of chest pain, dyspnea and abdominal pain, whereas hemoptysis and weight are less commonly noticed[49] (See Chapter 156 for details).

PARADOXICAL RESPONSE

Paradoxical response in tuberculosis includes the unusual expansion of old lesions or formation of new tuberculous lesion during antituberculosis therapy.[50] Paradoxical responses are known to occur in tuberculous pleural effusion, pulmonary tuberculosis, tuberculous lymphadenopathy and intracranial tuberculoma. Paradoxical worsening occurs with rapid mycobacterial killing and release of products that stimulate the T-helper subtype 1 (Th1) lymphocyte subpopulation, which in turn liberate various proinflammatory cytokines, including TNF-α, interleukin IL-2, IL-6 and IL-8, responsible for worsening of tuberculous lesions.[51] Paradoxical reaction is particularly common in up to 30% patients with cervical lymphadenopathy whereas it is rare in those with intrathoracic lymphadenopathy.[52]

PHYSICAL EXAMINATIONS

There are several reactive immunologic phenomena, such as erythema nodosum, erythema induratum, reactive arthritis and amyloidosis, associated with *M. tuberculosis* infections.[53] These are more common in primary TB. Erythema nodosum usually occurs acutely and is clinically characterized by the sudden eruption of erythematous tender nodules and plaques located predominantly over the extensor aspects of the lower extremities. It may occur in a disseminated form in severe reaction and heal without scarring. Erythema induratum, on the other hand, presents with a more indolent course, often precipitated by cold weather, tends to form blue plaques and heal with atrophic scars. Histologically, it is associated with vasculitis and granuloma formation.[54] Poncet's disease is a reactive arthritis characterized by aseptic inflammatory polyarthritis in the patients of active pulmonary TB, which tends to affect knees, ankles and elbows.[55]

Amyloidosis (AA type) may complicate chronic infections and tuberculosis is a common cause of secondary amyloidosis in the developing countries, can occur as early as two to four weeks after the diagnosis of active tuberculosis.[56] The pathogenesis of secondary amyloidosis involves the release of proinflammatory cytokines (such as interleukin (IL)-1, IL-6, and TNF-α), which stimulate the synthesis of serum amyloid in the liver and its subsequent deposition in various organs. This stimulation occurs even during the inactive stage of the disease.[57] Wasting is a classic feature of tuberculosis, caused by a combination of factors, e.g. lack of appetite, increased losses and altered metabolism as part of the inflammatory and immune responses.[58] Wasting also carries poor prognosis by causing increased mortality in patients with tuberculosis.[59] It is usually seen in advanced disease and indicates the loss of both fat and lean tissues.[58]

A major constraint of physical examination of respiratory system is its failure to detect mild or even moderate illness despite apparent radiographic abnormalities. Post tussive rales constitute an important sign, demonstrated on deep inhalation followed by full exhalation and coughing at the end of exhalation. Fine rales are heard over the areas of TB infiltrations, particularly at the apices. In endobronchial TB, localized wheezing may be heard. In tubercular consolidation, high pitched bronchial breathing, whereas in superficial large cavities, cavernous breathing may be audible. In tubercular pleurisy, pleural rub is often detected. Signs of volume contraction are often present in advanced disease with extensive fibrosis.

DIAGNOSIS OF TUBERCULOSIS

Routine Laboratory Testing

Mild anemia and leukocytosis are the most common hematologic abnormalities in TB. Anemia is caused by the inflammatory cytokines mediated suppression of erythropoiesis, most often described as normochromic, normocytic anemia, while some patients may show leukemoid reactions. Pancytopenia with hypocellular bone marrow has also been reported with *M. tuberculosis* infection.[60] Hematological manifestations are more common in disseminated/miliary tuberculosis patients. Patients of disseminated/miliary tuberculosis with granuloma in bone marrow showed significantly higher incidence of severe anemia, peripheral monocytopenia and bone marrow histiomonocytosis as compared to patients without granuloma.[61] In countries where TB is endemic, including in India, TB should be carefully excluded in patients presenting with various hematological manifestations.

Hyponatremia and hypercalcemia have been observed in tuberculosis. Hyponatremia is more commonly noticed in tubercular meningitis than in pulmonary TB, is due to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). It has been reported in 7 to 10% of active TB cases.[62,63] In addition, hyponatremia in tuberculosis can be due to Addison's disease. Adrenal tuberculosis was reported in 6% of patients with active tuberculosis and bilateral adrenal involvement in 70% cases.[64]

Hypercalcemia is the other electrolyte abnormality in active TB, but symptoms of hypercalcemia are uncommon. Prevalence rate of hypercalcemia in different studies vary from 15 to 51%.[65] The most plausible theory is extra renal production of 1, 25-dihydroxycholecalciferol. Unfortunately, all these findings are nonspecific. Erythrocyte Sedimentation Rate (ESR) estimation is also an unreliable indicator of disease activity.

Early diagnosis of TB and initiation of optimal therapy is important not only for the patient, but is also equally so for the community to decrease the possibility of transmission of infection to others. Any diagnostic modality for tuberculosis should have certain desirable features:

- It should have acceptable sensitivity, specificity and predictive value.
- It should be quantitative and reproducible.
- Its turn around time should be rapid.

Further, the test should be cost-effective, safe, easy to use, and should perform equally well in resource poor settings and HIV prevalent areas. Laboratory testing for tuberculosis includes tests for latent tuberculosis infection as well as for tuberculosis disease. In latent TB infection, individuals are harboring live *M. tuberculosis,* but do not show any clinical evidence or signs and symptoms of active disease. Tuberculosis, on the other hand, is the clinically manifested illness caused by *M. tuberculosis* complex. Tests for Latent Tuberculosis Infection (LTBI) include Tuberculin Skin Test (TST) and Interferon-Gamma Release Assays (IGRA).

Latent Tuberculosis

Tuberculin Skin Test (TST)

Tuberculin skin test is the oldest diagnostic test still in use in the modern medical practice. The material used for this purpose is Purified Protein Derivative (PPD). It is injected intradermally, indicates delayed type hypersensitivity response in exposed individuals. In tuberculin test, the area of induration (not erythema is measured after 48 to 72 hours of administration of PPD). In India, induration of >15 mm is taken as positive TST in immunocompetant person with no known risk factors for TB. PPD despite being in use for a century, possesses many short comings, including low sensitivity particularly in immunocompromised individuals (elderly, malnourished, HIV infection and other immunosuppressive conditions). In HIV infected patients, a cut-off of ≥ 5 mm of induration is considered as positive response. Overall, 75 to 90% of patients with active TB react to TST.[66]

Tuberculin testing also lacks specificity since PPD is a mixture of more than 200 proteins derived from *M. tuberculosis*, many of which are shared by other mycobacteria, including the Nontuberculous Mycobacteria (NTM) and Bacillus Calmette Guérin (BCG) strain.[67] A systematic meta analysis, showed minimal effect of BCG vaccination received in infancy on TST, the effect was virtually nil beyond 10 years of vaccination.[68] NTM usually produce induration smaller than 10 mm in diameter and are a cause of false positive TST only in areas with the high prevalence of NTM infections. Despite the diminished specificity of the TST in BCG vaccinated individuals, the American Thoracic Society recommends to ignore vaccination history when interpreting TST.[69] Other shortcomings are the inter-reader and intra reader variability in reporting and the need for a return visit.

Tuberculin skin test does not distinguish between the latent infection and the active disease. To increase the specificity of TST, we need to purify antigens that are specific to *M. tuberculosis* complex. Recently, a recombinant antigen (DPPD, not present in NTM) encoded by a gene unique to the *M. tuberculosis* complex organisms, has shown some promise in increasing the specificity of skin testing in the diagnosis of tuberculosis.[70] Another potential antigen that has shown promise in skin testing is the *M. tuberculosis* Early Secreted Antigenic Target -6 (ESAT-6).[71]

Interferon Gamma Release Assays (IGRA)

Interferon gamma release assays are the new T-cell based assays that measure the interferon gamma release, by sensitized lymphocytes in response to specific *M. tuberculosis* antigens such as the ESAT-6 and Culture Filtrate Protein 10 (CFP10).[69] These antigens, encoded by genes in the Region of Difference-1(RD1), are present in *M. tuberculosis,* but are absent in BCG vaccine strain and most nontuberculous mycobacteria except *M. marinum, M.szulgai* and *M. kansasii*.[72] Different currently available assays are the Enzyme Linked Immunosorbent Assay (ELISA), such as QuantiFERON TB and QuantiFERON TB Gold assays and enzyme linked immunospot assay, e.g. T-SPOT TB assay. In general, these tests are more specific and potentially more sensitive than the traditional TST.[73] Result of IGRA is not affected by prior BCG vaccination. The IGRA does not require a return visit, has no variability of skin test readings and there is no induction of boosting phenomenon on repeat testing. High diagnostic sensitivity has also been observed in young children for T-SPOT TB test and in immunosuppressed populations for both T-SPOT TB test and to a lesser extent to QuantiFERON TB Gold.[74]

Use of IGRA tests cannot differentiate latent infection from active disease. This is particularly problematic in high TB burden countries where the prevalence of latent infection is very high. Reactivation of latent TB infection reflects an impaired immune response, at least temporarily; so IGRAs may be falsely negative at the time of the development of disease.[75] Sensitivity in active TB ranges from 64 to 92%. Thus, IGRAs can potentially miss 10 to 30% of active TB cases and are hence unsuitable for use as "rule-in" tests.[76] Sensitivity of IGRAs also varies between high and low burden countries, clearly emphasizing the need to perform large studies in different settings.[76] The higher cost and need for sophisticated instruments prohibit their widespread use in the developing countries. Chemokine Inducible Protein 10 (IP-10) is another potential biomarker, which can be used in the immunodiagnosis of *M. tuberculosis* infection. Combination of IP-10 and IFN-gamma also increases the detection rate for LTBI.[77]

Diagnosis of Pulmonary Tuberculosis

Chest Radiology

Chest radiography is an important tool in suspecting the diagnosis of pulmonary tuberculosis. Chest X-rays are mostly abnormal in immunocompetent patients, but may be normal in about 10 to 15% of HIV-infected patients. No radiological features are typical of tuberculosis various other lung diseases can radiologically mimic TB. Radiological manifestations have been traditionally described in children and adults on the basis of primary and post primary tuberculosis.[78] Recently, these agewise distinctions of radiological manifestations have been blurred due to several reasons. Primary infection can occur at any age in an endemic area, further, primary tuberculosis accounts for 23 to 34% of all adult cases of tuberculosis.[79] Cavitation, generally considered as a sign of reactivation, can occur even after primary infection. HIV infection is also responsible for atypical radiographic manifestations. Two recent studies based on genotyping *M. tuberculosis* isolates with Restriction Fragment Length Polymorphism (RFLP) also show that the radiographic features are often similar in both primary and reactivation TB.[80,81]

In primary tuberculosis, classical radiological features include the presence of parenchymal disease, lymphadenopathy, pleural effusion, miliary disease and atelectasis. Parenchymal disease affects the areas of greatest ventilation in the lung and the most common sites are the middle lobe, lower lobe and anterior segment of upper lobe; however, it can affect any segment.[82] Dense and homogeneous consolidations are generally observed, but nodular and linear pattern are also occasionally seen.[83,84] A right sided predominance of parenchymal lesion is often seen, reflecting greater statistical probability of an airborne infection involving the right lung. Lymphadenopathy usually unilateral, is the most characteristic radiological feature in primary tuberculosis.[85] Hilar and paratracheal regions are most commonly affected. The combination of parenchymal focus and lymphadenopathy is called "Ghon complex."[86] On contrast enhanced Computed Tomography (CT) scan, TB lymphadenopathy, particularly when more than 2 cm in diameter, shows the characteristic "Rim sign" consisting of the central areas of low attenuation associated with peripheral rim enhancement and obliteration of surrounding perinodal fat.[87] This corresponds to central caseation necrosis with inflammatory, hypervascular capsular and perinodal reaction and is highly suggestive of active disease.[88] However, rim sign may also be present in other conditions, such as atypical mycobacterial infection, lymphoma, metastases, particularly from testicular carcinoma, Whipple's disease and Crohn's disease.[84]

The radiological features of post primary tuberculosis can be broadly classified as the parenchymal miliary disease, cavitation (Figs 40.1 and 40.2), tracheobronchial TB, and pleural extension of parenchymal disease and complications. The most common sites for parenchymal opacities are apical and posterior segments of the upper lobe and the superior segment of the lower lobe. Multiple segments are affected in about 88% of cases, bilateral upper lobe disease observed in 32 to 64% cases.[89] Poorly defined nodules and linear opacities are seen adjacent to parenchymal opacities in approximately 25% of patients.[90]

Cavities are most commonly seen within the areas of consolidation and are reported in 40 to 50% cases of post primary tuberculosis.[86] Cavitation usually indicate active disease. The number of bacilli are in the order of 10^7 to 10^9, therefore, a high likelihood of sputum positivity is there in cavitary lesions.[91] One important feature, which differentiates tuberculosis from other cavitary diseases is the presence of clearly defined, nodular opacities around the cavity.[82] Most common complication of cavitation is the bronchogenic spread due to the liquefaction of caseous necrotic material and subsequent communication with the bronchial tree. On chest radiography, bronchogenic spread is detected in approximately 20% of cases, but on CT scans, it can be identified in 95% of cases with post primary TB.[84]

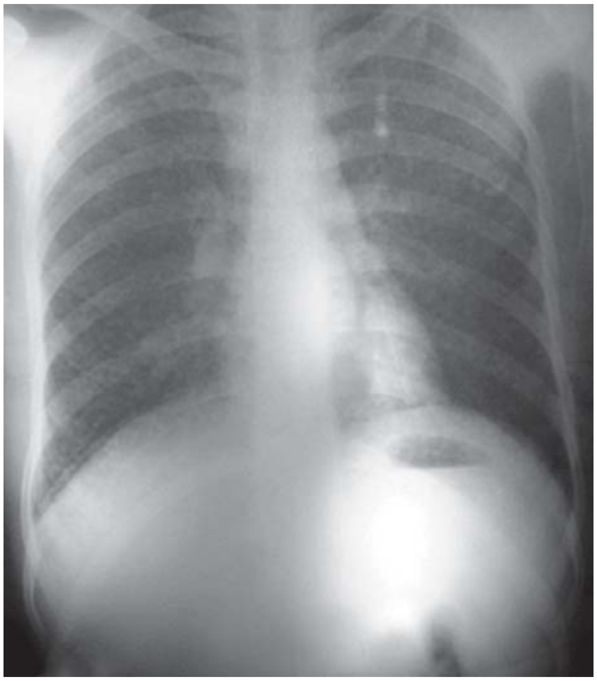

Fig. 40.1: Chest X-ray showing miliary shadow through both lung fields

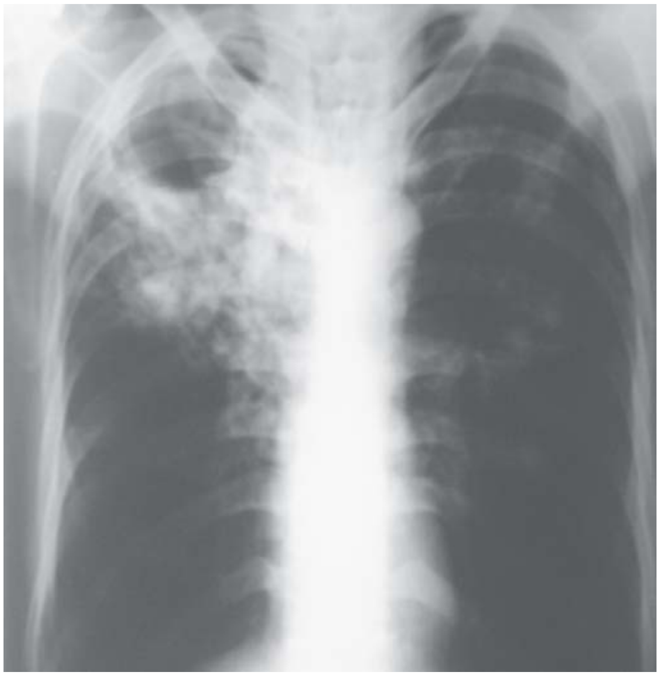

Fig. 40.2: Chest X-ray showing right upper lobe cavity with infiltration

Characteristics HRCT finding of bronchogenic spread is a "tree-in-bud" appearance, i.e. centrilobular nodules of 2–4 mm in size and sharply marginated linear branching opacities corresponding to the tuberculous involvement of the small airways. Air fluid level within tuberculous cavities may be seen in 9 to 21% of cases and usually indicates superimposed bacterial or fungal infection.[92-94] Hilar and mediastinal lymphadenopathy are not a common manifestation of post primary TB, occurs in only 5% of cases.[95]

Pulmonary TB with normal chest radiograph is increasingly being reported in the literature.[96] This is much more so in HIV positive persons (7 to 14%).[97-99]

The radiographic appearance of pulmonary tuberculosis is often "atypical" in HIV infected patients. It most commonly resembles with that of primary disease. Miliary disease and pleural effusion has been reported in up to 19 and 10% patients respectively.[99,100] Normal chest radiographs have been reported in 12 to 14% of HIV infected patients with smear or culture positive pulmonary tuberculosis.[99,100] Radiological manifestations may also depend on the degree of immunosuppression at the time of overt disease.

Chest CT is required in patients with high clinical suspicion of TB, but normal or nonspecific chest radiography. CT is more sensitive than chest radiography in detecting cavities, intrathoracic lymphadenopathy, miliary disease, bronchiectasis, bronchial stenosis and pleural disease. High Resolution Computed Tomography (HRCT) is superior to standard CT in the evaluation of pulmonary parenchymal disease.[101] In HRCT thorax, most commonly detected abnormalities in pulmonary TB are micronodules (100%) followed by "tree-in-bud" appearance (87%) and cavitation (73%).[102] The micronodules are typically centrilobular in location having indistinct margins. They are usually 5–6 mm in diameter, located in the peripheral parts of consolidations or cavities. Detection of micronodule is indeed highly suggestive of active tuberculosis.[101] Their presence indicates inflammatory lesions in the bronchioles and the peribronchiolar alveoli. Micronodules and "tree-in-bud" appearance are not detected by standard chest radiography. There is a significant correlation between consolidation and cavitation on conventional CT with increase in a number of bacilli in the sputum.[103] Consolidation pattern is also suggestive of active pulmonary TB, detected in 82% of patients.[102]

Tuberculoma is a sharply marginated round or oval lesion of 0.5–4.0 cm in diameter, detected in approximately 5% of patients with post primary TB. The location of tuberculoma has been variably reported in upper and lower lobes.[104] About 20 to 30% of tuberculomas in adults may ultimately calcify. In up to 80% of cases, smaller satellite lesions were seen in the immediate vicinity of the main lesion.[105] Tuberculomas are generally multiple, of similar size in 20% of cases.[106]

Miliary disease is less common in post primary than in primary TB.[79] Plain chest radiography can be normal in 25 to 40% of patients at initial presentation since typical miliary lesions need three to six weeks after hematogenous dissemination to manifest radiographically.[107] The typical radiological appearance is myriad, 1–3 mm, noncalcified nodules distributed throughout both the lungs, with mild basal predominance (Fig. 40.3). Other associated radiological features include consolidation, cavitation, calcified lymph nodes and lymphadenopathy observed in up to 30% of patients.[107] HRCT can detect miliary disease before it becomes apparent on standard chest radiography. Intralobular and interlobular septal thickening and areas of ground glass opacity may also be present. A diffuse alveolar pattern has been described in the patients of adult respiratory distress syndrome due to miliary TB.[108]

Sputum Microscopy

Sputum microscopy, the most widely available test for active TB, is the diagnostic centerpiece of the Directly Observed Treatment Short Course (DOTS) strategy. It is cheap, rapid, easy to perform and widely available diagnostic procedure to detect mycobacteria in clinical specimens. However, there are certain limitations of sputum microscopy. Sputum microscopy is not a highly

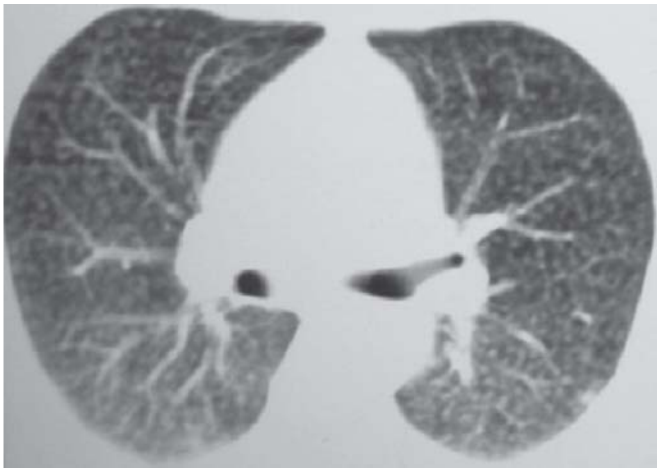

Fig. 40.3: HRCT Thorax showing miliary shadow through both lung fields

sensitive tool, it requires a minimal of 5,000–10,000 bacilli per ml of sputum to reliably identify the bacilli.[109] It can not differentiate *M. tuberculosis* from other mycobacteria. Sputum microscopy may also fail to diagnose paucibacillary and extrapulmonary tuberculosis, the incidence of which is disproportionately higher in high HIV prevalent areas. The sensitivity of sputum microscopy ranges from 34 to 80%.[110] The smear is more likely to be positive in patients who have cavitary disease and multilobar infiltrates. The result of smear microscopy is influenced by several variables like type of the specimen, thickness of the smear, technical preparation of the slide and experience of the laboratory personnel examining the smear.

Sensitivity of sputum microscopy is increased if sputum is liquefied and concentrated by centrifugation or sedimentation prior to acid fast staining.[111] In a systematic review of 83 studies, it has been demonstrated that sputum processed by centrifugation and use of various chemicals increased the sensitivity of microscopy by 18% compared to direct smear microscopy.[112] The most widely studied sputum processing method is liquefaction of sputum with sodium hypochlorite usually known as household bleach (NaOCl), followed by centrifugation or sedimentation. There are several advantages of using NaOCl; it is widely available and kills both the mycobacteria and HIV, therefore, tends to increase the safety and acceptability in the laboratory. However, this technique is not suitable for sample intended to be used for culture. Studies done in Ethiopia have reported that a single digested smear can equal the sensitivity of three direct smears.[113] Furthermore, there are certain limitations of these procedures, particularly in the context of resource limited, high prevalence countries. Irregular power supply, potential biohazard of centrifugation, and limited human and financial resources may impede its widespread applicability in the developing countries. Moreover, there is insufficient data to determine the value of sputum processing methods in HIV infected patients.

There are several staining methods such as the Ziehl-Neelsen, Kinyoun's (cold staining) and fluorescent staining methods.[114] The core principle of these methods is based on the avidity of the lipid rich cell wall to different dyes. In Ziehl-Neelsen method, heat is applied to encourage the cell wall to take up the stain followed by decolorization with acid or acid alcohol, and finally counterstaining with methylene blue or malachite green. In cold Kinyoun's method, higher concentrations of phenol and basic fuchsin are used.[114] The mycobacteria in these staining methods appear red against blue or green background. Performance of Kinyoun's stain has been reported to be inferior to that of Ziehl-Neelsen stain in several studies.[115,116] Other microorganisms that may take up acid fast stains, albeit weakly, are Rhodococcus, Nocardia, Legionella micdadei, and cysts of Cryptosporidium, Isospora, and Cyclospora.

Fluorescence microscopy requires staining with the dye auramine rhodamine. The mycobacteria appear bright yellow rods against inky black background. There are several advantages of fluorescent microscopy over conventional staining methods:[117]

- Rapid turnaround time with fluorescence microscopy as it uses a lower power objective lens (typically 25X) than conventional microscopy (typically 100X), allowing much faster reading of specimens than smears stained with the Ziehl-Neelsen method. It takes one to two minutes per slide in contrast to 15 minutes required for Ziehl-Neelsen staining method
- It is more sensitive than conventional microscopy. In comparison with Ziehl-Neelsen microscopy, fluorescence microscopy has shown a 10% increase in sensitivity. The major problem of its implementation in the developing countries is the cost of fluorescent bulb, which is costly and is of a short life span (typically 200–300 hours). The use of light emitting diodes as a light source is an attractive, inexpensive alternative to mercury vapor lamps.[118]

In recently revised policies on smear microscopy, WHO now recommends two sputum specimens examination instead of three for screening of TB cases, in places where a well functioning external quality assurance system exists and where the workload is very high and human resources are limited.

Smear microscopy is likely to retain its pivotal role in the diagnosis of TB in major parts of the world. Optimization of smear microscopy should be an important goal of any tuberculosis control program. Smear negative patient who is unable to produce sputum, should undergo further diagnostic testing such as Sputum Induction (SI), Fiberoptic Bronchoscopy (FOB) and sometimes Gastric Washings (GW).

Induced Sputum Examination

There are several advantages of sputum induction:

- Diagnostic yield of single induced sputum is atleast equivalent to that of one bronchoscopy with Bronchoalveolar Lavage (BAL) in the terms of positivity on both smear and culture for mycobacteria.[119,120] The diagnostic yield of induced sputum can be increased with significantly higher detection rates than with bronchoscopy alone when multiple (three or more) specimens are used. Smear microscopy and culture positivity rates of 91 to 98% and 99 to 100% respectively, have been reported with multiple specimens.[121]

- Induced sputum is a very safe procedure with extremely few adverse events, unlike invasive procedure such as bronchoscopy. Most common adverse events are headache, bronchospasm/cough and the risk of transmission of TB to attending staff, if appropriate protection measures are not applied
- Cost analysis studies also favor sputum induction over bronchoscopy[122]
- Sputum induction performs equally well in both resource poor and resource rich countries and is also useful in HIV positive and negative patients.[114]

Therefore, sputum induction should be used as the primary modality in patients who are either unable to provide spontaneous sputum samples or who are AFB smear negative.[123] Sputum induction has been shown to improve sputum microscopy result by 29% in patients with suspected TB who previously had negative smear.[124] It is also superior to gastric aspirate specimens in the terms of sensitivity and speed to culture positivity.[125]

Fiberoptic Bronchoscopy (FOB)

The main role of FOB in diagnosing pulmonary tuberculosis includes patients who are sputum smear negative for AFB or who do not produce adequate sputum, particularly if an immediate diagnosis is required or if alterative diagnoses are being entertained. It is also useful for follow-up studies in endobronchial tuberculosis to detect bronchostenosis. Different bronchoscopic modalities to obtain samples include the bronchial aspirate, bronchoalveolar lavage, brushings, Transbronchial Lung Biopsy (TBLB) and Transbronchial Needle Aspiration (TBNA). Among the various bronchoscopic procedures to retrieve samples, the yield of BAL for *M. tuberculosis* is superior to that of bronchial washings.[125] The higher yield in BAL is due to the large quantity of saline used in BAL, which lowers the concentration of aspirated local anesthetic, which can inhibit the growth of *M. tuberculosis*. A small amount of 2 ml of 2% lignocaine can produce a bronchial aspirate concentration of up to 1% at which most strains of *M. tuberculosis* are inhibited.[126,127]

Culture of TBLB and bronchial brushing specimens provide little additional yield. Various studies using FOB as a modality, have demonstrated early diagnosis in 4 to 79% cases and exclusive diagnosis in 2 to 52% cases.[126] FOB use in high prevalent areas of TB has successfully led to early diagnosis in a larger percentage of patients (72 to 73%).[128,129]

Use of FOB in miliary TB seems particularly attractive because of inherent problems with conventional diagnostic procedures. Presence of miliary mottling on chest radiography varies from 50 to 93% of cases.[130,131] Smear microscopy and sputum cultures are positive in one-third and less than two thirds of patients respectively.[131] Delay in diagnosis can be associated with significant mortality in miliary tuberculosis. Using FOB, immediate (or early) diagnosis (positive AFB smear, transbronchial biopsy specimens revealing caseating granulomas with or without AFB) can be achieved.

FOB is also useful in the diagnosis of tuberculous intrathoracic lymphadenopathy by using TBNA technique. Incidence of isolated intrathoracic tuberculous lymphadenitis varies from 0.25 to 5.8%, poses a diagnostic challenge. FOB in tuberculous intrathoracic lymphadenopathy also helps because of the presence of endobronchial involvement in a large percentage of patients (75%), which also explains frequent erosion of bronchial tree by intrathoracic tuberculous lymphadenopathy.[132] Endobronchial ultrasound is another tool, which can further ease the procedure of TBNA.

Mycobacterial Cultures

Mycobacterial culture is the gold standard for the diagnosis of tuberculosis. It is more sensitive than sputum microscopy, requires 10–100/ml organisms to detect *M. tuberculosis*.[110] About 25 to 60% of patients with culture positive pulmonary TB may show negative smears. Sensitivity and specificity of culture is 80 to 93% and 98% respectively.[110,133] Culture not only increases the sensitivity of *M. tuberculosis* diagnosis, but also helps in species identification, drug susceptibility testing and genotyping.

Culture media are of various types: Solid media, which can be egg based (Lowenstein-Jensen) or agar based (Middlebrook 7H10 and 7H11) media; and liquid media (Middlebrook 7H12 and other broths). Most laboratories in the developing countries use solid media for mycobacterial culture. The greatest isolation rates are obtained from a combination of solid and liquid media. The main constraint of solid media is long time required for growth (mean time of at least four weeks). Other problems in the developing countries are the nonavailability and the inaccessibility of reliable laboratories for good quality cultures. Liquid culture media based on

Middlebrook 7H12 broth give faster results than the solid media. They are also more sensitive than solid media for the detection of mycobacteria and may increase the diagnostic yield by 10%.[134,135] Disadvantages of liquid culture media include a high risk of contamination and the lack of colony morphology examination, which may help in detecting unexpected growth of non TB mycobacteria.

Following are the rapid culture methods which are available:

i. *BACTEC (Becton Dickinson) culture medium:* A BACTEC 460 radiometric system (Becton Dickinson Instrument Systems, Sparks, MD, USA) is an automated method. It is based on the measurement of $^{14}CO_2$ liberated from ^{14}C palmitic acid by metabolizing mycobacteria. There is a rapid turn around time with 87% of positive cultures recorded at 7 days and 96% by 14 days.[136] Major constraints with this method are the high costs and the problem of disposal of radioactive materials.

ii. *Mycobacterial Growth Indicator Tube (MGIT):* MGIT is a nonradiometric system. It contains Middlebrook 7H9 broth and a fluorescent compound embedded in a silicone sensor, which is sensitive to oxygen consumption in the medium emitting luminescence. Growth is detected visually using the ultraviolet light. Both manual and automatic (BACTEC MGIT 960) systems are available. Results are comparable to that of BACTEC 460 radiometric system.[137] The mean time for the detection of growth of mycobacteria in MGIT ranges from 8 days to 16 days.

iii. *Microcolony detection on solid media:* Growth of mycobacteria is detected by microscopic examination of plates covered with the thin layer of Middlebrook 7H11 agar medium. Though this technique is less expensive and requires lesser time than conventional culture, recovery of mycobacteria is less efficient and labor intensive.

iv. *Septi check AFB method:* It is biphasic culture system made up of a modified Middlebrook 7H9 broth with a three sided paddle containing chocolate, egg based, and modified 7H11 solid agar. The growth is observed by the three sided paddle. The main characteristic of this system is the simultaneous detection of *M. tuberculosis*, nontubercular mycobacteria and even, contaminants.

v. *MB/BacT system:* This is a nonradiometric system based on the colorimetric detection of CO_2. The disadvantages are the increased contamination and slightly longer time required for the detection of growth as compared to BACTEC 460 system.[138]

vi. *ESP II culture system:* This is a fully automated continuously monitoring system based on the detection of pressure changes in the culture medium of a sealed vial during mycobacterial growth. It should be used in combination with solid medium only.

vii. *Microscopic Observation of In Broth Culture (MODS):* It is suitable for high tuberculosis burden country, but it requires high laboratory biosafety, relatively costly media, antimicrobial supplements and high technical skills.

EXTRAPULMONARY TUBERCULOSIS (EPTB)

In immunocompetent adults, EPTB constitutes about 15 to 20% of all cases of TB, whereas in HIV positive patients, it accounts for more than 50%.[139] The commonly reported extrapulmonary sites of tuberculous involvement are the lymph nodes, pleura, bones or joints, and Central Nervous System (CNS). However, it can involve any organ. Lymph node tuberculosis is the commonest form of EPTB in India and other developing countries.[130]

Diagnosis of EPTB can pose a challenge to the clinicians due to various reasons:

- Signs and symptoms are most often nonspecific
- Paucibacillary nature of samples decreases the sensitivity of diagnostic tests
- EPTB involves relatively inaccessible sites so the retrieval of samples for diagnosis is a difficult job.

In a retrospective study done in Tanzania involving patients with extrapulmonary tuberculosis, bacteriological or histological confirmation of diagnosis was possible in only 18% cases.[140] So misdiagnosis is common in almost all countries, which may lead to unnecessary presumptive treatment in patients without TB, or greater morbidity and mortality if the diagnosis of TB is delayed, especially in persons with concomitant HIV infection.

Microscopic examination of sputum and culture lacks sensitivity in extrapulmonary disease. In a prospective study in Malawi, sputum positivity rate in EPTB patients was dismal (1.7%).[141] But, in some form of EPTB, e.g. pleural TB, sputum samples may be beneficial. Conde et al.[142] reported a remarkably high yield of mycobacterial culture (52%) in a single specimen of induced sputum with sputum smear-positivity in 12% of cases. Therefore, resource limited countries where invasive diagnostic procedures are less accessible, sputum induction should be advised.[143]

Chest radiology may sometimes provide useful clue of the presence of associated pulmonary TB and may obviate the need for further invasive diagnostic modality in the developing countries. Abnormal chest radiography has been reported in 5 to 44% of lymph node tuberculosis, 30 to 50% of pleural effusion, 20 to 28% of abdominal tuberculosis and 32% of pericardial TB patient's respectively.[143]

Adenosine Deaminase (ADA) enzyme estimation especially in pleural fluid has shown great promise in the diagnosis of tubercular pleural effusion. In pleural effusion, sensitivity and specificity of ADA have varied from 85 to 100% and 80 to 97% respectively.[144] ADA levels are also elevated in a number of extrapulmonary sites in patients with TB, including Cerebrospinal Fluid (CSF) and BAL. However, the utility of measuring ADA levels in these fluids has not been rigorously studied.

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Molecular Diagnosis of Tuberculosis

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INTRODUCTION

Only 5 to 10% of the individuals who get infected with *Mycobacterium tuberculosis* (*M. tb*) progress to clinical TB;[1,2] the remaining individuals who get infected develop immune responses that arrest the progression of the infection to clinical TB, although they continue to harbor a Latent Tuberculosis Infection (LTBI). Approximately, 10% of the latently infected subjects reactivate their LTBI and progress to clinical TB sometime later during the years/decades postinfection. Despite this relatively limited progression of *M. tb* infection to clinical disease, more than 8 million new cases of TB occur every year and approximately two million individuals die because of TB.[3,4] The spread of Human Immunodeficiency Virus (HIV)-infection in the TB endemic countries and the synergistic relationship between HIV and TB is further accelerating the morbidity and mortality caused by TB.[4] The WHO has implemented Directly Observed Therapy Short-term (DOTS) programs for TB diagnosis and treatment in most parts of the world. However, the success of the DOTS programs is hampered by the lack of rapid and accurate diagnostic tools.

DIAGNOSIS OF TB IN LOW-INCOME COUNTRIES

Tuberculosis is a chronic, slow progressing infection (except in immunocompromised individuals), which can manifest as pulmonary or extrapulmonary disease. Even pulmonary TB is not a single-stage acute disease and patients present with a spectrum of clinical, radiological and bacterial indications.

There is no single diagnostic test that can detect TB at all the different stages or the different forms of TB, a combination of clinical suspicion, microscopic examination of smears made directly from sputum for presence of Acid-fast Bacilli (AFB) and radiological findings are used for diagnosis. Clinically, TB can present with symptoms that vary from mild cough or chest pains in an otherwise asymptomatic patient to fever, night sweats, wasting, hemoptysis, etc. and therefore, often does not provide unambiguous diagnosis. Acid-fast bacilli microscopy is highly specific and low-cost,[5,6] but visualizing bacteria in smears made without processing and concentration of sputum specimens requires the presence of 5 to 10 thousand AFB per ml of the sputum; this occurs only when the patient has progressed to advanced disease.

Microscopy requires careful examination of multiple specimens from each patient, which is tedious and requires good microscopes; factors that decrease sensitivity in settings that have high patient burden and meager resources. As a result, the sensitivity of the AFB smear test varies from 30 to 80% in culture confirmed TB in different laboratories. Microscopy fails to identify about 50% of the patients who have less advanced disease (smear negative) and performs poorly in pediatric cases, patients with extrapulmonary TB and HIV-infected TB patients. Thus, AFB smear-based diagnosis results in significant under-diagnosis of TB, resulting in increased morbidity and mortality and continued transmission into the communities.[6] Chest X-rays can aid diagnosis when the disease is advanced, but their utility is limited by patient variability in that there may be no pulmonary involvement, or patients may have a typical infiltration or may have progressed to different levels of cavitation and pulmonary damage. Culture of AFB although can enhance the sensitivity of diagnosis, permits identification and drug sensitivity testing of isolated mycobacterial species. However, because *M. tb* is a slow growing pathogen, cultures require several weeks (6 to 8 weeks) and are significantly more expensive than microscopy. In developing countries, culture is not a feasible option because of the high patient burden and the requirement for expensive laboratory infrastructure and the associated expenses. Rapid and simple tests that can replace AFB microscopy, and can improve diagnosis of paucibacillary TB are urgently required.

DIAGNOSIS OF TB IN HIGH-INCOME COUNTRIES

The speed and accuracy of TB diagnosis is significantly better in the resource-rich countries (US, Western Europe, etc.) that have a low incidence of TB. Microscopy has significantly improved sensitivity because the smears are prepared from sputum samples that are digested, decontaminated and concentrated; fluorescence microscopy, which is more sensitive, is routinely used. Culture of bacteria on solid (Middlebrook, Lowenstein-Jensen) and/or liquid media complements microscopy and several sensitive broth-based culture systems are routinely used (Becton, Dickinson and Company, Sparks; MB/BacT, Organon Teknika Corporation, NC; ESP, TREK Diagnostic systems Inc, Cleveland, OH; Wampole laboratories, Princeton, NJ; etc). Fully automated systems where the vials inoculated with the patient specimen are monitored continuously for bacterial growth are available in most mycobacteriology labs. Coupled with the highly sensitive and specific nucleic acid amplification tests (NAAT, GenProbe, San Diego, Ca; Amplicor, Roche, Basel, Switzerland) that are available for the confirmation of *M. tb*, the sensitivity of TB diagnosis of multibacillary TB cases in these countries is very high (95 to 98%) and a large proportion of paucibacillary cases (48 to 53%) are also detected.[7,8]

Despite the use of multiple diagnostic methods, diagnosis of smear negative TB cases can take several weeks as chest X-rays/CT scans and microscopy take several days and another 7 to 14 days are required for culture confirmation even in smear-positive patients. Additional sensitive methods for the identification of *M. tb* from liquid cultures are available (HPLC, GLC) and may be useful for the difficult-to-diagnose cases, but the costs and complexity limit their use in routine diagnosis. Despite the use of multiple tests, no bacteriological confirmation can be obtained for approximately 10 to 20% of the TB patients, who are determined to have TB based on clinical and/or radiological improvement while on anti-TB medications.[9] Clearly, there is a definite need for improved diagnostic tests even for the resource-rich countries and tests that can rapidly identify paucibacillary TB would be an asset to TB control.[1,10]

Detection and treatment of LTBI is an integral component of TB control in the high-income settings. The detection of LTBI is based on the Tuberculin Skin Test [TST; also called the purified protein derivative (PPD) skin test], which measures delayed hypersensitivity responses elicited by the mycobacterial antigens.[2] Because PPD is actually a crude mixture of more than 200 different secreted and somatic proteins of *M. tb*, many of which are shared among Nontuberculosis Mycobacteria (NTM) and *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG), the specificity of the PPD test is low, especially in individuals vaccinated with BCG or cross-sensitized with nonpathogenic environmental mycobacteria. The sensitivity of the PPD test is also suboptimal and it fails to identify approximately 20 to 30% of confirmed TB cases. Although PPD testing is relatively inexpensive, it fails to differentiate between a latent infection that may never progress to clinical TB and active subclinical or clinical TB[11-13] and cannot predict if and when the infection will progress to clinical TB. As a result, even though approximately 5 to 10 % of the *M. tb* infected individuals actually progress to clinical TB, all PPD-positive individuals require clinical, bacteriological and radiological evaluation and individuals believed to be infected and at risk for TB are required to take preventive therapy with Isoniazid (INH) for six to nine months.[2] Thus, PPD test-based decisions result in treatment of latent infection in individuals who may never progress to clinical TB, monotherapy in individuals who may have an active but subclinical infection or are infected with INH-resistant *M. tb* and no treatment in infected individuals with false negative responses.[2]

According to the CDC estimates, there are approximately 15 million latently infected individuals in the US, and better diagnostic tests that can accurately identify *M. tb* infection and can discriminate between latent and incipient subclinical TB in high risk populations are required to eliminate TB from the US.[10,14] More accurate diagnostic tests for M. tb infection, the Interferon Gamma Release Assays (IGRAs; described below) have become available in recent years and are increasingly being used in these countries instead of TST.

TB DIAGNOSIS IN HIV+ INDIVIDUALS

The immune dysfunction caused by HIV infection leads to increased reactivation of latent TB, increased incidence of primary TB and accelerated course of disease progression in HIV+ individuals.[15-19] The risk of developing TB doubles as early as in the first year after acquiring HIV infection and continues to increase in subsequent years.[20] As a result, in sub-Saharan Africa and Southeast Asia where TB is endemic, approximately 50 to 70% of the HIV+ individuals develop TB.[4,21-24] Concomitant TB accelerates the progression of HIV infection.[15,16] The dysfunctional cellular immune responses in HIV+ patients result in reduced pulmonary pathology and progression to cavitary lesions, which in turn results in reduced smear positivity. For these reasons, the limitations of the current diagnostic tests for TB are amplified in HIV coinfected individuals.[25] TB is thus the single most important cause of morbidity and mortality in HIV+ patients in TB-endemic countries. As in nonHIV *M. tb* infected individuals, preventive therapy with INH in HIV co-infected individuals with latent *M. tb* infection has also been shown to reduce the risk for developing TB.[1]

In TB-endemic countries the rates of latent infection are high, preventive treatment with anti-TB drugs, and the accompanying clinical, bacteriological and adherence monitoring is impossible, and treatment of unrecognized active TB with one or two drugs enhances the risk of fostering drug resistance.[26-28] For these reasons, preventive treatment for HIV-infected persons is not recommended in these settings unless active TB can be ruled out on the basis of clinical evaluation.[29,30] No diagnostic tests that can discriminate between latent TB and incipient, subclinical TB in HIV-infected individuals are currently available. This is problematic because undiagnosed active TB in asymptomatic HIV+ patients with no clinical, radiological or bacteriological indications of TB has been reported from several settings.[18,19] Thus, tests that can rapidly discriminate between LTBI and incipient subclinical TB and identify patients with subclinical TB prior to progression to bacteriologically detectable, clinical TB are urgently required. Such a test would prevent progression of *M. tb* infection to clinical TB, contribute to interruption of transmission into communities, and retard the progression of HIV-infection in patients who are unable to obtain antiretroviral therapy.[27]

DIAGNOSIS OF TB: BEYOND MICROSCOPY

Direct sputum microscopy has been used for TB diagnosis since the 1880s and it remains the primary tool for TB diagnosis, 120 years later. More sensitive and specific diagnostic tests have emerged in the last few decades, but are too expensive and technically challenging for implementation in the high burden, low-resource settings. While an unprecedented interest has arisen in devising new diagnostic tools for TB in the last decade or so, and some new tests have been devised, there is still a significant lack of tools that will be required to control and eliminate TB. An overview of the diagnostic tests that are used in the developed world or are currently under development is provided (Table 41.1).

Nucleic Acid Amplification (NAA) Detection Based Diagnostic Tests for TB

The use of NAA based diagnosis has led to significant improvement in rapid diagnosis of TB in the resource-rich countries. Several commercial NAA tests are currently available, each using a different method to amplify a

TABLE 41.1: Molecular methods used for diagnosis of tuberculosis

1. Nucleic acid amplification (NAA) detection based tests
    i. Amplified MTB Direct test (MTD)
    ii. Amplicor MTB test (Amplicor)
    iii. COBAS Amplicor MTB test
    iv. COBAS TaqMan test MTB
    v. BD ProbeTec MTB test
    vi. Polymerase chain reaction (PCR) based ‘in-house’ NAA tests targeting DNA or RNA sequences
2. Molecular tests for species identification
    i. MicroSeq 500 system
    ii. AccuProbe assay
    iii. INNO-LiPA Mycobacteria
    iv. Geno Type MTBC and Geno Type Mycobacterium
3. Tests for drug-resistance
    i. The line probe assay (LiPA)
    ii. Geno Type MTBDR-Plus
    iii. Cepheid GeneXpert System
4. Bacteriophage-based tests
    i. Luciferase reporter phage assay
    ii. In-house phage amplification tests
    iii. Microarray technology
5. Diagnosis of latent tuberculosis
    i. Tuberculin skin test (TST)
    ii. Interferon gamma release assays (IGRA)
        a. Enzyme linked immunospot assay (Elispot and TSPOT.TB)
        b. QuantiFERON-TB Gold
6. Antibody detection based diagnosis
    Serodiagnostic assays – (38 kDa, LAM and other antigens)

specific region in *M. tb* genome. These include: The Amplified *M. tuberculosis* Direct test (MTD, Gen-Probe Inc, CA), the Amplicor M tuberculosis test (Amplicor), the COBAS Amplicor MTB test, the COBAS Taqman test MTB (Roche Diagnostics Inc, NJ) and the BD ProbeTec MTB test (Becton Dickinson, MD). Of these, the MTD test was the first NAAT approved by the United States Food and Drug Administration (FDA) in 1995 for *M. tb* detection in AFB smear-positive respiratory specimens. Later, in 1999, a second-generation MTD (enhanced MTD or E-MTD) test was approved for use in respiratory specimens from all patients suspected to have TB regardless of their smear status.[31] The Amplicor *M. tb* test was approved by the FDA in 1996 for testing in AFB smear positive TB patients using respiratory specimens only.[31]

The MTD test is based on isothermal amplification of 16S rRNA transcripts (transcription mediated amplification, TMA) that is detected using acridinium ester labeled *M. tb* complex-specific DNA probes in a hybridization protection assay.[32] The entire process is carried out at 42°C. Although entirely manual, the test is rapid with a turnaround time of about 2.5 hours. The results however, require a luminometer for interpretation. Several studies have confirmed the sensitivity and specificity of MTD test; the sensitivity ranges between 90 to 100% in smear-positive and 63 to 100% in smear-negative specimens.[33] Enhanced-MTD, the modified version of the original MTD test, uses larger sample volume, requires less processing time and is simpler to perform due to the elimination of hybridization controls and amplification termination step.[34] Both MTD and E-MTD are highly specific (>95%) however, sensitivity of E-MTD has been shown to be higher than the original MTD test.[35,36]

The Amplicor is a DNA-based test that amplifies 16S rRNA gene using genus-specific primers followed by hybridization to specific probes. The binding of probes is detected by a colorimetric reaction in a microwell plate format.[37] Turnaround time for the Amplicor test is six to seven hours. The Amplicor MTB test provides 90 to 100% sensitivity in smear-positive respiratory samples and 50 to 95.9% in smear negative samples. Overall specificity has been reported in the range of 90 to 100%.[33,38] An automated version of the test, the COBAS Amplicor is also available that uses the COBAS Amplicor analyzer and allows rapid amplification and detection in one system.[39] A qualitative COBAS TaqMan MTB test based on integration of real-time PCR technology with standard hybridization is also available. The turnaround time for analyzing 48 samples simultaneously using COBAS TaqMan is 2.5 hours.[38] Recent studies suggest that accuracy of COBAS TaqMan is superior to Amplicor for detecting *M. tb*, but the test is not yet approved by FDA.[40,41]

BD ProbeTec MTB test (Becton Dickinson, MD) is another commercially available test for the direct detection of *M. tb*. It is a semiquantitative assay that involves strand displacement method for enzymatic amplification of target sequences located in IS6110 and 16s rRNA genes.[42] The products of amplification are detected using a luminometer. The test has shown high sensitivity in both smear-positive (100%), as well as smear-negative (92 to 100%) patients using respiratory samples.[42,43] However, the sample preparation is time consuming. An improved version of BD ProbeTec ET that includes an internal amplification control to detect the presence of inhibitors showed higher sensitivity in smear-positive than smear-negative samples.[44] This test also awaits approval from FDA.

The CDC guidelines recommend that "NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is considered but not established and for whom the test result would alter case management and TB control activities."[31] However, because all the current tests require trained personnel, specialized equipment and are expensive, they are rarely used in the TB-endemic countries and cannot be integrated into routine patient care.

Efforts to develop cheaper, simpler and less technology-oriented NAA-based molecular tests are ongoing. A Loop-Mediated Isothermal Amplification (LAMP) (Eiken Chemical Co., Japan) test has been developed for simple and sensitive detection for TB.[38] The technique involves autocycling strand displacement DNA synthesis using the large fragment of *Bacillus stearothermophilus* DNA polymerase. Pyrophosphate produced as a byproduct during DNA synthesis in LAMP assay is visible as a white precipitate of magnesium pyrophosphate in the reaction vial. DNA detection is based on presence or absence of the precipitate.[45,46] Moreover, the turbidity of the reaction mixture is directly proportionate to the amount of DNA synthesized. The entire procedure is carried out in a single tube by incubating very small volume of DNA at 63°C for 1 hour. A prototype LAMP assay with simplified manual DNA extraction method to detect *M. tb* in respiratory samples has been used for clinical evaluation in peripheral microscopy centers in Peru, Bangladesh, and Tanzania.[47] The test outperformed microscopy in these studies and demonstrated the feasibility of performing the assay without the use of sophisticated equipment and specialized training.[47,48] More extensive field evaluations of the assay are under way.

Several in-house assays employing simple PCR as well as real-time PCR-based techniques have been reported from different laboratories for the diagnosis of TB. PCR based in-house NAA tests involve amplification of either various target DNA or RNA sequences followed by detection using agarose or acrylamide gel electrophoresis or by hybridization.[49-53] Real time PCR is a quantitative method based on the hybridization of the amplified segments (DNA) with different fluorescent probes, such as TaqMan probes Fluorescence Resonance Energy Transfer (FRET) probes molecular beacons and bioprobes.[54,55] The intensity of fluorescence is detected in a thermal cycler and is directly proportional to the amount of amplified product in the reaction tube. The main advantage of Real time PCR is its speed to yield the results reducing the time to 1.5 to 2 hours after DNA extraction. In addition, the problems with cross contamination are less likely as detection takes place in a closed system. The adaptation of these in-house assays to commercial formats is awaited.

Tests for Species Identification of Mycobacteria

Prompt identification of *Mycobacterium* species has become increasingly important with the increase in NTM infections, especially in HIV-infected individuals.[56] NTMs require a different treatment regimen and a lack of response to standard antituberculous drugs can be confused with drug-resistance.[57] Thus, adequate disease management requires precise classification of mycobacteria. Conventional methods of *Mycobacterium* species identification include biochemical tests and phenotypic characteristics that are simple and do not require any sophisticated equipment, but these tests are laborious and cumbersome, and take several days for results, thus delaying prompt and accurate identification of bacteria. Newly developed molecular methods are attractive alternatives for rapid identification of mycobacteria, especially *M. tb* complex. Several molecular commercial tests are available for rapid identification of mycobacterial species from culture isolates.[58] These include the MicroSeq 500 system (Applied Biosystems, Foster City, CA), AccuProbe assay (Gen-Probe Inc, CA), INNO-LiPA Mycobacteria (Innogenetics NV, Belgium), GenoType MTBC and GenoType Mycobacterium (Hain Lifescience, Nehren, Germany).

The MicroSeq 500 is a microbial identification system based on sequencing of a 16S ribosomal DNA. The test has shown high sensitivity with clinical isolates, but is time consuming and requires sophisticated instrumentation for data analysis.[59,60] The AccuProbe assay, one of the first introduced and the most widely used molecular technique for species identification, utilizes species specific DNA probes. Hybridization of these probes with species specific target rRNA sequences can differentiate and identify *M. tb* complex, *M. avium, M. intracellulare, M. avium complex*, *M. kansasii* and *M. gordonae*.[61-66] The sensitivity and specificity of these probes is reported to be more than 90%.[38] The turnaround time using AccuProbe on culture is two hours, but the test can identify only a limited number of species and is unable to differentiate *M. tb* from the other species in the complex.[67]

The INNO-LiPA Mycobacteria v2 (Innogenetics NV, Belgium) system for mycobacterial species identification simultaneously detects and identifies the genus *Mycobacterium* along with 16 different species. It is a line probe assay based on nucleotide differences in the 16s–23s rRNA gene spacers. The test can be performed on liquid or solid cultures and shows high specificity (94%) and sensitivity (100%)[68-70] in a variety of mycobacterial species. The other two commercially available molecular systems, GenoType MTBC and GenoType Mycobacterium use reverse line probe hybridization assays to identify mycobacterial species and differentiate members of the *M. tuberculosis* complex.

The basic technique for both the assays involves PCR amplification followed by the hybridization of the amplified products to specific oligonucleotide probes immobilized on the membrane strips. The interpretation is based on the appearance of bands in specific combinations. The GenoType *Mycobacterium*, based on regions of 23s rRNA, is able to identify 35 different species of mycobacteria, including *M. tb*.[38,71] The GenoType MTBC uses 23s rRNA fragment and gyrB sequence polymorphism to differentiate members of *M. tb* complex. Further, it targets RD1 deletion for identification of *M. bovis* BCG.[72] The GenoType MTBC test has been widely used for the speciation of mycobacteria in different studies and shows consistently high sensitivity and specificity.[73-75] However, these assays are labor intensive, require extensive training and being culture dependent, are restricted to use in reference laboratories.

In addition to commercial molecular tests, several in-house assays have been reported for mycobacterial species identification. These include sequencing of DNA fragments from various conserved and hypervariable regions of mycobacterial genome, such as 16s rRNA,[76] 23s rRNA,[38] 65-kDa heat-shock protein encoding gene[77] rpoB,[78] SoDA[79] and recA.[80] PCR- restriction length polymorphism has also been studied using hsp65[81,82] rpoB[83] and gyrB[84] genes to determine different species of mycobacteria, including *M. tb*. In addition, recent reports from the developing countries describe the use of real-time PCR for species identification of mycobacteria.[85-88]

Diagnostic Tests for Drug-Resistance of MTB

Even as efforts to devise improved diagnostic tests for TB are ongoing, there has been an alarming increase in the incidence of Multidrug-Resistant TB (MDR-TB) and Extensively Drug-Resistant Tuberculosis (XDR-TB) in several parts of the world.[89-91] MDR-TB is defined as resistance to both INH and rifampicin and XDR-TB is defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of the three injectable Second-Line Drugs (SLDs)—capreomycin, kanamycin and amikacin. As per the WHO estimates, almost 25% of the 5 million cases of MDR-TB that emerged globally in 2006, were from India. Recent studies have reported both MDR-TB and XDR-TB in India.[92-94]

Conventional diagnosis of DR-TB by the proportion method, absolute concentration method or the resistance ratio method takes several weeks even with the rapid-culture (BACTEC 460, MB/BacT, MGIT) based methods since the primary isolation and culture of *M. tb* from the clinical specimen is followed by susceptibility testing in cultures. During this time, transmission of resistant bacteria continues and patients are treated with inappropriate regimens, potentially amplifying resistance.

Rifampicin (Rif) is the key drug in the first-line chemotherapy of TB and it is estimated that over 90% of the Rif-resistant strains are also INH-resistant. Two commercial assays for rapid detection of drug resistance in *M. tb* have become available: The Line Probe Assay (LiPA) (INNO-LiPA RifTB Assay, Innogenetics) for the detection of resistance to rifampicin and the GenoType MTBDRPlus (Hain Lifescience) for simultaneous detection of rifampicin and isoniazid resistance. The basis of both assays is reverse solid phase hybridization. The line probe assays involve extraction of DNA from *M. tb* isolates, either from cultures or directly from clinical specimens, followed by PCR-amplification of the resistance-determining region of the gene in question using biotinylated primers. The PCR products are hybridized with specific oligonucleotide probes that are immobilized on a strip. The captured hybrids are detected by colorimetric development. The mutations are identified by lack of hybridization of the amplified PCR products to wild type probes as well as hybridization to specific probes for most commonly occurring mutations.

Results from systematic reviews and meta-analysis commissioned by WHO in 2008[95] showed that line probe assays are highly sensitive (>97%) and specific (>99%) for the detection of rifampicin resistance, either alone or in combination with INH. Moreover, the assay performance was maintained even when sputum specimens were used. Since these assays require processing of sputum specimens, use of BSL3 facilities is recommended for using these tests. Moreover, reagents for these assays require refrigeration and/or freezing, which translates into regular power supply, molecular grade water and enzyme (Taq polymerase) and several different equipment (thermal cycler, shaker platform, water bath, heating block, sonicator, hybridization chambers, etc.). Clearly, these tests require significant infrastructure and training and will be difficult to implement except in the few sophisticated labs in developing countries.

A new nucleic acid amplification-based diagnostic technology called Cepheid Gene Xpert® System for simultaneous detection of *M. tb* and rifampicin resistance has just been reported.[96] The Cepheid system is an integrated diagnostic system that performs sample processing and real-time PCR analysis test in a single hands-free two-hour step. The assay is designed to perform a hemi-nested molecular beacon assay, which uses six molecular beacons to amplify a sequence of the rpoB gene specific to the *M. tb* complex organisms and probe for mutations in the RRDR (Rifampicin Resistance Determining Region) of the rpoB gene. This is an 81bp long region in the rpoB gene, mutations in which occur in 95 to 98% of the rifampicin-resistant *M. tb*. Fluorescent dyes and quenchers that allow multiplexing of the different molecular beacons within the same reaction make this system extremely sensitive for the detection of *M. tb*. The sensitivity of the assay is similar to the culture-based diagnostics making it an attractive new diagnostic system for rapid detection of drug resistance. However, currently instrumentation and reagent costs are unacceptably high, and validation in true third-world settings is still to be performed.

Another technology being developed for the detection of *M. tb* drug resistance is based on using bacteriophages. There is currently only one commercial manufacturer of phage-based tests on the market, Biotec Laboratories Limited (Ipswich, Suffolk, UK), which produces the FASTPlaque™ assay. Their first generation test for the detection of rifampicin resistance, FASTPlaque-RIF™ or FASTPlaque-MDRi™, was used only with *M. tb* isolates.

This has now been replaced by the FASTPlaque-Response™, which can be used directly on patient specimens. The basic principle underlying these drug-sensitivity tests is that since the mycobacteriophage D29 replicates only in viable *M. tb*, the inclusion of drugs to which the *M. tb* is sensitive results in abrogation of phage replication.

The other phage-based assay for detection of MDR-TB strains is based on the Luciferase Reporter Phages (LRP), which emit light after infection of, and amplification in *M. tb*.[97-99] The LRP assay is an in-house format and earlier efforts were made to develop a commercial semi-automated version (Sequella Inc, Rockville, MD, USA) of this assay but now the company has discontinued development.[100] Compared to the conventional tests the sensitivity of detection of rifampicin resistance in LRP assay has ranges from 92 to 100% while the specificity is reported to range from 89 to 100%. All studies that have evaluated drug-resistance with the LRP-based assay have used bacteria that were cultured from the sputum specimens and its performance with direct evaluation of sputum bacteria is not known.[97-99]

Recently, a meta-analysis of commercial FASTPlaque™ assays, LRP assays and in-house phage amplification tests based on findings of 31 studies (with 3,085 specimens) was performed. For the detection of rifampicin resistance, commercial phage amplification assays yielded more variable ranges of sensitivity (range 81 to 100%) and specificity (range 73 to 100%) compared to in-house amplification assays (sensitivity range 88 to 100%, specificity range 84 to 100%). LRP evaluations yielded the most consistent estimates of diagnostic accuracy, with seven of eight studies reporting 100% sensitivity and four of eight reporting 100% specificity. The major drawback of the commercial assay included high rate of contaminated and indeterminate results particularly during direct detection of Rif resistance from patient specimens. Thus, phage-based assays need further development to maximize interpretable results and reduce technical failures and as per the recommendations of WHO Expert Group, there is insufficient evidence to recommend the use of phage based assays for rapid screening of patients suspected of having MDR-TB.[101]

Recently, microarray technology has also been evaluated for drug resistance detection in *M. tb*.[102-104] The microarrays or DNA biochips allow simultaneous detection of multiple mutations. A low-density oligonucleotide chip has been reported to detect mutations associated with INH, RIF, SM, KM, and EMB with sensitivities of 69%, 93%, 86%, 80% and 85%, respectively.[105] Gel-based biochips have been used for epidemiological studies of drug resistance on a large scale in Kyrgyz Republic.[106] The latest generation of TB biochips for analysis of second line fluoroquinolone antibiotics resistance along with rifampicin/isoniazid susceptibility biochip is the first in the world to be certified by a national regulatory agency, Ministry of Public Health of Russian Federation for clinical application.[106] However, the usefulness of molecular tests, including biochips is limited by the fact that not all drug-resistant isolates have mutations in the hot spots of genes associated with drug resistance. These strains still require phenotype based assays for detection. Secondly, the molecular tests are unable to detect minor populations of drug resistant organisms in primary culture from clinical samples.[105]

Interferon Gamma Release Assays

Besides the sensitivity and specificity issues discussed earlier, a major limitation of the TST is that the administration and reading of the test is subject to inter-operator variability and repeated visit of patients to the clinic are required for the measurement of induration and erythema. Significant advances in mycobacterial genomics and cellular research in last decade has resulted in the development of two new commercial blood tests, the enzyme-linked immunospot assay (ELISpot) (T-SPOT.TB, Oxford Immunotec, Oxford, UK) and the Enzyme-Linked Immunosorbent Assay (ELISA) (QuantiFERON-TB Gold;QFT-G/ QuantiFERON-TB Gold In-Tube; QFT-GIT, Cellestis, Carnegie, Australia). These tests, which are collectively known as IGRAs, detect LTBI by measuring Interferon (IFN)-γ release in response to overlapping peptides of two proteins, ESAT6 and CFP10, that are present in *M. tb*, but not Bacille Calmette-Guérin (BCG) vaccine and most nontuberculous mycobacteria. This is done through the enumeration of IFN-γ-secreting T cells (ELISpot) or by measurement of IFN-γ concentration by ELISA (QFT-G/ QFT-GIT).The QFT-GIT assay also includes peptides of another *M. tb* protein, called TB7.7 in addition to the peptides of ESAT6 and CFP10.[107] These tests have European CE Mark and US FDA approval.

A comprehensive review on utility of the IGRAs in diagnosis of clinical and latent TB has been published recently.[108] The ability of these antigens to elicit γIFN from PBMCs of active TB patients has been evaluated by many different labs and sensitivities ranging from almost 80 to 90% have been reported.[108] The similar sensitivity in smear-positive or smear-negative TB patients and in pulmonary and extrapulmonary TB and the ability to obtain results within two to three days as opposed to waiting for weeks for AFB cultures to become positive are advantages of these tests.[108-110] It is important to recognize that IGRAs are tests of infection, rather than disease, and cannot distinguish between LTBI and active TB, but since infection with *M. tb* is a prerequisite for active TB, a negative test result might in theory rapidly exclude TB from the differential diagnosis.

The ability of IGRAs to identify false positive responses that are detected by PPD is an asset to TB control in developed nations, in terms of avoiding unnecessary preventive therapy. For these reasons, IGRAs are becoming a part of the algorithm for identifying *M. tb* infected patients in non-endemic countries and is being considered for initial and serial testing of persons with increased risk for LTBI (recent immigrants, injection drug users, prisoners and jail personnel) and for individuals who may be at high risk for exposure (health care workers, military personnel). Recent meta-analysis based on the studies investigating sensitivity and specificity of the commercial T-Spot. TB and QFT-GIT assay as compared to TST among definitely confirmed TB cases concluded that the newest commercial IGRAs are superior, in comparison with the TST, for detecting confirmed active TB disease in developed countries.[111] Recently, guidelines and recommendations for the use of the QFT tests for detection of LTBI have been provided by the CDC.[112]

There is no gold standard for the detection of LTBI, which makes it difficult to determine the sensitivity and specificity of these tests in identification of latent infection, however, the major advantage of IGRAs is their improved specificity in detecting *M. tb* infection in subjects who are BCG vaccinated. In several studies of contacts of infectious TB patients, an excellent correlation between the degree of exposure to *M. tb* and the extent of γIFN responses or presence of T cells making γIFN in response to these antigens was observed and most studies provide estimates of improved sensitivity and specificity as compared to the PPD test.[113-116] Although IGRAs have impacted the diagnosis of LTBI in low burden countries, their value in high-burden settings is limited where large proportions of the subjects have LTBI and preventive therapy is not feasible or provided.[26,114] Moreover, increasing proportions of TB patients are coinfected with HIV and tests based on cellular immune responses have limitations in individuals with compromised immunity. For these reasons, the impact of these new tests on global TB control is likely to be insignificant.

Antibody-Detection Based Diagnosis of TB

Efforts to devise a serodiagnostic test for TB have been made for decades and a vast body of confusing and contradictory literature is available and over 20 serodiagnostic assays are currently marketed in developing countries. Most of the tests are based on the 38 kDa antigen of *M. tb* or LAM and/or other undisclosed antigens. In recent years, the WHO Special Program for Research and Training in Tropical Diseases (TDR) commissioned two systematic reviews on serological tests, which have performed a careful and thorough meta-analysis of the accuracy of these tests for the diagnosis of pulmonary and extrapulmonary TB. A list of the commercial tests evaluated is available in the published reviews.[117,118] These reviews concluded that all the tests provided highly variable sensitivities and specificities and none of them could be used for reliable diagnosis of TB, either in non-HIV or HIV-infected patients or in pediatric patients.

In addition to having high sensitivity and specificity, for any new diagnostic markers to have any impact on the TB epidemic, and to be integrated into the already overburdened TB control programs in the developing countries, they must be rapid, low-cost, operationally simple requiring minimal laboratory infrastructure and personnel training, robust and stable to withstand the poor storage conditions in these countries, and be amenable to large-scale production. For these reasons, despite the dismal history, two factors have continued to spur interest and effort from the academic community in devising serodiagnostic test for TB. First, the availability of the new tools of genomics and proteomics has accelerated the pace at which antigens of *M. tb* can be identified, cloned and tested. Also, once the optimal antigens/epitopes are identified, immunoassays can be adapted to easy, rapid format, inexpensive Point-of-Care (POC) tests that can be integrated into the TB control programs in developing countries without the requirement for investment in establishment and the maintenance of sophisticated laboratory infrastructure. Several new antigens have been reported in recent years.[119-129]

In 2008, the WHO/TDR commissioned a review of the immunodiagnostic potential of all new protein and non-protein antigens reported from different laboratories since 1990. These meta-analysis revealed that while no single antigen could detect all sputum smear-positive TB patients, one recombinant antigen, the malate synthase (Rv 1836c) provided the highest sensitivity (73%; CI 58–85) of all antigens identified so far.[130] These analysis also showed that compared to single antigens, multiple antigens provided improved sensitivities and the combination of a TB protein called DPEP plus a multiepitope protein TbF6 provided similar sensitivity as the malate synthase.[130] Other studies have shown that malate synthase and MPT51 (Rv 3803c) together provide a sensitivity of more than 80% in both HIV+ and non-HIV sputum smear-positive TB patients.[131] Importantly, the specificities obtained with these purified recombinant proteins are high.[130]

An interesting and important advancement in devising serodiagnosis for TB has been the demonstration that epitope mapping of carefully selected, highly immunogenic proteins of *M. tb* can potentially yield peptides that may be used to devise diagnostic tests for TB.[132,133] The use of peptide microarrays can potentially enable rapid screening of thousands of peptides representing the immunologically relevant proteins.[134,135] Although no peptide-based diagnostic test for TB is currently available, it is likely that diagnostic tests based on immunodominant peptides derived from *M. tb*–specific proteins that are highly immunogenic in TB patients will become available in the next few years.

The Optimal TB Test

It is important to appreciate the differences between the developed and developing countries in regards to TB. The former countries have a low-burden of TB, possess adequate resources to subject TB suspects to intensive expensive investigations (sophisticated microscopy, IGRAs, cultures, nucleic acid detection based tests), which result in earlier and accurate diagnosis, and to carefully monitor not only treatment of the patients, but also conduct contact investigations and identify and treat contacts who have LTBI. The goal in these settings is to eliminate TB. Unfortunately, the diagnostic tests that are used in mycobacteriology labs in the industrialized world as well as the resources required for monitoring treatment are too expensive and technically difficult for routine use in resource-limited countries. The patient burden is enormous; accuracy of microscopy is limited and facilities for culture-confirmation are rarely available.

Some laboratories in the developing world are beginning to introduce automated culture systems, nucleic acid probes, etc. Their integration into routine patient care will likely not be possible. For these reasons, these countries focus on control of TB, and maximum effort and resources are directed towards detection and treatment of the highly infectious cases, which seek medical intervention; by the time this passive case-finding identifies a patient, considerable transmission has already occurred. Even affordable new diagnostic tests that can replace and improve upon microscopy, and be integrated into routine patient care would impact TB control in these countries. Unfortunately, the few diagnostic tests that have been devised so far or are in development continue to be useful primarily for the high end of the TB market.

The ideal diagnostic marker for TB would be a universal marker that can be the following:

a. Replace and improve upon sputum microscopy
b. Identify patients with extrapulmonary TB, which can occur at different sites (TB meningitis, skeletal TB, genitourinary TB, gastrointestinal TB, TB lymphadenitis) many of which are not accessible to microscopy[8,136,137]
c. Identify HIV-infected TB patients, in whom TB progresses rapidly and fatally, but the low bacterial burden in the sputum makes detection of bacteria or bacterial molecules difficult, and the immune dysfunction preclude use of cellular immune-based diagnostic assays[4,25]
d. Diagnose pediatric TB patients who rarely produce sputum and are currently diagnosed based on epidemiologic, clinical and radiological suspicion rather than microbiological confirmation[138,139]
e. Because *M. tb* has a long generation time and the period from infection to clinical disease can be several months, the ideal markers would identify a potential TB patient during this window of time and so must differentiate between an incipient subclinical infection (where *M. tb* is replicating actively and the infection is progressing to clinical TB) and a truly latent infection that is unlikely to result in disease

In the absence of a single universal marker, a set of new diagnostic tests may be able to fulfill these criteria. Not only must the new diagnostic tests detect the myriad forms and stages of TB with high sensitivity, they must be highly specific. Thus, although almost 84% of the *M. tb* genome encodes proteins that are cross-reactive with other mycobacteria or other prokaryotes,[140] the diagnostic markers must be able to distinguish between infection with *M. tb* and infection or exposure to other bacteria and mycobacteria. In addition to having high sensitivity and specificity, for any new diagnostic markers to have any impact on the TB epidemic and to be integrated into the already overburdened TB control programs in the developing countries they must be rapid, low-cost, operationally simple requiring minimal laboratory infrastructure and personnel training, robust and stable to withstand the poor storage conditions in these countries and be amenable to large-scale production.

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42

Management of Tuberculosis*

D Behera

CHEMOTHERAPY OF TUBERCULOSIS

The modern era of tuberculosis treatment—short-course chemotherapy—began with the first East-African/BMRC study in the early 70s and subsequent studies at different parts of the world,[1] which demonstrated that the addition of rifampin to isoniazid and streptomycin allowed a dramatic curtailment from 18 months to 6 months in the duration of drug therapy required to elicit cures in 95% or more of patients, which is considered as the gold standard of the efficacy of any chemotherapy program. Subsequently, a number of clinical trials all over the world continued in a wide variety of populations and health service conditions, which have confirmed that the duration of treatment can be reduced to 6 to 9 months from the earlier 12 to 18 months with the use of suitable combinations of antitubercular drugs.[2-12] Since then, short course chemotherapy is now widely accepted as the treatment of choice for pulmonary tuberculosis. From the results of clinical trials and of complimentary laboratory studies, the mechanisms of action of the main antitubercular drugs and their contributions to regimens are becoming increasingly well understood.

The antituberculosis drugs vary in (i) their bactericidal action, defined as their ability to kill large numbers of actively metabolizing bacilli rapidly, (ii) their sterilizing action, defined as their capacity to kill special populations of slowly or intermittently metabolizing semidormant bacilli: The so called "persisters", (iii) their ability to prevent the emergence of acquired resistance by suppressing drug-resistant mutants present in all large bacterial populations, and (iv) their suitability for intermittent use.[13]

Prevention of Drug-Resistance

Drugs can be graded according to their activity in preventing the emergence of resistance to a second drug, usually isoniazid. Even populations of tubercle bacilli, which are not exposed to antitubercular drugs, contain small proportions of drug-resistant mutants. The proportion of such mutants in wild strains is 1 in 10^5 to 10^6 for streptomycin, isoniazid and ethambutol and 1 in 10^7 for rifampicin. If inadequate drug combinations are used, these mutants are likely to replace the killed susceptible bacilli and give rise to drug-resistant disease. The effectiveness of drugs in preventing the emergence of acquired resistance depends upon the extent to which they can inhibit bacilli continuously, whatever their rate of metabolism, even if there is some irregularity in taking drugs. Isoniazid and rifampicin are the most effective at preventing the emergence of resistance to other drugs, and streptomycin and ethambutol are only slightly less. Pyrazinamide is less effective, and PAS and thiacetazone are the least effective. Activity of a drug is assessed from the results of clinical studies of the treatment of smear positive pulmonary tuberculosis in which the drug concerned is given in a 2-drug combination with isoniazid. Drug gradings are based on the proportion of patients who failed during treatment with the emergence of isoniazid-resistance. This proportion is about 0.5% for rifampicin (high activity) and 13 to 15% for thiacetazone (low activity).

Early Bactericidal Activity

Jindani examined the early bactericidal activity of drugs and others[14] in patients with pulmonary tuberculosis treated for 14 days with single drugs or with various drug combinations, followed by conventional regimens. Most of the antitubercular drugs (INH, rifampin, streptomycin, pyrazinamide) have bactericidal activity. Of them isoniazid kills the largest number of bacilli early during the first two days of chemotherapy in a rate of 0.72 $\log_{10}$ cfu/ml/day when given alone and the kill of other drugs is increased considerably by 0.36 $\log_{10}$ cfu/ml/day when isoniazid is added to them in treatment. Next in order of bactericidal activity are ethambutol and rifampin with rates of kill of 0.25 $\log_{10}$ cfu/ml/day and 0.19 $\log_{10}$ cfu/ml/day, respectively. They add little or nothing to the activity of second drugs. Streptomycin, thiacetazone, and pyrazinamide are just bactericidal with rates of kill of 0.09 to 0.04 $\log_{10}$ cfu/ml/day.

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*D Behera. Textbook of Pulmonary Medicine. Tuberculosis. 2nd edition. New Delhi: Jaypee Brothers Medical Publishers; 2010. pp. 540-7.

Sterilizing Action

Sterilizing activity is the ability to kill all or virtually all of the bacilli in the lesions as rapidly as possible. As the speed of killing gets progressively slower during chemotherapy, sterilizing activity measures the speed with which the last few viable bacilli are killed. This activity is assessed in man by (i) proportion of sputum cultures that are negative at two months, or round about that time, after the start of treatment, and (ii) the proportion of relapses that occur after chemotherapy has been stopped. The sterilizing activity of a drug indicates its suitability for incorporation in short course regimens. The two drugs with the greatest sterilizing activity are rifampicin and pyrazinamide. Isoniazid is less active, taking longer time to sterilize lesions. Though less active than isoniazid, addition of streptomycin or thiacetazone to a regimen probably increases its sterilizing activity to a very small extent.[15] Ethambutol virtually has no sterilizing activity.

Mitchison in 1979[16] had suggested a special populations hypothesis and subsequently an extension of this hypothesis explaining the bactericidal and sterilizing activities of various drugs. This is shown in Figure 42.1.

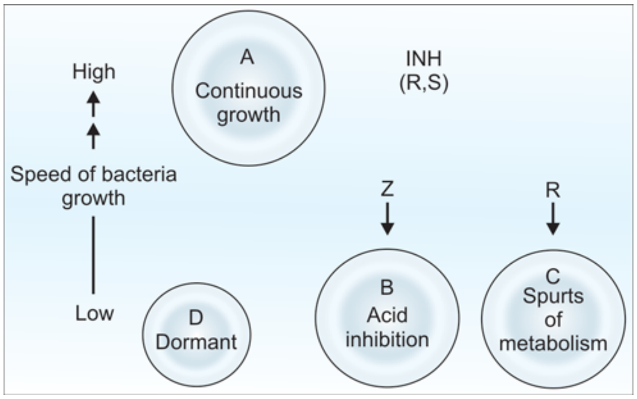

Fig. 42.1: Special bacterial population hypothesis by Mitchison R-rifampin, S-streptomycin, Z-pyrazinamide

The majority of the tubercle bacilli in the lesions at the start of treatment are growing more or less rapidly (*population A*). Isoniazid kills them during the first few days of chemotherapy. Other drugs contribute to the bactericidal activity, only if INH is not included or the bacilli are resistant to it. Other bacilli are almost dormant and, therefore antitubercular drugs, including INH kill them only slowly. Some of these semidormant bacilli are in an acid environment, perhaps inhibited by acidity or by poor oxygen supply because of low pO_2 (inside macrophages or in areas of inflammation) and are best killed by pyrazinamide, because it is active only at a pH of about 5.5 or less (*population B*). Other semidormant bacilli have occasional spurts of active metabolism, lasting perhaps for few hours (*population C*) and these are killed most efficiently by rifampicin because its bactericidal action starts very quickly during the spurts of metabolism, before isoniazid has a chance to start killing. The organisms may be in neutral or an acid environment, so that there is some overlap between populations B and C. Finally, there is a completely dormant population of bacilli (*population D*), which is unaffected by any drug. Thus, early bactericidal activity kills population A, while populations B and C are killed by drugs with high sterilizing activity throughout the entire period of chemotherapy. However, subsequent observations proved that these assumptions are not entirely correct, and, therefore, an "extended special population theory" was proposed (Fig. 42.2). According to this hypothesis, most of the bacilli in the lesions at the start of treatment exist in extracellular sites, including the areas of caseation where they are not closely surrounded by inflammatory cells. These bacilli (corresponding to population A in Fig. 42.1) are in a mildly acid environment (6.5–7.0) and most are growing fairly rapidly. These population of bacilli are killed rapidly by INH actively, streptomycin is weakly bactericidal because of overall acidic pH, and pyrazinamide is not bactericidal because the pH is not sufficiently acidic.

As further inflammatory reaction proceeds, the pH falls and the organisms are partially inhibited (population B and C of Fig. 42.1). Pyrazinamide and rifampicin are now more bactericidal than INH and streptomycin is completely inactive. There is a steady transfer of bacilli from population A to population B in open cavities that contains majority of the bacilli. After several weeks of

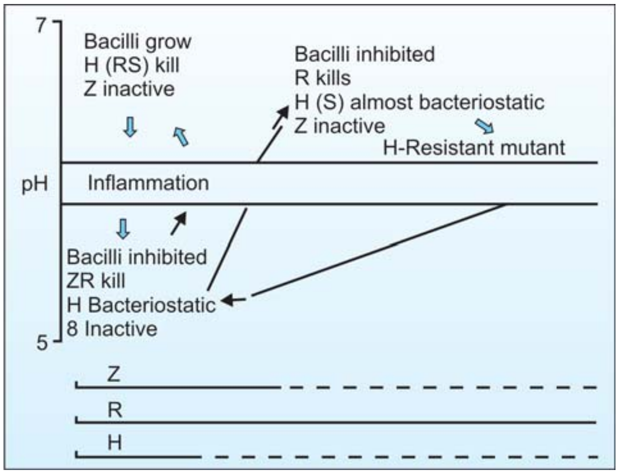

Fig. 42.2: Role of pH and inflammation in modifying the growth of *M. tuberculosis*. The circulation of periods of rapid killing by ZR and H is indicated in the lower part

TABLE 42.1: Grading of activities of antituberculosis drugs

Extent of activity	*Prevention of resistance*	*Early bactericidal*	*Sterilizing*
High	Isoniazid	Isoniazid	Rifampicin
	Rifampicin		Pyrazinamide
		Ethambutol	
	Ethambutol	Rifampicin	Isoniazid
	Streptomycin		
		Streptomycin	Streptomycin
	Pyrazinamide	Pyrazinamide	Thiacetazone
Low	Thiacetazone	Thiacetazone	Ethambutol

treatment, the inflammation starts dying down, and the pH reverts towards the 6.5 to 7.0 ranges. The bacilli, corresponding to population C, are persisters and are relatively refractory to chemotherapy. Rifampicin has the greatest activity against them, and INH and streptomycin are slow killers. Because of higher pH, pyrazinamide is inactive and therefore, the drug has no sterilizing activity after the first-two months of short course chemotherapy.[17] However, if the bacilli again start to multiply, because of any reason (i.e. isoniazid resistance) local inflammation begins again, the pH falls and the situation is repeated with the necessity of pyrazinamide to kill the bacilli. Thus in multidrug short course regimens, the main killing activity of pyrazinamide occurs during the first few weeks of chemotherapy, while killing by rifampicin continues throughout treatment and isoniazid has its main activity during the first few days.

Suitability for Intermittent Use

Isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol are all effective when given twice or thrice a week. Thiacetazone is less effective when given intermittently than when given daily. From the above discussion, it is quite clear that the three functions of early bactericidal activity, sterilizing activity, and ability to prevent drug resistance are unrelated. In the combinations, in which they are given, are effective because one or the other drug is having different grade of above activities. For example, while rifampicin has early bactericidal activity (rapidity of killing), in fact it is weakly bactericidal compared to isoniazid. Similarly, the importance of ethambutol in short course chemotherapy lies not because it is a bactericidal or sterilizing drug, but it plays part in the prevention of failure as a result of initial drug resistance. The relative activities of the main antitubercular drugs in each of the above three functions are summarized in Table 42.1.

The existence of dormant tubercle bacilli or the persisters for long periods after chemotherapy was shown by McCune et al nearly 40 years ago, soon after the discovery of isoniazid, and is known as the "Cornell Model".[18] These studies supplemented by other experimental studies formed the basis of short course chemotherapy.[19] The success of short course chemotherapy regimens containing rifampicin showed that the drug could kill tubercle bacilli even with the shorter periods of contact, whereas other powerful drugs like isoniazid require about one generation time (24 hours). Based on these explanations and other clinical trials, the established short course chemotherapy became widely acceptable. Unfortunately, the emergence of new molecular biology techniques like Polymerase Chain Reaction (PCR), Single-Strand Conformation Polymorphism (SSCP) analysis, and Restriction Fragment Length Polymorphism (RFPL) have shown persistence of mycobacterial DNA in the animal tissues as well as in human material after discontinuation of therapy.[20,21] The relevance of these reports in the context of clinical practice is not clear and whether these may be indicators of reemergence of tuberculosis are yet to be answered.

With the available information, many countries have developed guidelines for the treatment of tuberculosis.[22-33] The basic principle is the same, i.e. short course chemotherapy of six months duration.

A number of National and International guidelines for the treatment of pulmonary tuberculosis are available. They are:

- World Health Organization (2003). Treatment of Tuberculosis: Guidelines for National Programs.

http://whq libdoc. who.int/hq/2003/WHO_CDS_TB_2003. 313_eng. pdf.

- Tuberculosis Coalition for Technical Assistance (The Hague) (2006). International Standards for Tuberculosis Care. http://www.who.int/tb/publications/2006/istc/en/index.html.
- National Institute for Health and Clinical Excellence (UK) (2006). Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. http://www.nice.org.uk/page. aspx?o=296605.
- American Thoracic Society, Center for Disease Control, Infectious Diseases Society of America (2003). Treatment of Tuberculosis. http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf.
- Centers for Disease Control and Prevention (2000). "Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection". American Thoracic Society. PMID 10764341. http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf.
- The Revised National Tuberculosis Control Programme (RNTCP) developed by the Central TB Division, Directorate General of Health Services, Govt. of India. *www.tbcindia.org.*

The Committee on treatment of the International Union Against Tuberculosis and Lung Diseases, at its meeting in Singapore in November 1986 has made specific recommendations on antituberculosis regimens and drug dosages to be used in the treatment of adults and children with active pulmonary or extrapulmonary tuberculosis requiring chemotherapy, which is given in Table 42.2.[23]

The committee has also recommended the use of drugs in various other situations like the presence of complicating diseases, the treatment of drug resistant cases, and management of patients who develops toxic reactions to a drug, but otherwise treatment should be continued. These will be discussed in brief. The dosages of the drugs are given in Table 42.3. The dosages are appropriate for all forms of tuberculosis, including meningitis and miliary tuberculosis and for children, as well as adults. In the past, a higher dose was used for children, especially for isoniazid, which should be avoided which otherwise leads to needless adverse effects.

The World Health Organization has published guidelines for the treatment of tuberculosis for national programs.[34] In order to standardize short course chemotherapy in national tuberculosis programs, case definitions are required. The main purposes of these case definitions are for the proper patient registration and case notification, to evaluate the trend in the proportions of new smear-positive cases and smear-positive relapse and other treatment cases, to allocate cases to standardized treatment categories, and for cohort analysis. There are four determinants of case definition—the site of tuberculosis, severity of the disease, bacteriology and the history of previous treatment. WHO recommends the following definitions.

TABLE 42.2: Recommendations of IUATLD regimens of chemotherapy

A. *Recommended standard six-month regimen* 2hrz/4hr
Variants of standard six-month regimen
- I. *When fully supervised intermittent chemotherapy can be organized*
  - 2 $HRZ/4H_3R_3$
  - 2 $HRZ/4H_2R_2$
  - 2 $E_3H_3R_3Z_3/4H_3R_3$
  - 2 $S_3H_3R_3Z_3/4H_3R_3$
- II. *When there is a high level of initial resistance*
  - 2 EHRZ/4HR
  - 2 SHRZ/4HR

B. *Alternative less potent regimens of longer duration*
- I. *With potent initial 4-drug phase*
  - 2 SHRZ/6HT
  - 2 $SHRZ/6S_2H_2Z_2$
- II. *With less potent or no initial phase*
  - 2 SHR/7HR
  - 2 EHR/7HR
  - 9 HR
  - 2 SHT/10HT
  - 2 SHE/10HE
  - 2 SHP/10HP
  - 2 $SHT/10S_2H_2$
  - 2 $SHP/10S_2H_2$

S: Streptomycin; H: Isoniazid; R: Rifampicin; Z: Pyrazinamide; E: Ethambutol; T: Thiacetazone; P-PAS. The numbers indicate duration in months. The subscript numbers indicate the frequency per week.

An active case of tuberculosis refers to symptomatic disease due to infection with *Mycobacterium tuberculosis* complex.

Site of Tubercular Disease (Pulmonary or Extrapulmonary)

In general, recommended treatment regimens are similar for both pulmonary and extrapulmonary tuberculosis and are the same irrespective of the site of disease, although some authorities recommend a prolonged continuation phase for tubercular meningitis. Pulmonary tuberculosis refers to disease involving the pulmonary parenchyma. Intrathoracic tuberculous lymphadenitis

TABLE 42.3: Dosages of antitubercular drugs

Daily dosage				*Intermittent dosage*		
	Adults and children	*Adults*		*Adults and children*	*Adults*	
Drug	*mg/kg*	*Weight*	*Dose*	*mg/kg*	*Weight*	*Dose*
H	5	—	300 mg	15	—	—
R	10	< 50 kg	450 mg	15	—	600-900 mg
		> 50 kg	600 mg			
S	15-20	< 50 kg	750 mg	15-20	< 50 kg	750 mg
		> 50 kg	1 g		> 50 kg	1 g
Z	35	< 50 kg	1.5 g	50	< 50 kg	2.0 g
		> 50 kg	2.0 g	3 times/wk	> 50 kg	2.5 g
				75	< 50 kg	3.0 g
				2 times/wk	> 50 kg	3.5 g
E	25 × 2 mo.	—	—	30	—	—
	then, 15			3 times/wk		
				45		
				2 times/wk		
T	4 (children)	—	150 mg	—	—	—
P	300	—	10-15 g	—	—	—
ET/PT	15-20	< 50 kg	750 mg	—	—	—
		> 50 kg	1 g	—	—	—
K	10-15	—	0.5-1g	—	—	—
C	15	—	1 g	—	—	—
Cy	15	< 50 kg	750 mg	—	—	—
		> 50 kg	1g	—	—	—

H: INH; R: Rifampicin; Z: Pyrazinamide; S: Streptomycin; E: Ethambutol; T: Thiacetazone; P-PAS; ET: Ethionamide; PT: Prothionamide; K: Kanamycin; C: Capreomycin; Cy: Cycloserine. Ethambutol and capreomycin are not to be used in children

and pleural effusions without radiographic parenchymal involvement are taken as extrapulmonary tuberculosis. A patient with both pulmonary and extrapulmonary tuberculosis constitutes a case of pulmonary tuberculosis. The case definition of an extrapulmonary case with several sites affected depends upon the site representing the most severe form of the disease.

Severity of Disease

Bacillary load, extent of disease and anatomical site involvement are taken into account in defining the severity of the disease. Involvement of an anatomical site results in classification as severe disease if there is either a significant acute threat to life as in pericardial tuberculosis, or a risk of subsequent severe sequel with handicap as in spinal tuberculosis or both as in tuberculous meningitis. Thus, the following forms of extrapulmonary tuberculosis are classified as severe: Meningitis, miliary, pericarditis, peritonitis, and bilateral or extensive pleural effusion, spinal, intestinal and genitourinary. Other forms of extrapulmonary tuberculosis like lymphadenitis, unilateral pleural effusion, and bone excluding spine, peripheral joint, and skin are classified as less severe.

Bacteriology (Result of Sputum Smear)

It is very important to define the smear result in pulmonary cases because smear-positive cases are the most infectious and they have an increased mortality and the positive cases are the only ones for which bacteriological monitoring of cure is possible. A smear-positive pulmonary tuberculosis is one if (i) at least two sputum specimens are positive for acid fast bacilli by microscopy; or (ii) if at least there is one sputum specimen is positive for acid fast bacilli by microscopy and radiographic abnormalities consistent with pulmonary tuberculosis and a decision by a physician to treat with a full curative course of antituberculous chemotherapy; or (iii) a patient with at least one specimen positive for acid fast bacilli by microscopy, and which is culture positive for *M. tuberculosis*. Under program conditions with microscopy services available, pulmonary tuberculosis smear-positive cases represent about 65% of the total pulmonary tuberculosis cases in adults and 50% or more of all tuberculosis cases when diagnostic criteria are properly applied. This proportion may be **lower in high in populations (author to kindly verify)** with a high incidence of Human Immunodeficiency Virus (HIV) infection. A smear-negative pulmonary tuber-culosis is one (i) if two sets of at least two sputum specimens negative for acid fast bacilli on microscopy examined at least two weeks apart; and (ii) radiographic abnormalities consistent with pulmonary tuberculosis and a lack of clinical response despite one week of a broad spectrum antibiotic; and (iii) a decision by a physician to treat with a full curative course of antitubercular drugs. The category also includes patients who are severely ill; and at least two sputum specimens negative for acid-fast bacilli by microscopy; and radiographic abnormalities consistent with extensive pulmonary tuberculosis like interstitial or miliary form of the disease; and a decision by a physician to treat with a full curative course of antitubercular chemotherapy. The other group of patients that comes under this category are those whose initial sputum were negative, who had sputum sent for culture initially, and whose subsequent sputum culture results are positive. Thus, in the absence of culture, standard chest radiography is necessary to document cases of smear-negative pulmonary tuberculosis. Fluoroscopy examination results are not acceptable as documented evidence of pulmonary tuberculosis.

History of Previous Treatment

By this information, a case is defined whether or a patient had previous antitubercular treatment or not. This is important because by this case definition patients are identified who are at increased risk of acquired drug resistance and the prescription of appropriate treatment; and for epidemiological monitoring. Accordingly the following five different categories of cases can be identified:

New Case

A patient who has never had treatment for tuberculosis or who has taken antitubercular drugs for less than four weeks.

Relapse

A patient who has been declared cured of any form of tuberculosis in the past by a physician, after one full course of chemotherapy, and has become sputum smear-positive.

Treatment Failure

A patient who, while on treatment, remained or became again smear-positive five months or later after commencing treatment. It is also a patient who was initially smear-negative before starting treatment and became smear-positive after the second month of treatment.

Treatment after Interruption (TAI) or Return after Default

A patient who interrupt treatment for two months or more, and returns to the health service with smear-positive sputum or sometimes smear-negative, but still with active disease clinically and radiologically.

Chronic Case

A patient who remained or became again smear-positive after completing a fully supervised retreatment regimen.

Although smear-negative and extrapulmonary cases may also be treatment failures, relapses, or chronic cases, this is rare. The importance of case definitions as above is important for registration, notification and to define treatment categories.

RATIONALE FOR RECOMMENDED TREATMENT REGIMENS

For new cases, treatment regimens have an initial or intensive phase for two months and a continuation phase lasting for four to six months. During the initial intensive phase of therapy four, drugs are administered wherein a rapid killing of bacilli takes place. Infectious patients become noninfectious within about two weeks. Symptoms improve. The vast majority of cases with sputum smear-positive tuberculosis become sputum negative within two months. In the continuation phase fewer drugs, usually two, are required, but for a longer period of four to six months. The sterilizing effect of the drugs eliminates remaining bacilli and prevent relapse. In smear-positive cases, there is a risk of selecting resistant bacilli as these patients harbor and excrete a large number of bacilli. However, short course chemotherapy consisting of four drugs initially and two drugs subsequently, reduce this risk of selecting resistant bacilli. These drugs are practically as effective in patients with initial resistant organisms as in those with sensitive organisms. In patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis, there is little risk of selection as these patients carry only a small bacillary load. Short-course chemotherapy regimens with three drugs initially with two drugs during the continuation phase are sufficient.

In retreatment cases there is a chance of drug resistance. They are more likely than new patients to harbor and excrete bacilli resistant to at least isoniazid. This regimen consists initially of five drugs, with three drugs in the continuation phase. The patient receives at least two drugs in the initial phase, which are still effective. This reduces further selection of resistant organisms.

From the public health perspective the priority of treatment is given to the infectious cases. Because of resource constrains, treatment is rationalized by resource allocation to priorities tuberculosis treatment categories according to the cost-effectiveness of the treatment of each category. Accordingly, treatment categories are ranked from I (highest priority) to IV (lowest priority). Recommended regimens for different categories may differ from country to country as per the National Tuberculosis Program, which in turn depends on the budget, health coverage by Primary Health Care services, and qualification of health staff at the peripheral level. The WHO recommendation of treatment regimens according to categories is shown in Table 42.4. Category IV has since been defined clearly.

Category I

In this group, smear-positive pulmonary tuberculosis gets the highest priority for treatment. Urgent treatment is also required for patients with the other forms of disease because of associated morbidity and mortality. When the patient completes the initial phase of treatment and the sputum is smear-negative, the continuation phase is started. However, if the smear is still positive at eight weeks, the initial phase of therapy should be extended for another two to four weeks. The patient is then started with the continuation phase regardless of the result of sputum result. In populations with low probability of initial resistance three drugs (R, H, Z) in the intensive phase is sufficient. Some experts recom-mend a seven month continuation phase with daily isoniazid and rifampicin (7 HR) for category I patients with TB meningitis, miliary tuberculosis, spinal tuberculosis with neurological signs. In the continuation phase, an alternative treatment regimen like six months of isoniazid and thiacetazone can be given daily. In proven or suspected cases of HIV infection (young adults from countries with a high incidence of HIV infection), ethambutol should be used in place of thiacetazone.

Category II

The treatment priority in this category is again highest. These patients are likely to have isoniazid-resistant and/or streptomycin-resistant disease. If possible, a pretreatment sputum specimen should be obtained for

TABLE 42.4: Possible alternative treatment regimens for each treatment category[33]

Treatment category	*Description of patients*	*Alternative treatment regimens*	
		Initial phase (daily or 3/week)	*Continuation phase*
I	New smear-positive TB New smear-negative TB with extensive parenchymal involvement; new cases of severe forms of extrapulmonary tuberculosis (see above))	2 EHRZ (SHRZ) 2 EHRZ (SHRZ) 2 EHRZ (SHRZ)	6 HE/6HT 4 HR 4 H_3R_3
II	Sputum-smear positive: Relapse; Treatment failure; Treatment after interruption	2 SHRZE/1 HRZE 2 SHRZE/ 1 HRZE	5 $H_3R_3E_3$ 5 HRE
III	New smear-negative TB (Other than in Category I) new less severe forms of extrapulmonary TB	2 HRZ 2 HRZ 2 HRZ	6 HE 4 HR 4 H_3R_3
IV	Chronic cases (still sputum positive after supervised retreatment)	Second-line drugs are to be used in specialized centers.	

culture and susceptibility testing to H, R, E and S. These patients are also at increased risk of developing multidrug-resistant disease and should receive fully supervised treatment for at least three months. If the sputum is still positive at the end of three months, they should continue to receive supervised therapy till sputum conversion is documented or till they are classified as a chronic case. When the patient is sputum-negative at the end of 12 weeks, the continuation phase is started.

If the pretreatment studies showed resistance to isoniazid or rifampicin alone, the patient should start the continuation phase under close supervision, preferably in a referral hospital. In this situation, sputum conversion is likely to occur, provided that all the doses of drugs are taken till the end.

If the pretreatment report showed resistance to both isoniazid and rifampicin, or resistance to both these drugs is found in patient who remains sputum-positive at the end of the initial phase, the chance of achieving sputum conversion is limited.

If the patient remains smear-positive after the completion of the continuation phase as outlined in Table above, he or she is no longer eligible for the retreatment regimen.

Relapse and treatment failure in patients in patients who are smear-negative may be managed according to the same principles. Those patients who failed to complete an adequate course of treatment, but who do not meet any of the above definitions of active disease when subsequently rediscovered should complete the retreatment regimen. The patient is best managed in a referral center.

Category III[@]

In this category childhood tuberculosis is one of the important groups as well as young people during adolescence with primary tuberculosis manifesting as pleural effusion or small parenchymal lesions. The treatment priority is higher as a proportion of these will become sputum-positive if not treated. The priority is lower in more benign forms of extrapulmonary tuberculosis. In pulmonary tuberculosis with parenchymal involvement exceeding a total of 10 cm^2 on chest skiagram, or in extrapulmonary tuberculosis with the incomplete remission of signs or symptoms, the continuation phase should be extended by administering isoniazid alone for an additional four months. Thiacetazone can be replaced for ethambutol where there is resource problem, but with precaution of HIV infection.

Category IV

The priority of treatment for this category is low. There is a high likelihood of multidrug-resistant tuberculosis. Even with optimal therapy, cure may be possible in only 50% of cases. Second line drugs are very expensive, toxic, and are less effective than conventional regimens in drug-susceptible cases. Prolonged hospitalization may be necessary.

If possible, the drug sensitivity of the bacilli should be established. A retreatment program may be attempted with second line and experimental drugs. In countries with limited resources, these cases are given low priority so that resources are not diverted from high priority cases. One may prescribe lifelong isoniazid for such patients where the renewed regimen as outlined is not feasible. The rationale of such single therapy with isoniazid is that the drug may diminish their infectivity and reduce the transmission of resistant organism.

SUPERVISION OF CHEMOTHERAPY

Poor compliance by the patient is by far the most important cause of poor results even from the most potent regimens under program conditions. The poor compliance is due to a number of factors, including the unpleasantness of taking tablets and capsules daily, forgetfulness (a common human nature), cost, inconvenience for the patient to collect drugs regularly, side effects of the drugs, etc. The importance of complying with the treatment throughout the whole duration of therapy must repeatedly be emphasized to the patient and to his family. Whenever possible every dose of the regimen should be administered under full supervision. In some countries this can be achieved by medical service staff on an entirely outpatient basis. In others, service staff can provide full outpatient supervision in the urban, but not in the rural areas, while in others treatment is rarely, if ever, fully supervised by service staff. Paramedical or laypersons, including a member of the patient's family, can be taught to do so.

It is well established that domiciliary therapy is preferable because of many socioeconomic reasons and is fully effective. It is not necessary to admit patients of tuberculosis for better supervision in hospitals except in certain special circumstances like a complication (hemoptysis, respiratory failure, cor pulmonale, etc.); for surgery, severe disease with hypotension, toxemia, complication due to drug therapy (hepatitis), surgery, and in cases of treatment failures for evaluation. It is better to accustom the patient to receive chemotherapy regularly and correctly on an outpatient basis from the

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[@] Category III has been now merged with Cat I as latest Oct 2010 revision of RNTCP.

start, organizing supervision as efficiently as circumstances allow.

Whatever may be the level of supervision, compliance should be monitored by measures like periodic pill counting, and surprising urine tests for isoniazid or inspection of the urine for red coloration of rifampicin or can be detected in urine by chloroform extraction.

Under program conditions, Direct Observed Therapy (DOT) is now the practice world over. The subject is discussed in more details subsequently.

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Antitubercular Drugs

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INTRODUCTION

Mycobacterium tuberculosis (MTB) is a slow growing organism that has the ability to enter a state of dormancy, which allows it to persist in the host despite adequate treatment. The low oxygen tensions prevailing in solid caseous tissue do not favor rapid multiplication of bacilli. Following liquefaction, caseation and cavity formation, the prevailing oxygen tension becomes higher, favoring extracellular bacillary multiplication. In a patient with Tuberculosis (TB), there are three kinds of populations of MTB organisms:[1] The first population is the actively growing extracellular organisms—huge numbers of organisms can grow extracellular in pulmonary cavities within liquefied caseous debris, it is this population, which develops drug-resistance most rapidly; the second population consists of slow growing or intermittently growing organisms (spurts of metabolism), which are inside macrophages; the third population is made up of slow growing organisms, which grow in solid caseous material. This environment is neutral in pH, but the penetration of drugs into this area may be compromised by a poor blood supply.

From studies of the fall in sputum bacterial counts in the early days of treatment with single drugs, it has been established that isoniazid is the most potent bactericidal agent, rifampicin is less bactericidal, while streptomycin and pyrazinamide have only low bactericidal activity.[2] Rifampicin is the only drug that is bactericidal against all three populations. Isoniazid and streptomycin are bactericidal against extracellular organisms (especially in cavity walls) and isoniazid also has bactericidal activity against intracellular bacilli. Pyrazinamide is bactericidal against intracellular organisms and works well in an acidic pH. Ethambutol is a bacteriostatic drug. Finally, a fourth population of totally dormant bacilli, not killed by any drug, is believed to exist. The sterilizing activity of drugs has been particularly studied in the experimentally infected mouse, where rifampicin and pyrazinamide were found to be very potent sterilizing drugs.[3] Among the alternative drugs, the quinolones have the highest bactericidal activity against MTB.[4]

It has been estimated that the population of slowly growing organisms in macrophages and caseous lesions/tissues is less than 10^5, whereas in cavities, the rapidly growing population numbers 10^7–10^9 organisms.[1] Since mutants resistant to streptomycin, isoniazid and ethambutol in wild strains of tubercle bacilli number 1 per 10^5–10^6 organisms and those resistant to rifampicin 1 per 10^7, such strains could easily be selected by therapy with one drug. Such selection is avoided by multiple drug therapy. Also, the other important factor leading to drug-resistance is adding a single drug to a failing regimen. In such case, the majority of the organisms, which are susceptible to that single drug will be killed, but the small number of organisms, which have spontaneously mutated will survive and multiply. Overtime, selection of drug-resistant organisms will occur. When formulating a therapeutic regimen for TB, it is important to remember that viable organisms from slow growing or intermittently growing population may persist if drugs are not continued for an adequate period of time.

It has now been established that the shortest course of chemotherapy required for adequate sterilization with currently available drugs is six months.[5] Modern drug treatment regimens consist of an initial or introductory phase of therapy followed by a maintenance or continuation phase of therapy. In order to prevent relapse and drug-resistance, clinicians must prescribe an adequate regimen and ensure that patients adhere to therapy. To ensure adherence, Directly Observed Therapy (DOT) should be considered for all cases. There are many factors that may influence patients' compliance, which include patients' social characteristics, personality, understanding of the illness and treatment, and patient-doctor relationship.[6]

The antitubercular drugs can be grouped into five categories depending upon their pharmacotherapeutic characteristics. Group 1 consists of first line oral agents– isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z); rifabutin (Rfb). Group 2 consists of injectable agents (streptomycin (S), kanamycin (Km); amikacin (Am); capreomycin (Cm)). Group 3 includes: fluoroquinolones (levofloxacin (Lfx); ofloxacin (Ofx); moxifloxacin (Mfx)). Group 4 features oral bacteriostatic second-line agents (ethionamide (Eto); protionamide (Pto); cycloserine (Cs); terizidone (Trd); *p*-aminosalicylic acid (PAS)). Group 5 consits of agents with unclear efficacy (Clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H) and clarithromycin (Clr)). These drugs are not recommended by WHO for routine use in MDR-TB patients.

First-line drugs are those used in initial and maintenance chemotherapy unless drug resistance is known. Rifabutin is not on the WHO List of Essential Medicines. It has been added here as it is used routinely in patients on protease inhibitors in several settings. High-dose H is defined as 16–20 mg/kg per day.

ISONIAZID

Domagk, the discoverer of the first sulphonamide, with Fox and others synthesized several thiosemicarbazone derivatives in which the benzene ring was replaced with a pyridine ring and found that such derivatives retained antituberculous effects.[7,8] These studies eventually led to the discovery that an intermediate product, isoniazid ($C_6H_7N_3O$) had the most potent antituberculous action. Isoniazid (H or INH), a hydrazide of isonicotinic acid was first synthesized from ethyl isonicotinate and hydrazine hydrate in 1912 by Meyer and Malley in Prague.[9] Its use was not considered until 1945 when the observation of the antituberculous effect of nicotinamide by Chlorine[10] stimulated others to test pyridine derivatives for their antimycobacterial effects. The first clinical trial of INH was initiated at Sea View Hospital, Staten Island, New York in 1951, reported in April 1952.[11] INH was the one of the most active compounds used to treat and prevent tuberculosis worldwide. Its low cost, good bioavailability, relatively low-toxicity, excellent intracellular penetration and narrow spectrum of action make it an almost ideal antimicrobial agent.

INH is readily absorbed after oral or parenteral administration, gets distributed into all body fluids and intracellular compartments.[12] After oral administration, peak plasma concentration is achieved in 1 to 2 hours. Heavy meals, including both carbohydrate and fatty foodstuffs result in delayed absorption, with maximal concentrations ranging from 9 to 50%.[13,14] Individuals with extensive gastric surgery or those with resected or dysfunctional terminal ileum may fail to have normal absorption. In CSF, the concentration reaches about 20% of that in plasma. INH is minimally bound to serum proteins. The dosage of INH for adults is 5 mg/kg if given daily (max 300 mg) and 15 mg/kg if given twice-thrice weekly (max 900 mg). Similarly, for children the dosage is 10–20 mg/kg, 20–40 mg/kg and 15 mg/kg if given daily (max 300 mg), twice-weekly and thrice weekly (max 900 mg) respectively. In fetus, the serum concentration reaches 50% of that in the mother. INH achieves a concentration of 16.6 mg/ml with 300 mg dose after 3 hours and 12 to 25% of the usual infant dose of 10–20 mg/day is available to the infant from milk.[15,16] This may be a problem for the infant who is given INH for either treatment or for chemoprophylaxis especially in higher dosage, since about 1/5th of the daily therapeutic dose of INH is also ingested form milk by the infant. Such infants may be predisposed to convulsions due to pyridoxine deficiency.[17]

Minimal Inhibitory Concentration (MIC) of INH for majority (80%) of susceptible *M. tuberculosis* strains is less than 1 mg/ml (0.025 to 0.05 mg/ml).[18] The peak serum concentration is 3–5 mg/ml, far in excess of MIC required. The MIC of other pathogenic mycobacterial species (*M. kansasii*, *M. avium*, *M. haemophilium*) is higher in the range of more than 1 to 10 mg/ml, and hence these may fail to respond to INH.

Most of INH (75 to 95%) is excreted in metabolized form in urine within 24 hours.[12] The major metabolites are acetylisoniazid formed by acetaylation of INH by hepatic acetyltransferase, and isonicotinic acid formed by hydrolysis. None of the other biotransformation products have biological activity. The half-life of INH ranges from 0.5 to 1.5 hours in rapid acetylators and 2 to 4.5 hours in slow acetylators. The acetylation rate is related to genetic differences in host acetyltransferase activity. There are three groups of acetylation status: Fast, intermediate and slow. The NATZ IZA allele codes for fast acetylation. Rapid acetylators are homozygous, intermediate acetylators are heterozygous and slow acetylators do not possess this allele.[19] Acetyltransferase is predominantly found in liver and small intestine. Liver disease can reduce acetylation rates. Neither age nor gender influences INH acetylation. Distribution of acetylation genotypes varies by race with approximately 50% of Whites, Blacks and South Indians being rapid acetylators whereas 80 to 90% of Chinese, Japanese and Eskimos have this trait.[20-22]

Earlier studies suggested that rapid acetylators who were more likely to have poor therapeutic response developed chronic tuberculosis.[23] However, careful monitoring of drug intake in such patients revealed that acetylation status does not influence treatment outcome.[24,25] This stands true for patients on daily, twice or thrice weekly regimens. By contrast, rapid acetylators have consistently less favorable outcomes in once-weekly regimens. Small amounts of INH are also excreted in saliva, sputum and feces. Isoniazid is removed by hemodialysis and peritoneal dialysis. The half-life of INH can be increased by drugs, such as Para-aminosalicylic Acid (PAS), procainamide, chlorpromazine and decreased by ethanol and other drugs that induce cytochrome P-450. Isoniazid may increase phenytoin, warfarin and carbamazepine serum levels.

The mechanism of action of INH consists of the inhibition of mycolic acid synthesis, depletion of Nicotinamide Adenine Dinucleotide (NAD), incorporation of INH derivatives into NAD to form NAD analogs (which lead to nonfunctional coenzymes) and catalase peroxidase.[26-30] Isoniazid is a prodrug, must be activated by a bacterial catalase-peroxidase enzyme called KatG.[31] KatG couples the isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex. This complex binds tightly to ketoenoylreductase known as InhA, thereby blocking the natural enoyl-AcpM substrate and the action of fatty acid synthase. This process inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall.

Kruger-Theimer[30] proposed that after uptake, INH is oxidized by the organism's catalase-peroxidase system to Isonicotinic Acid (INA) and other products incorporated to NAD analog. These NAD analogs are no longer functional as coenzymes, hence the tubercle bacilli become unable to oxidize hydrogen by the usual dehydrogenase-cytochrome oxidase system to form water. Also, a compensatory oxidation of hydrogen by flavin enzymes sets in, which leads to intracellular accumulation of hydrogen peroxide and inhibits bacterial multiplication.

Adverse Effects

The hepatotoxicity associated with INH was reported to result from the toxic effect of the intermediate products monoacetylhydrazine and diacetylhydrazine produced by liver cytochrome P-450 mixed function oxidase. After a standard 300 mg dose of oral INH, rapid acetylators excrete 23% of the drug as monoacetylhydrazine and slow acetylators excrete 5%.[29] Hence, the former phenotype was believed to be associated with increased hepatotoxicity. Larger studies have shown no significant differences in the incidence of hepatotoxicity by host acetylation rate status.[32,33]

The incidence of hepatotoxicity increases with advancing age.[34] It is 0% for persons younger than 20 years, 0.3% for persons 20–34 years of age, 1.2% for persons of age 35–49 years and 2.3% for persons 50 years or older.[35] Other factors that predispose INH associated liver damage include excessive alcohol consumption, Intravenous (IV) drug abuse and pre-existing liver disease. Asymptomatic elevation of serum transaminase levels occur in as many as 20% of cases.[36] The incidence of hepatitis was higher in those who were taking both INH and rifampicin than those who took either INH plus other drugs without RIF or RIF plus other drugs without INH.[37] RIF induces an INH degradation pathway whereby more of the INH is hydrolyzed to form increased amounts of hydrazine, a potentially toxic compound.[38] Although the rate of acetylation does not change in the presence of liver disease, clearance of drug is diminished in severe liver impairment, hence the dose of INH must be reduced to 150–200 mg daily and serum levels monitored.[39,40]

Since only a small proportion of INH is excreted renally, the dose needs to be reduced only in patients with severe renal insufficiency (creatinine clearance < 10 mg/dl). However, normal daily doses of INH (300 mg or 5–6 mg/kg) can be given to patients with severe renal impairment as the administration of these doses in such cases will be equivalent to 8–9 mg/kg, which is well tolerated.[41] It has been demonstrated that reducing INH doses to 200 mg/day results in significant reduced therapeutic potency.[42] Keeping this background information in mind, most clinicians do not alter normal doses of isoniazid in the patients of Chronic Renal Failure (CRF). In patients undergoing periodic hemodialysis, INH must be given in usual dose just following hemodialysis for rapid acetylators, a reduced dose may be appropriate for slow acetylators.[43]

Isoniazid has been shown to interfere with the biological functions of the pyridoxine compounds resulting in various toxicities like peripheral neuropathy and anemia.[44] The likelihood of toxicity is related to the nutritional status of the patient, is dosage related, rarely occurring with standard 300 mg daily dose. Conditions that predispose to neuropathy increase the risk of this manifestation in INH therapy. Hence pyridoxine supplementation must be given for chronically undernourished persons, chronic alcoholics, pregnant women, adolescent girls, diabetic patients, patients with uremia, seizure disorders, advanced age and cancer patients. Because of the potential for interference by high doses of pyridoxine with the antituberculous activity of INH, no more than 10 mg per day should be used.[44]

The peripheral neuropathy is characteristically a "stocking-glove" type that commences with numbness and tingling, usually worse in the feet. Untreated, it may progress to disabling paresthesias, pain and weakness. The therapeutic dose of pyridoxine is 100 mg daily in such patients. Other less frequent neurological adverse effects that have been reported with INH are toxic encephalopathy, optic neuritis, cerebellar ataxia and psychiatric disturbances.[45,46] The mechanism by which these side effects occur has not been elucidated. Hypersensitivity reactions to INH are occasionally encountered, manifesting by the way of fever, pruritis, cutaneous eruptions (morbilliform, maculopapular, eruptive rash). The other rare side effects of INH are lupus like reactions, arthralgias, hematological disorders (anemia, agranulocytosis).[47,48]

The ingestion of toxic amounts of isoniazid causes recurrent seizures, profound metabolic acidosis, coma and even death. In adults, toxicity can occur with the acute ingestion of as little as 1.5 g of isoniazid. Doses larger than 30 mg per kg often produce seizures. When ingested in amounts of 80–150 mg/kg or more, isoniazid can be rapidly fatal. The first signs and symptoms of isoniazid toxicity usually appear 30 minutes to 2 hours after ingestion and include nausea, vomiting, slurred speech, dizziness, tachycardia and urinary retention, followed by stupor, coma and recurrent grandmal seizures. The seizures produced by isoniazid toxicity are often refractory to anticonvulsant therapy. Given in gram-per-gram amounts of the isoniazid ingested, pyridoxine (vitamin B_6) usually eliminates seizure activity and helps to correct the patient's metabolic acidosis. Isoniazid toxicity should be suspected in any patient who presents with refractory seizures and metabolic acidosis.

Mechanisms of Resistance to INH

1. Mutation in KatG gene reduces catalase-peroxidase (KatG) ability to activate prodrug INH to a range of highly reactive bactericidal species. This mutation is responsible for 22 to 64% of INH resistant cases.
2. Inh A gene produces NADH-dependent enoyl-ACP reductase, which is necessary for the production of mycolic acid in tubercle bacilli. Mutation of this gene leads to the upregulation of INH A and hence increased the production of mycolic acid. This mutation occurs in 20 to 34% of INH resistance (low level resistance, MIC ≤ 1 mg/ml) and this can be overcome by increasing the dosage of INH.
3. kas A gene produces β-Ketoacyl ACP synthase and mutation of this gene reduces INH ability to interfere with mycolic acid synthesis (low level resistance). Occurs in 14% of INH-resistant cases.
4. ahpC gene produces alkyl hydroperoxide reductase and mutation of this gene reduces INH activation (in 10% cases).
5. Mutation of the gene ndh (NADH dehydrogenase) results in the increased competition of NADH with INH-NAD to bind with inhA site.

RIFAMPICIN

Rifampicin (RIF) is a semi-synthetic broad-spectrum bactericidal antibiotic derived from *Amycolaptosis mediterranei* (formerly classified as *Streptomyces mediterranei).*[49] Out of many biologically active compounds identified from the crude extract, rifamycin B was the most stable, least toxic, but with moderate level of therapeutic activity. Further refinement of rifamycin B led to the synthesis of rifampin (rifamycin B to rifamycin O to rifamycin SV to rifampicin).[50,51] Rifampicin was synthesized initially in Italy in 1957, but introduced in to clinical use only in 1966, employed initially for the retreatment of drug-resistant treatment failure cases.[52] Several large clinical trials have demonstrated that RIF containing regimens effectively reduce the duration of the chemotherapy to less than nine months.[53-57] Also, RIF has contributed to the success of intermittent therapy.[57,58] Both the shortened duration and increased interval of dosages have improved patient compliance, hence RIF became a standard element of therapy by late 1970s.[59] In addition to its antituberculosis activity, it has a wide range of activity against other bacteria, including *Staphylococcus*, *Streptococcus*, *Clostridium*, coliforms, *Pseudomonas*, *Proteus*, *Salmonella*, *Shigella*, *Bacteroides* and *Legionella*.

Rifampicin's target is β subunit of mycobacterial RNA polymerase, which read the DNA target sequence and catalyzing the polymerization of the complementary RNA chain with ribonucleic triphosphate monomers.[60]

Binding of RIF with β subunit of RNA polymerase either inhibits the nascent RNA chain form translocating into the polymer site allosterically or decreases the affinity of the active site for short chain RNA transcripts.[61,62] This results in short oligoribonucleotides that rapidly diffuse out of the active center.

Although RIF has lesser Early Bactericidal Activity (EBA) than INH, it has superior sterilizing activity.[2,63] This sterilization activity has been attributed to RIF's ability to affect semidormant bacilli, which are sporadically active for the short periods of time (population-C).[64] These brief periods of time are insufficient for other equally effective bactericidal agents to work, but sufficient for RIF to exert its effects.[64] Rifampicin is better absorbed in acidic environment, hence both food and antacids must be avoided in relation to the time of its administration. When taken on an empty stomach, peak plasma levels of 6–7 μg/ml are reached at 3 hours and the drug has a half-life of about 5 hours.[65] The MICs of susceptible strains range from 0.06 to 0.25 μg/ml.[66]

It is partly deacetylated in the liver, excreted almost entirely in the bile; but there is enterohepatic circulation, some drug does appear in urine.[67] During the first few weeks of therapy, RIF induces accelerated rates at which it is deacetylated in the liver.[68] Since, desacetyl-rifampicin is excreted in the bile more rapidly than plain RIF, the peak concentration and serum half-life reduces during initial few weeks. Thus, the peak levels initially may reach 20 μg/ml or higher, the usual range seen later is between 8 and 12 μg/ml. No adjustment in dosage is necessary in patients with renal failure. The dosage of RIF is 10 mg/kg body weight (max 600 mg/day). Dosages of RIF exceeding this limit result in more drug bye-passing the liver and increased serum levels. Divided daily doses of RIF result in lower serum concentration, hence it must be given in a single daily dose. Although about 75% of the drug is protein bound, it penetrates well into tissues and cells. Therapeutic concentrations are reached in Cerebrospinal Fluid (CSF) when the meninges are inflamed.

Rifampicin accelerates the hepatic cytochrome P450 pathway and reduces the serum levels of many drugs, including the antifungal agents, corticosteroids, warfarin and oral hypoglycemic agents (Table 43.1). Rifampicin also reduces the levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors used to treat Human Immunodeficiency Virus (HIV) infection.[69] This interaction may lead to the rapid development of resistance in HIV strains to the protease inhibitors. Rifampicin reduces the effectiveness of oral contraceptives[70] and patients should be advised to use nonhormonal contraception during, and for one month after, treatment with rifampicin-containing regimens.

TABLE 43.1: Drug interactions of rifamycins with other compounds[71-73]

A. Cytochrome P450 pathway induction, resulting in more rapid elimination of:

1. Corticosteroids
2. Oral contraceptives
3. Warfarin
4. Protease inhibitors
5. Azole antifungal agents
6. Anticonvulsants (phenytoin)
7. Oral hypoglycemic agents
8. Opiates (methadone)
9. Benzodiazepines
10. Antiarrhythmic agents
11. Chloramphenicol
12. Theophylline
13. Cyclosporine

B. Drugs that inhibit Cyp P450, hence retard elimination of rifamycins

1. Ciprofloxacin
2. Macrolides
3. Azol antifungals

Rifampicin is the most potent inducer of Cyp P450 enzyme, rifapentine is about 50% as active and rifabutin about 10%. Maximum induction of the Cytochrome P450 pathway may require 7 to 10 days; conversely these effects do not resolve for 7 to 14 days following the discontinuation of rifampin. If major drug-drug interactions are feared one may either substitute rifabutin or adjust upward the doses of the other drugs.

Rifampicin may be detected in urine following the extraction of 10 ml urine by analytical-grade chloroform in a screw-capped tube by gentle tilting.[74] The test is negative if no color develops, a yellow to orange color in the chloroform layer indicating the presence of rifampicin. The test is valid for up to at least 6 hours and, in some patients, up to 12 hours after the ingestion of rifampicin. Tetracyclines, nitrofurantoin and phenothiazine derivatives also give a yellow color.

Adverse Effects

Rifampicin is well-tolerated by most patients at the currently recommended dosages. Unlike other drugs, RIF produces some adverse reactions more frequently with intermittent than with daily regimens. Moreover, the risk of adverse effects increases with the interval between doses, thus toxicity is high, if treatment is taken only once a week.

The drug is excreted in body fluids, all patients should be warned that their urine, sweat and tears may be colored orange-pink. It may also discolorize soft contact lens. Of the Gastrointestinal (GI) reactions, nausea, anorexia and mild abdominal pain are most common, vomiting and diarrhea occurring less frequently. The incidence of these effects varies from 0 to 17%, more common in the elderly.[75,76] They may be resolved by giving the drug at night or, if this fails, during a meal. Transient elevations in aspartate aminotransferase levels are common (14 to 40% of patients), are of no clinical significance.[77] Major elevations of aspartate aminotransferase (>150 IU/l) occur in 4% and hepatitis with jaundice in about 1% patients. Rifampicin can also competitively interfere with the excretion of bilirubin and transiently elevate serum bilirubin.[78] Risk groups for jaundice include elderly women, alcoholics and those with a previous history of liver or biliary disease.[79] Rifampicin should be administered with care to these groups.

Cutaneous reactions are usually mild, consist of flushing with or without itching or a rash, commonly occur 2–3 hours after taking the drug. Patients usually desensitize themselves to these reactions, but occasionally an antihistamine may be required. Severe conjunctivitis and chronic papular acneiform reactions of the head, neck and shoulders have also been described. Cases of osteomalacia, pseudomembranous colitis, pseudoadrenal crisis, light-chain proteinuria with renal failure and cutaneous vasculitis have also been described.[80-82] Several other syndromes may occur with the intermittent regimens of rifampicin.

The "flu syndrome", with flu-like symptoms, lasting for up to 8 hours after administration of the drug, may occur a few months after treatment has been started, attributed to the development of circulating rifampicin-dependent antibodies.[83] It may resolve spontaneously or necessitate a switch to a daily regimen. Thrombocytopenic purpura constitutes an absolute indication for stopping therapy with rifampicin permanently. Asthmatic and hypotensive syndromes may occur separately or together, require corticosteroid therapy before conversion to a daily regimen. Acute hemolytic anemia and acute tubular necrosis have also been reported. Cutaneous syndromes usually start during the first month, and gastrointestinal symptoms are spread over the first-six months. The "flu" syndrome, observed only with intermittent regimens, generally begins in the third to fifth month of the treatment.[84] The incidence of side effects in recent reports of intermittent therapy have been gratifyingly low.[85,86] Anyone who develops serious allergic drug reactions, such as renal failure, thrombocytopenia or respiratory insufficiency should not receive rifampin again.

Mechanism of Resistance to RIF

Single base pair changes in the central region of the RNA polymerase beta subunit gene (rpo B) result in rifampin resistance. These mutations lead to decreased enzyme affinity for RIF.[87,88]

STREPTOMYCIN

Streptomycin (SM) was originally isolated from two strains of an actinomycetes species *(Streptomyces griseus)* by Selman Waksman and coworkers in 1943. Streptomycin was the first clinically effective drug available for the treatment of tuberculosis. Utility of this drug has been limited by the need for large doses that cannot be administered orally; frequent side effects and rapid emergence of resistance. Sole therapy with streptomycin in the late 1940s and early 1950s demonstrated the difficulty of treating TB with a single agent. As many as 80% of patients with cavitary disease harboring the large number of bacilli developed resistance to SM after the three months of therapy. It soon became evident that combination chemotherapy with newer agents prevented the emergence of drug resistance, hence SM was used along with PAS until isoniazid was developed.

Streptomycin does not cross most membranes due to its large size and cationic charge, hence oral absorption is very poor. It must be given by either intramuscular or intravenous route. It diffuses readily into most body tissues, but penetration into CSF is less, with maximum levels obtained in inflamed meninges, of about 25% of serum levels.[89] For this reason, SM is not usually recommended for TB meningitis. When no other agents are available, intrathecal or intraventricular administration is advisable in life-threatening cases.[90] The peak plasma levels in the range of 40 µg/ml are achieved 1 hour after injection and MICs are maintained for at least 8 hours.[91] Most strains of *M. tuberculosis* are inhibited *in vitro* at a concentration of 8 µg/ml. The drug is excreted almost entirely by glomerular filtration, dosage must be modified in renal failure to avoid toxicity. A safe rule is to multiply the daily dose by the ratio of the patient's creatinine clearance to normal creatinine clearance.

Streptomycin binds with 30S subunit of ribosomes, reduces protein synthesis and induces misreading of mRNA. Some experts do not feel this sufficiently explains the bactericidal action of SM as agents that affect protein synthesis are generally bacteriostatic, not lethal to cells.[92] The other proposed mechanisms of action include increased permeability of membranes and enhanced uptake of drug.

It crosses the placenta, fetal serum levels are about half those in maternal blood. Use of streptomycin showed increase in the incidence of malformations in infants, 16.9% versus 1.4 to 6.0% in controls.[93] Aminoglycosides should not be used in pregnancy. The level of the drug in breast milk ranges from 12 to 47% after 6 hours of a dose. Thus, the potential for side effects exist and SM should not be used if alternatives are available. Streptomycin sulfate for intramuscular injection is supplied as a powder in vials and should be reconstituted immediately before use. The dose of SM in adults is 15 mg/kg body weight daily or thrice weekly. The dose should be reduced to 0.5 gm/day for patients of age more than 50 years.

Adverse Effects

Streptomycin is toxic to the eighth cranial nerve, with vestibular damage more common than auditory damage. The patient usually complains of the progressive giddiness and unsteadiness of gait. Nystagmus may be present. The damage to the nerve is permanent, but most patients eventually compensate via ocular and proprioceptive compensatory mechanisms. The risk increases with the dose of drug and age.[94,95] The sensorineural deafness is most marked at higher frequencies. The first sign of ototoxicity is usually tinnitus or headache, which should prompt testing for hearing acuity with particular attention to deficits in the higher frequencies.

Streptomycin is ototoxic to the fetus. Other adverse effects include rashes, anaphylaxis, renal tubular damage, precipitation of heart failure, visual scotomas, peripheral neuritis, perioral paresthesia and blood dyscrasias, including hemolytic and aplastic anemia, agranulocytosis and thrombocytopenia. Streptomycin potentiates the neuromuscular block produced by curare, is contraindicated in individuals suffering from myasthenia gravis.

Mechanism of Drug Resistance

Mutation of rpsL gene (which encodes for S12 ribosomal protein) reduces the binding of streptomycin to S12 ribosomal protein and leads to the resistance.

PYRAZINAMIDE

Pyrazinamide (PZA), an amide derivative of pyrazine-2-carboxylic acid, was synthesized by Kushner and coworkers, and found to be the most active nicotinamide analog against *M. tuberculosis*.[96] The first clinical trial of PZA given as single agent, at an average dose of 2.8 gm/day demonstrated bacteriological and clinical improvement in most patients.[97] However, this effect was not sustained and resistance to PZA developed rapidly. In all earlier clinical trials, the dosage of PZA was very high (ranges from 40 to 70 mg/kg), which resulted in lethal hepatotoxicity.[98,99] Thus, PZA was used as second line agent until 1970. Trials of short-course chemotherapy for tuberculosis in the 1970s revived interest in PZA and suggested that PZA was essential to reduce the duration of therapy for smear positive pulmonary tuberculosis to six months. The relapse rates were very low (1.4 to 2.4% at 5 years) without increased toxicity. It was also noted in subsequent studies, that there was no additional utility of PZA if used beyond initial two months.[100] A modest, but significant reduction in serum RIF level was observed when PZA was given simultaneously.[101] Also, PZA caused a slight reduction in the bactericidal activity of RIF.[102] These studies clearly indicated that PZA need not be used beyond the first-two months, unless drug resistance was detected.

Currently, PZA is considered a first line agent, is the third most important drug used in the treatment of tuberculosis. The exact mechanism of the antimycobacterial action of PZA is not completely known. It is bactericidal in an acid environment ($pH<5.0$), hence its activity can be demonstrated *in vitro* only in low pH environment. Initially, it was thought that such acidic milieu was present in the phagolysosomes of macrophages. The tubercle bacilli produces an enzyme called “pyrazinamidase”, which converts PZA to Pyrazinoic Acid (POA),[103] reduces the pH and is inhibitory to tubercle bacilli. At the same time, the bacilli produces ammonia, neutralize pH, hence the effect of PZA on macrophage diminishes 4 to 7 days after infection.[104] Extreme regional acidity within the localized regions of the diseased host has been offered as another theory to explain PZA’s activity. It had been suggested that the local milieu in necrotic, caseating lesions is acidic that results in the inhibition or semidormancy of the tubercle bacilli, therefore PZA may contribute uniquely to chemotherapy by killing bacilli in this state, wherein they are not vulnerable to other agents, which only act on proliferating bacilli.[105,106] However, this activity of PZA was termed as "sterilizing" rather than a classic "bactericidal" effect. *M. bovis* is resistant to this drug.

It is well absorbed from the gastrointestinal tract, with the peak concentrations of about 50 µg/ml occurring 1.5 to 2 hours after ingestion. At a pH of 5.5, the minimal inhibitory concentration of pyrazinamide for *M. tuberculosis* is 20 µg/ml. It penetrates well into tissues, including the CSF. The drug is excreted in urine, 40% as pyrazinoic acid and 3% as unchanged PZA. The dose of pyrazinamide is 25–35 mg/kg body weight, daily. Lyophilized form of morphazinamide may be used for intravenous therapy if required, administered by drip infusion in a dose of 1G following reconstitution with solvent.

Adverse Effects

Hepatitis was commoner when the higher doses of the drug were used than are now recommended. It occurs in about 1% of patients, but milder subclinical derangement of liver function tests is common. The drug should be administered with caution to those with a history of liver or biliary tract disease. There is no significant increase in hepatotoxicity when pyrazinamide in standard dosage is added to a regimen of isoniazid and rifampicin during the initial two months of therapy.[107] Unlike RIF or INH-induced hepatitis, wherein values typically normalize in 10 to 14 days, PZA induced hepatitis may persist for 4 to 6 weeks after the drug has been discontinued.

Cutaneous reactions in the form of faintly erythematous rash and mild pruritus are rarely reported. Arthralgia is a common adverse effect (occurs in 40% of patients) that appears in the first-two months of treatment, more frequently in Chinese patients. It is due to the inhibition of renal tubular secretion of uric acid by pyrazinoic acid, the main metabolite of pyrazinamide, can be treated with nonsteroidal anti-inflammatory agents.[108] High serum concentration of uric acid may uncommonly precipitate gout. Rarer adverse effects include anorexia, nausea, vomiting and sideroblastic anemia.

Mechanism of Drug Resistance

Mutation of pncA gene (which encodes for pyrazinamidase) results in the blocking of conversion form PZA to pyrazinoic acid (active intermediate).

ETHAMBUTOL

Ethambutol (d-ethylenediimino-di-1-butanol) is a singular compound, not related to any other family of antimicrobial agents. The effectiveness of this drug in tuberculosis was first described in 1961.[109] Ethambutol (EMB) is generally considered as a bacteriostatic drug, although it is bactericidal *in vitro*.[110] It interferes with synthesis of arabinogalactan and with the transfer of mycolic acids into mycobacterial wall.[111] It has high Early Bactericidal Activity (EBA), reducing the number of bacilli in sputum over 14 days at a rate second only to INH.[2] Studies of EMB activity have indicated that high concentrations of EMB (10 µg/ml) have considerable bactericidal activity against *M. tuberculosis*.[112] Since, these high concentrations were achievable with dosages given in intermittent therapy, there appeared a role for EMB in twice-thrice weekly treatment. However, the available data indicate that EMB has only modest activity in drug susceptible tuberculosis, if given in the regimens containing INH, RIF and PZA. The major utility of EMB was demonstrated in the BMRC trials for cases with initial drug resistance to INH and/or SM.[113] In such cases, the primary effect of EMB is to prevent the treatment failure and further acquisition of drug resistance. However, SM appears slightly more potent than EMB as a fourth drug to accompany INH, RIF and PZA.

It is well absorbed after ingestion, with the peak plasma levels of 4 µg/ml occurring 2 to 4 hours after a dose of 15 mg/kg; food does not interfere with EMB absorption. The dose of EMB is 15–20 mg/kg body weight daily, 30 mg/kg thrice weekly and 40 mg/kg if given twice weekly. Peak levels correlate with the dosage. CSF concentrations of EMB are low (1–2 µg/ml with a dose of 25 mg/kg) even in the presence of meningitis. The drug is excreted in the urine, dosage adjustment is required for patients with renal insufficiency.[114] In patients on hemodialysis, a daily dose of 5 mg/kg body weight or a dose of 1.5 mg/kg every 8 hours has been suggested, with the testing of serum EMB levels and visual acuity, the serum levels should not exceed 5 µg/ml.[115] Levels of 1.5 mg/l and 4.6 mg/l have been observed in the milk of lactating mother. Hence an infant of 3.5 kg body weight would ingest 0.5–0.9 mg/kg/day from breast milk (2.8 to 6.9% of pediatric therapeutic dose), this is not likely to be toxic for the infant.[116]

Adverse Effects

The principal adverse effect of EMB is retrobulbar neuritis, presenting with blurred vision, central scotomas and disturbance of red–green vision.[117,118] Recovery is the rule if the drug is stopped at the first sign of visual problems, but if these are ignored, optic atrophy may result. This complication is uncommon at a dose of

15 mg/kg, but increases with a daily dose of 25 mg/kg. Pre-existing ophthalmic diseases may predispose to EMB toxicity. Patients should be warned to report visual symptoms immediately and to stop treatment if symptoms develop; pretreatment testing and recording of visual acuity is advised for patients taking this drug. The renal clearance of urates is decreased by EMB in a significant number of normal patients, and acute attacks of gout have been precipitated in patients at risk.[119] Other adverse reactions of EMB occasionally described are: Anaphylaxis, skin rashes, hepatic dysfunction, blood dyscrasias, interstitial nephritis and peripheral neuropathies.

Mechanism of Drug Resistance

Mutation of embB gene (which encodes for a membrane protein) reduces the binding of ethambutol with the membrane protein and leads to resistance to EMB. This mutation is responsible for 48 to 62% of cases resistant to EMB.

QUINOLONES

The quinolones are derivatives of pyridinecarboxylic acid, initially derived from an intermediate in chloroquine synthesis.[120] The 6-fluoroquinolones are potent antibacterial agents that interfere with a wide variety of DNA related processes, primarily through their action on A subunit of DNA gyrase (topoisomerase), the enzyme responsible for introducing supercoils into bacterial DNA. The fluoroquinolones have both bactericidal and sterilizing activities. These are well absorbed in gastrointestinal tract and the bioavailability approaches 100%. It is distributed widely in the body, 30 to 50% of serum concentration is attained in CSF with inflamed meninges. It has minimal hepatic metabolism; 87% of dose is excreted unchanged in the urine within 48 hours via glomerular filtration and tubular secretion. Dose reduction is necessary in patients with renal failure. Animal data demonstrated arthro-pathy in immature animals, with erosions in joint cartilage. Quinolones should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Ciprofloxacin is no longer recommended to treat drug-susceptible or drug resistant tuberculosis.[121] Currently, the most potent available fluoroquinolones in descending order based on *in vitro* activity and animal studies are: Moxifloxacin = gatifloxacin > levofloxacin > ofloxacin.[122,123] While ofloxacin is commonly used because of relatively lower cost, the later-generation fluoroquinolones, moxifloxacin and levofloxacin, are more effective and have similar adverse effect profiles. Furthermore, the later-generation fluoroquinolones may have some efficacy against ofloxacin-resistant strains.[124] Although similar to moxifloxacin in its efficacy against TB, gatifloxacin is associated with serious cases of hypoglycemia, hyperglycemia and new-onset diabetes. If gatifloxacin is used, it should undergo close monitoring; the drug has been removed from the markets of many countries. Levofloxacin is, for the time being, the fluoroquinolone of choice until more data confirm the long-term safety of moxifloxacin. A later-generation fluoroquinolone is recommended for the treatment of XDR-TB, although there is inadequate evidence on whether this is an effective strategy.

Adverse Effects

The quinolones are generally well-tolerated. Gastrointestinal intolerance, headache, malaise, insomnia, restlessness, dizziness, allergic reactions, diarrhea, photosensitivity, tendon rupture and peripheral neuropathy have rarely been reported. Quinolones have the potential to cause tachycardia and QTc prolongation, can cause serious arrhythmia. This potential has been most marked for gatifloxacin and sparfloxacin, less seen in other quinolones. These drugs should be avoided in the presence of hypokalemia and in those patients taking drugs that can prolong QT such as cisapride, tricyclic antidepressants, phenothiazines, class IA and class III antiarrhythmics and macrolides.

Mechanism of Drug Resistance

Mutation of gyrA gene (which encodes for bacterial DNA gyrase A subunit) results in the inability of fluoroquinolones to inhibit DNA gyrase.

PARA-AMINOSALICYLIC ACID (PAS)

Lehman studied 50 related compounds of salicylates and found PAS the most active against tubercle bacilli.[125] In a BMRC trial,[126] it was observed that there was no significant difference in the efficacy of streptomycin plus PAS versus streptomycin alone; however, a marked decrease in the development of streptomycin-resistant strains was noticed with addition of PAS. It was considered a first-line agent in combination with INH and SM until 1963 when ethambutol was approved for clinical use and replaced PAS as the first-line agent.

Para-aminosalicylic acid is a structural analog of Para-aminobenzoic Acid (PABA). It exerts a bacteriostatic effect on *M. tuberculosis* by competitively blocking the conversion of PABA into folic acid (which is essential for DNA synthesis), hence inhibits bacterial growth.[127] The MIC of sensitive strains ranges from 0.5 to 2.0 mg/ml.[131] The drug is readily absorbed from the gastrointestinal tract. The peak serum level of 7–8 mg/ml is reached within 1 to 2 hours after an oral dose of 4 gm. About 60 to 70% of the drug is bound to plasma proteins. PAS is metabolized in the liver by acetylation and excreted in urine as metabolites.[128] It does not cross non-inflamed meninges, rapidly diffuses into caseous lesions within 30 minutes, but rapidly disappears from the lesion as soon as drug administration is dis-continued.[129] The drug is excreted rapidly, thus larger doses must be given. The dose of PAS is 150 mg/kg daily in divided doses or 10–12 gm/day.

Adverse Reactions

Nearly all patients suffer gastrointestinal upset in the form of nausea, vomiting, anorexia or diarrhea. Many patients stop taking PAS prematurely. Hypersensitivity reactions manifested by fever, rashes, pruritus and hepatic dysfunction occur in about 5 to 10% of patients. In some patients, lymphadenopathy, joint pains and pulmonary infiltrates with eosinophilia have been reported. Most of these symptoms disappear with the discontinuation of therapy. It can cause fluid retention from excessive sodium load in patients with congestive cardiac failure. Hemolytic anemia has been reported in patients with G6PD deficiency. PAS partially inhibits the uptake of iodine by thyroid, thus can cause hypothyroidism.[130]

Mechanism of drug resistance to PAS is not known.

ETHIONAMIDE/PROTHIONAMIDE

Ethionamide (Alpha-ethyl-thioisonicotinamide) is a thioamide of isonicotinic acid that was synthesized by Lieberman in 1952.[131] The exact mechanism of action is unknown, but it appears to be similar to that of INH. Ethionamide is believed to exert its action on the outer envelope of tubercle bacilli, which includes the inhibition of mycolic acid synthesis.[131] The MIC of susceptible strains of *M. tuberculosis* is 0.3 µg/ml. The drug is well-absorbed from the GIT, the peak serum level is about 1.4 µg/ml after 3 hours of administration. After absorption, the drug gets widely distributed in the body, inactivated by liver and to a lesser extent by the kidney.[132] It is excreted in the kidney mainly as metabolites, about 5% as active drug. The drug readily crosses both the inflamed and the non-inflamed meninges, the concentration in CSF equals to the serum concentration.

Prothionamide is the N-propyl derivative of ethionamide, similar to ethionamide in its action, clinical effectiveness and toxicity. However, prothionamide is considered to be unpleasant of the two.

The maximum optimum daily dose of ethionamide and prothionamide is 15–20 mg/kg (max. 1 g/day), usually 500–750 mg. The dose must be reduced to 250–500 mg/day in patients with creatinine clearance of less than 30 ml/minute. Resistance develops rapidly if used alone, there is complete cross-resistance between ethionamide and prothionamide (partial cross-resistance with isoniazid and thiacetazone). Thiacetazone-resistant organisms are often sensitive to prothionamide, but the reverse does not apply.

Adverse Reactions

The most common side effect of ethionamide/prothionamide is gastrointestinal upset, which includes nausea, vomiting, unpleasant metallic taste and epigastric burning pain. Gastrointestinal effects may be minimized by decreasing dosage, by changing the time of drug administration, or by the concurrent administration of an antiemetic agent. Most of the symptoms disappear in a week, but in some the symptoms are severe requiring the discontinuation of therapy. Hepatitis with jaundice has been reported to occur in 4.3% of patients. Other side effects include mental depression, psychological disturbances, peripheral neuritis, convulsion, hypoglycemia, photosensitivity, gynecomastia, hypothyroidism, alopecia and acne. The drug is teratogenic in animals, should be avoided in pregnancy (at least during the first trimester) and care should be taken in the presence of diabetes, liver disease, alcoholism or mental illness. Ethionamide is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in animals and *in vitro* systems.

Mechanism of Drug Resistance

Mutation of inhA gene (similar to that in isoniazid) lead to resistance to ethionamide in 40% of resistant cases.

CYCLOSERINE/TERIZIDONE

Cycloserine introduced in 1955, is an antibiotic isolated by Harned and Kropp from the culture of *Streptomyces orchidaceous*. Cycloserine is a structural analog of D-alanine. It competitively blocks the enzymes alanine racemase and D-alanyl-D-alanine synthetase, which are necessary for the synthesis of D-alanine dipeptide. This dipeptide is essential for mycobacterial cell wall synthesis, inhibition of which leads to the inhibition of cell growth.[127] Cycloserine is bacteriostatic, the MIC is 10 µg/ml for susceptible strains. The drug is rapidly absorbed orally, a mean peak serum level of 50 µg/ml is achieved in 4 hours of drug intake. The drug is widely distributed in the body, crosses the meninges promptly regardless of inflammation. There is no cross-resistance with other antituberculosis drugs, 60 to 70% of the drug is excreted unchanged in the urine via glomerular filtration; small amount are excreted in feces and a small amount is metabolized.

Terizidone contains two molecules of cycloserine. It is used in some countries instead of cycloserine, assumed to be as efficacious; however, there are no direct studies comparing the two drugs. Terizidone is not yet recommended by the WHO. The dosage of cycloserine is 10–15 mg/kg daily (max. 1000 mg), usually 500–750 mg per day given in two divided doses.

Adverse Reactions

The frequently encountered adverse effects of cycloserine are neurological and psychiatric problems, including headaches, irritability, sleep disturbances, aggression, tremors, gum inflammation, pale skin, depression, confusion, dizziness, restlessness, anxiety, nightmares, severe headache and drowsiness. Occasionally, visual changes, skin rash, numbness, tingling or burning in hands and feet, jaundice, eye pain, rarely seizures, and suicidal thoughts may also occur. Neurotoxicity is dose related, monitoring of the blood level is recommended to avoid levels in excess of 30 µg/ml.

CAPREOMYCIN

Capreomycin has a different chemical structure from the aminoglycosides, but the mechanism of antibacterial activity is similar. Polypeptides appear to inhibit the translocation of the peptidyl-tRNA and the initiation of protein synthesis. Capreomycin is bactericidal in action. It has got no cross-resistance with aminoglycosides. It penetrates meninges, only if inflamed. Excretion of 50 to 60% of the drug is through kidneys and a small amount through biliary excretion. There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently. Capreomycin is given in a daily dose of 15–20 mg/kg with a usual dose of 1 g in a single daily dose. When necessary, it is possible to give the drug at the same dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse effects. Levels should be monitored for patients with impaired renal function. Interval adjustment (12–15 mg/kg 2 or 3 times per week) is recommended for patients with creatinine clearance of less than 30 ml/min or on hemodialysis.

Adverse Reactions

Animal studies show teratogenic effect, hence it is contraindicated in pregnancy. The frequent side effects are nephrotoxicity (20 to 25%), tubular dysfunction, azotemia, proteinuria, urticaria or maculopapular rash. The other side effects that have been reported include ototoxicity (vestibular>auditory), electrolyte abnormalities (decreased blood levels of calcium, magnesium and potassium), pain, induration and sterile abscesses at injection sites.

THIACETAZONE

Thiacetazone is a low-potency, cheap drug given orally and frequently used as a companion drug for isoniazid in developing countries. It is bacteriostatic in its action. The mechanism of action is unknown. It is well absorbed in the gastrointestinal tract and excreted in urine. It crosses placental barrier and excreted in milk in a concentration equal to that in the mother's blood. It is given in an oral dose of 150 mg daily.

Adverse Reactions

The most frequent side effect is the GI upset, which includes nausea, abdominal discomfort, vomiting and diarrhea. Other adverse effects include anemia, agranulocytosis, thrombocytopenia, cerebral edema, conjunctivitis, blurred vision and jaundice. Thiacetazone may enhance the ototoxicity of streptomycin. Generalized reactions are common. Cutaneous hypersensitivity reactions progressing to toxic epidermal necrolysis have been reported in a significant percentage of patients with HIV-associated tuberculosis treated with thiacetazone-containing regimens. HIV-positive patients or those with clinical markers for Acquired Immunodeficiency Syndrome (AIDS) should have ethambutol substituted for thiacetazone in their treatment regimen.

GROUP 5 DRUGS

Group 5 drugs are not recommended for routine use in the treatment of drug-resistant tuberculosis because their contribution to the efficacy of multidrug regimens is unclear. Although they have demonstrated some activity *in vitro* or in animal models, there is little or no evidence of their efficacy in humans for the treatment of drug-resistant tuberculosis. Most of these drugs are expensive, in some cases require intravenous administration. However, they can be used in cases where adequate regimens are not possible to design with the medicines from Groups 1–4. They should be used in consultation with an expert in the treatment of drug resistance. If a situation requires the use of Group 5 drugs, it is recommended to use at least two drugs from the group, given the limited knowledge of their efficacy.

CLOFAZIMINE

Clofazimine (Cfz) is orally active (40 to 70% absorbed) and accumulates in many tissues, especially in fat. Usual adult dose is 100 to 300 mg daily. Some clinicians begin at 300 mg daily and decrease to 100 mg after 4 to 6 weeks.

The major side effect is reddish-black discoloration of skin, especially on exposed parts. Discoloration of hair, conjunctiva and body secretions can also occur. Dryness of skin and itching is often troublesome. Acneiform eruptions and phototoxicity have been reported. Enteritis with intermittent loose stools, nausea, abdominal pain, anorexia and weight loss can occur at higher dosage. The early syndrome is a reflection of irritant effect of the drug, subsides with dose adjustment and administration along with meals. A late syndrome occurring after the few months of therapy is due to the deposition of clofazimine crystals in the intestinal mucosa. Clofazimine is to be avoided in early pregnancy and in patients with severe liver or renal impairment.

LINEZOLID

Linezolid (Lzd) is a new class antimicrobial agent termed "Oxazolidinones", active against resistant gram-positive aerobes and anaerobes. It inhibits bacterial protein synthesis by binding to the 23S fraction of 50S ribosome and interferes with the formation of tRNA, stops protein synthesis at an early step. As such, there is no cross resistance with any other class of antimicrobial agents. It is rapidly and completely absorbed orally, partly metabolized nonenzymatically and excreted in urine. Usual adult dose is 600 mg twice daily, reduced to 600 mg once a day after 4 to 6 weeks to decrease adverse effects.

Side effects are mostly limited to abdominal pain and bowel upset. Occasionally, rashes, pruritus, headache and oral/vaginal candidiasis have been reported. It can cause thrombocytopenia and bone marrow depression.

AMOXICILLIN/CLAVULANATE

Amoxicillin/Clavulanate (Amx/Clv) is generally well tolerated, but GI tolerance is poorer especially in children. Dosages for the drug-resistant cases of tuberculosis are not well-defined. Normal adult dose is 675/125 mg twice a day or 500/125 mg three times a day. Dosages of 1000/250 have been used, but adverse side effects may limit this dosing. Candida stomatitis/vaginitis, rashes and hepatic injury have been reported.

IMIPENEM/CILASTATIN

Imipenem/cilastatin (Im/Cn) belongs to the subgroup of carbapenem. Imipenem has a broad-spectrum of activity against both sensitive and resistant aerobic and anaerobic gram-positive, as well as gram-negative bacteria. It acts by inhibiting cell wall synthesis. It remains very stable in the presence of beta-lactamase. Usual adult dose is 500–1000 mg IV every 6 hours. Common adverse drug reactions are nausea and vomiting. Those who are allergic to penicillin and other beta-lactam antibiotics should not take imipenem. It can also cause seizures.

CLARITHROMYCIN

Clarithromycin (Clr) belongs to the group "Macrolide" having a macrocyclic lactone ring with attached sugars. It is rapidly absorbed and has greater tissue distribution. No dose modification is needed in liver disease and in mild-to-moderate renal failure. It inhibits hepatic oxidation of many drugs and leads to rise in the plasma levels of theophylline, carbamazepine, valproate, warfarin, terfenadine, astemizole and cisapride. Usual adult dose of clarithromycin is 500 mg twice daily.

Side effects can occur in the form of GI upset, but it is better tolerated than erythromycin. A few cases of pseudomembranous enterocolitis, hepatic dysfunction or rhabdomyolysis have been reported. Several cases of Q-T prolongation and serious ventricular arrhythmia are reported due to the inhibition of CYP3A4 resulting in the high blood levels of concurrently administered terfenadine/astemizole/cisapride.

HIGH-DOSE ISONIAZID

Many experts feel that high-dose isoniazid (16–20 mg/kg daily) can still be used in the presence of resistance to low concentrations of isoniazid (>1% of bacilli resistant to 0.2 µg/ml, but susceptible to 1 µg/ml of isoniazid), whereas isoniazid is not recommended for high-dose resistance (>1% of bacilli resistant to 1 µg/ml of isoniazid).[133] One study from a low-resource setting where a standardized regimen was used, suggested that routine inclusion of high-dose isoniazid (16–20 mg/kg/day) could improve outcomes.[134]

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Historical and Non-pharmacological Management of Pulmonary Tuberculosis

KB Gupta

INTRODUCTION

Since ancient time, tuberculosis (TB) has taken a heavy toll of lives. The disease is known for centuries and there have been continuous attempts to find a cure that involves many types of measures such as physical, chemical and others. The therapy for TB is directed to achieve five major purposes:

i. To kill the bacilli by adopting specific chemotherapy
ii. To eliminate the diseased tissue by resectional surgery
iii. To assist the healing of lesions by collapse measures
iv. To improve general resistance of the body
v. To improve quality of life by rehabilitation program.

HISTORY

Tuberculosis is known by different terms, including consumption, phthisis, scrofula, Pott's disease, white plague, Koch's disease, yaksma, consumption, "chaky oncay", each of which make reference to the "drying" or "wasting" effect of the illness.[1-3]

Signs of the disease have also been found in the Egyptian mummies dated between 3000 and 2400 BC.[4] The first reference to tuberculosis in Asian civilization is perhaps found in the Hindu "Vedas", the oldest of them (Rig-Veda, 2000 BC) calls the disease "yaksma." The "Atharvaveda" calls it by another name: "Balasa". It is in the Atharvaveda that the first description of scrofula is given. The "Sushruta Samhita", written around 600 BC, recommends that the disease be treated with breast milk, various meats, alcohol and rest. The "Yajurveda" advises sufferers to move to higher altitudes. The "Manusmriti", written around 1500 BC states that sufferers of yaksma are impure and prohibits "brahmans" from marrying any women that has a family history of the disease.

The first mention of tuberculosis in Chinese literature appears in a medical text written by emperor Shennong of China (2700 BC).·Yellow emperor, wrote "Huangdi Neijing", in which he describes "xulao bing" (weak consumptive disease), which is believed to be tuberculosis. Hippocrates (460–377 BC) described the characteristics, while Aristotle and Celsus also mentioned about the disease. Galen proposed a series of therapeutic treatments, including opium as a sleeping agent and painkiller, blood letting and a diet of barley water, fish and fruit.[3] In the famous library of Leipzig there is a folio, which contains information that Jesus had suffered from this illness.

During the dark ages (400-1400 BC), all the knowledge of the disease was lost. With the spread of Christianity, monarchs were seen as religious figures with magical or curative powers. It was believed that "royal touch", the touch of the sovereign of England or France, could cure diseases due to the divine right of sovereigns,[5] King Henry IV of France usually performed the rite once a week. Scrofula became known as the "King's evil". Touching the king's feet for the cure of king's evil (as tuberculous was then known) was prevalent during the 11th and 12th centuries in England and elsewhere. The infectious nature of the disease was described by Girolamo Fracastoro of Verona (1483-1553). Franciscus Sylvius of Leyden (1614-1672) first employed the term "tubercle" and stated that tubercles were seen in patients of consumptives.[5]

Seventeenth and Eighteenth Century

Franciscus Sylvius began differentiating between various forms of tuberculosis. He recognized that the skin ulcers caused by scrofula resembled tubercles seen in phthisis, thus, noted that "phthisis is the scrofula of the lung".[4] Thomas Willis concluded that all diseases of the chest must ultimately lead to consumption. Willis did not know the exact cause of the disease, but he blamed it on sugar or an acidity of the blood.[4] Benjamin Marten proposed in a new theory of consumption of the lungs that the cause of tuberculosis was some type of animacula: Microscopic living beings that were able to survive in a new body. Robert Whytt gave the first clinical description of tuberculosis meningitis.[6]

Nineteenth Century

The disease began to represent spiritual purity and temporal wealth, leading many young, upper-class women to purposefully pale their skin to achieve the consumptive appearance. Jean-Antoine Villemin demonstrated that the disease was indeed contagious, after conducting an experiment in which tuberculous matter from human cadavers was injected into laboratory rabbits, who then became infected.[3]

Robert Koch revealed for the first time on March 24, 1882, the causal agent of the disease: *Mycobacterium tuberculosis* or Koch's bacillus.[2,3,7] Rudolf Virchow (1821-1902), the founder of cellular pathology described the development of caseation in tuberculous tissue and believed that susceptibility to the disease was inherited and not the disease itself. In 1890, Koch developed tuberculin, a purified protein derivative of the bacteria.[8,9] It proved to be an ineffective means of immunization, but in 1908, Charles Mantoux found it was an effective intradermal test for diagnosing tuberculosis.[10]

Vaccine: The first genuine immunization against tuberculosis was developed from attenuated bovine-strain tuberculosis by Albert Calmette and Camille Guérin in 1906. It was called Bacille Calmette-Guérin (BCG).[11] The BCG vaccine was first used on humans in 1921 in France, but it was not until after the World War II that BCG received widespread acceptance in the United States, Great Britain and Germany.

Treatment: As the century progressed, some surgical interventions, including the pneumothorax or plombage technique—collapsing an infected lung to "rest" and allow the lesions to heal—were used to treat tuberculosis. Giorgio Baglivi reported a general improvement in tuberculosis sufferers after they received sword wounds to the chest. F Ramage induced the first successful therapeutic pneumothorax.[6]

In 1944, Albert Schatz, Elizabeth Bugie and Selman Waksman isolated *Streptomyces griseus* or streptomycin, the first antibiotic and the first bacterial agent effective against *M. tuberculosis*. This discovery is generally considered the beginning of the modern era of tuberculosis, although the true revolution began some years later in 1952, with the development of isoniazid, the first oral mycobactericidal drug. The advent of rifampin in the 1970s hastened recovery times and significantly reduced the number of tuberculosis cases until the 1980s.[6]

ANCIENT DRUGS IN THE TREATMENT OF TUBERCULOSIS

Before the discovery of conventional antituberculosis drugs, treatment of tuberculosis was mainly passive in nature. Many drugs, chemical or herbal, had been tried and used for the treatment of tuberculosis. Some of them are still in use while others have been abandoned due to their unacceptable benefit to risk ratios.

Drugs Used in the Past

Since ages, drugs like gold, arsenic, calcium, sulfur, plant extracts and animal products have been used in the hope of curing tuberculosis.

Gold compounds: Treatment of pulmonary tuberculosis with these compounds was introduced first by Robert Koch and later popularized by Danish physicians, in the mid-1920s, despite consistently negative experimental results, based on Paul Ehrlich's theories of antimicrobial drug effects. Although found as an effective antituberculosis drug, its toxicity resulted in its discard.[12]

Arsenic: Initially introduced by Koch, Burrow found that potassium arsenite prevented the growth of tubercle bacilli *in vitro*. The result of Burrow were contradicted by Nürnberger who observed no specific action in tuberculosis, or on the tubercle bacilli, *in vitro*.[13]

Calcium: Peterson and Levinson have reported more deaths among tuberculous patients with low blood calcium. Those patients with a higher blood calcium evidenced a healed or healing lesion and therefore, a good prognosis.[14]

Cod liver oil: Introduced as a treatment for pulmonary tuberculosis between the 1770s and the 1930s, cod liver oil was introduced into the British Pharmacopeia in 1771. By the end of the 18th century, it was a prominent treatment in the Manchester Infirmary. Cod liver oil entered medical practice in the United States in the 1840s, quickly gaining widespread use. After the discovery of the tubercle bacillus, some claimed that cod liver oil had specific action against the bacillus.[15]

Copper: Initially started by the Swiss physician Koechlin, based on a Chinese original, it was widely used in Central Europe to treat a range of skin, neurological and infectious diseases, including tuberculosis. Copper treatment for tuberculosis continued until the 1940s and various physicians reported on their success in using copper preparations in intravenous injections.[16]

Antimony: Percy Moxey used intramuscular injections of colloidal antimony for the treatment of tuberculosis.[17]

Mercury: It acts as tonic and renders the blood bactericidal, producing an antitoxin, which has direct effect on the bacilli.[18]

Herbal Drugs

In the great Vedas, there has been mention of certain herbs having medicinal properties against *M. tuberculosis*. Herbal drugs are used in Ayurvedic medicine, may have some role in the treatment of tuberculosis. Several herbal drugs as below, have been used in the past, but none has been shown to have a proven clinical value.

i. *Ashwagandha:* Its extract contains at least 13 heterogeneous alkaloids, which are chemically identified as, pyridine, pepindinine, sonine and free amino acids.[19] These alkaloids show:
    - Anti-inflammatory and antipyretic effects
    - Inhibit growth of gram-positive aerobic and mycobacterial organisms
    - Suppress granuloma formation
    - Antitumor activity and immunomodulation
    - Increase in T lymphocytes level in TB patients.

ii. *Licorice (Glycyrrhiza glabra L.; Family: Papilionaceae/ Fabaceae):* The activity guided fractionation of ethanolic extract from the roots of Glycyrrhiza glabra and subsequent phytochemical analysis resulted in identifying glabridin as the active constituent and hispaglabridin B as inactive constituent against *M. tuberculosis*. The antimycobacterial activity of root ethanolic extract was observed at 500 gm/ml against *M. tuberculosis* H37Ra and H37Rv strains through BACTEC assay. The MIC of test compounds was noted on the basis of GI (growth index) value. Further, the ethyl acetate fraction showed better activity at a concentration range of 100 to 250 g/ml.[20]

iii. *Allium sativum:* The inhibitory effect of garlic on *M. tuberculosis* has been mentioned in clinical reports for nearly 100 years. Delaha and Vincent studied the inhibitory effect of garlic extract on mycobacteria.[21] In an another study in patients of tubercular lymphadenitis, garlic extracts or compounds have shown a good potential as antitubercular(s) drug, if given as a supplement to ATT.[22]

iv. *Asparagus racemosus:* Roots of asparagus racemosus Willd (Shatavari) are widely used in Ayurveda as “Rasayana” for immunostimulation.[23]

Other Plant Extracts

In South Africa, antimicrobial properties of certain plant extracts, which were used by traditional healers for the treatment of tuberculosis like Artemisia afra Jacq. ex Willd, Carpobrotus edulis L, Tulbaghia violacea Harv. were studied for activity against *B. cereus, E. coli*, *Klebseilla pneumoniae*, *S. aureus* and *Mycobacterium aurum* A+ strain using two fold microdilution bioassay.[24]

Astragalus membranaceus is a herb used in traditional Chinese medicine to boost immunity.[25]

Plant extracts obtained from Euphorbia cerebrosides and Cetraria usnic acid have inhibitory activities comparable to standard antituberculosis drugs. Rhododendron, Melaleuca and Leptospermum essential oils had minimal inhibitory concentration in a range of 0.25 to 0.025%. Most plant extracts had no toxic effect against human cells *in vitro*.[26]

Certain plant extracts like Emblica officinalis and Tinospora cordifolia showed hepatoprotective properties against antituberculosis drug-induced liver injury.[27]

Homeopathic medicines used for the treatment of scrofula tuberculosis.[28] For example, Calcarea carbonica, sulfur, Baryta carbonica, silicea, graphite and mercurius.

Drugs used in Unani system[29] for the symptomatic treatment of:

i. *Fever:* Tukhm anisoon (pimpinella anisum) seeds, rRb-u-soos, Persiawashan, barley husk cooked with crab, massage of sandal, camphor and rose water on chest.

ii. *Cough:* White opium seeds, gum, starch, Kateera, Bambusa arundinacea

iii. *Hemoptysis:* Curd milk from which cream is removed and hot iron pieces are added to it and cooked.

SANATORIUM TREATMENT

Sanatorium is an institute in good climate. The sanatoria started in 18th century and continued in the 19th century

TABLE 44.1: Evolution of sanatoria for treatment of tuberculosis

A-Global	
Year	*Name of sanatorium*
19th Century	
1863	Brehmerschen Heilanstlt für Lungenkranke in Gabersdorf (Sokolowsko), Silesia.
1882	Adirondack Cottage Sanatorium in Saranac Lake, New York
20th Century	
1911	Burkevillae, Virginia's Piedmont Sanatorium, USA Waverly Hills Sanatorium, USA
1930	Paimio Sanatorium, Finland Helianitia Sanatorium in Valadares, Purtgal
B-India	
Year	*Name of Sanatorium*
1906	Missionary TB Sanatorium, Tilonia, Ajmer
1908	Missionary TB Sanatorium, Almora
1909	TB Sanatorium, Dharampur, Shimla
1912	United Mission Tuberculosis Sanatorium, Madanapalle
1917	TB Dispensary, Bombay and Madras[30,31]

till the development of the concept that domiciliary treatment is as effective as sanatorium treatment (Table 44.1). The essential features of sanatorium treatment are the following:

i. Close and skilled supervision in good surroundings.
ii. Proper training of the individual in hygienic living, particularly in respect to breathing fresh air, taking adequate rest, feeding rationally and preventing infection.[32,33]

Role of Sunlight

Throughout history, the sun has been respected for its healing power. In ancient Greece, physicians employed symptom-specific techniques of solar therapy by placing patients in specially constructed healing temples in the suncity of Heliopolis. Early in the 20th century, prior to discovery of antibiotics, European physicians sent their tuberculosis patients to hospital in Swiss and Austrian Alps. Sunlight promotes good immune function and helps to fight infection, stimulate metabolism, and relieves insomnia and depression. Sunlight is much like a nutrient on which the body depends for smooth functioning of its glandular and metabolic systems. It also acts as an important cofactor in the proper activity of vitamins in the body.[34]

Role of Rest and Exercise

Rest and properly graded exercise are important factors in the treatment of tuberculosis. When a patient recovers to full weight with no fever, he should have graded exercise to gradually adjust to considerable endurance. Deep breathing exercise should never be taken while the disease is active and considerably advanced. There is also a reported danger of tearing loose adhesions by such exercise.[35,36]

Nutrition

It is clear that TB affects nutritional status. Many patients with active TB experience severe weight loss and show signs of vitamin and mineral deficiencies. Patients with TB/Human Immunodeficiency Virus (HIV) coinfection are even worse, nutritionally. However, the evidence for best practices for nutritional management is very limited.[37]

Collapse Therapy

The main role of collapse therapy is to provide rest to the diseased part of lung and to facilitate healing. [38]

Surgery

The earlier attempts in the 1880, of removing the affected portion of the lung had been unsuccessful and resection was given up being too dangerous a procedure.[39]

Tuberculin Therapy

It was advised by Robert Koch after his discovery in 1882.

Modern Chemotherapy

It had its beginning with the discovery of streptomycin by Waksman in 1944. Soon other drugs were discovered—PAS (1948) and INH (1952) followed by rifampicin, pyrazinamide and other drugs. Standard chemotherapy with SM, INH and PAS became the right choice for the treatment of tuberculosis after the 1950. Studies conducted at Tuberculosis Research Centre (TRC), Madras (India) and other countries in 1956 had shown that domiciliary treatment with chemotherapy was as good as sanatorium treatment with chemotherapy.[40,41] Consequently, patients with pulmonary tuberculosis who were slightly active were allowed to exercise themselves in the open air.

Sanatorium Versus Home Treatment for Pulmonary Tuberculosis

Pulmonary tuberculosis is recognized at the present time as the most curable of chronic diseases. The first essential component in the treatment is to control the mental and the emotional state of the patient, without which the physical reactions cannot be controlled. To carry out these essentials, one must first be able and have an opportunity to thoroughly study the patient and his disease processes, and be able to place the patient in an environment that will assist him to the fullest extent in adjusting his psychic reactions to the circumstances.[42]

The patient in a sanatorium profits by the examples and mistakes of other patients. Education and information acquired in such an atmosphere constitute the keystone to the discipline, which is so essential in the proper treatment of pulmonary tuberculosis. In the sanatorium, the patient has a much greater opportunity to be protected from the nervous and over-anxious members of his family and the disturbances, which occur in the ordinary routines of the home.

Finally, in the sanatorium the patient learns that flare ups in the course of pulmonary tuberculosis are more or less the rule, when these occur, his reaction is entirely different from that of the patient having a similar experience in a home environment.[43-45]

SURGERY

Historically, surgery has played a major role in the treatment of pulmonary tuberculosis, while the introduction of multidrug therapy in 1970s significantly reduced its role. However, the increased prevalence of Multidrug-Resistant (MDR) TB has again renewed the interest in surgery.

Historical Procedures

The Cavernostomy Era

During 18th century, large TB cavities in the lungs were opened through the thoracic wall (cavernostomy)/ Monaldi operation.[45] Others performed “open cavernostomy” in a staged manner, which invariably caused bronchopleurocutaneous fistula which would drain.

Collapse Therapy Era

The period between 19th and 20th centuries, marked the era of bed rest and collapse therapy. Bed rest was introduced by Dettweitter in Germany and Turban in Switzerland around 1880.[46] Collapse therapy was used in 70% of sanatorium patients. The purpose of collapse therapy was relaxation of the diseased lung and a better chance for the scar tissue to contract.

Phrenic Nerve Paralysis

In the 1930s, this was the commonest procedure of lung collapse. It was supposed to help in different ways:

i. Rise of ipsilateral diaphragm reduces the distance between apex and base of lung thus relaxing the diseased portion.
ii. Decreased excursion of diaphragm provides rest to lung.

Cavities at the base of lung responded favorably to this procedure.

Artificial Pneumothorax

The use began in the late 19th century and came into wide use between 1920 and 1940. A specially designed pneumothorax apparatus was used; if there were no intrapleural adhesions, the pneumothorax relaxed the lung effectively. For cases with intrapleural adhesions, intrapleural pneumonolysis was done.

In addition, artificial pneumothorax was found to be useful in achieving culture negativity in new cases with cavitary pulmonary TB and in retreatment cases.[47]

Pneumoperitoneum

For sometime, pneumoperitoneum was used as collapse therapy by causing the elevation of diaphragm. The results of pneumoperitoneum alone were unpredictable. Combined procedure of pneumoperitoneum and phrenic nerve paralysis were often effective in the closure of a basal cavity.[48]

Extrapleural Pneumonolysis

In this procedure, a space was created between the apex of lung and the chest wall. This space was filled up with paraffin, which eventually became encapsulated with the fibrous tissue and remained in place permanently.[49]

Thoracoplasty

Alexander is considered to be the father of thoracoplasty in USA.[50] He perfected the technique of staged posterior lateral thoracoplasty with an operative mortality of less than 2% and cavity closure and sputum conversion in over 80% of cases.[50] In Plombage thoracoplasty, material substances are used to maintain collapse (Plombe), including paraffin, polythene sphere and sheets. Recently, a new modality of collapse therapy, which uses percutaneous tissue expanders (the Perthese tissue expander) has been described.[51-59]

IMMUNOTHERAPY

Anti-TB drugs are not able to fully eradicate *Mycobacterium tuberculosis* from all sites because of their relative inactivity against semidormant or persisting organisms, particularly those in lung granulomas. Several immunotherapies are being evaluated in human clinical trials as adjunctive immunotherapy together with chemotherapy having potential to:

1. Improve success rates in treatment of MDR-TB and XDR-TB
2. Shorter duration of treatment of drug susceptible TB.
3. Improve immunity
4. Reduce the pathology in individuals cured by chemotherapy thereby preventing recurrence.

Immune Protection and Immunopathology

Protective immunity is comprised of bacteriostatic and bactericidal components. Although a bacteriostatic response may transiently protect the host from an invasive pathogen, it does so at cost of creating dormancy, a source of recurrent infection, which is difficult to eradicate. Thus, the challenge for immunotherapy is to convert a predominantly bacteriostatic response into bactericidal response.

Immune protection results from phagocytosis and killing of mycobacteria by activated macrophages, this cellular response is regulated by antigen-specific T cells that produce IFN-γ, which together with TNF-α and IL-15 (refer as Type I cellular response) are essential for macrophage activation and immune protection. Other immune mechanisms that lead to bactericidal activity are autophagy, apoptosis and killing by cytotoxic T lymphocytes.

These immunoprotective mechanisms are susceptible to downregulation by combination of Th2 cytokines and TGF-β. Thus, downregulation is dependent on IL-4 expression IL-4 and TGF-β together downregulate cytotoxic T lymphocyte response. The aim of immunotherapy is to improve the immune response and to optimize the balance between Th1/Th2 immune response by downregulating Th2 response.

Immunotherapy Agents

Various immunotherapeutic agents (Table 44.2) have been used for adjunctive treatment.[60-72]

The role of some immunosuppressive agents, as well as of supplementary effect or cytokines has been also reported, but largely limited to experimental designs for the present.[73-83]

Several other agents that have been tried in the past includes the following:

i. *Pentoxifylline*[84]*:* It acts by competitive nonselective phosphodiesterase inhibition, which raises intracellular CAMP, inhibits TNFα and leukotriene synthesis and reduces inflammation and innate immunity. Combination of pentoxifylline and dexamethasone, when used to treat *M. avium* infected macrophage from normal and HIV-infected person *in vitro* showed decrease in TNFα by 48%.[84]

ii. *Imiquimod:* It is an oral inducer of IFN and other cytokines. It is a low molecular weight compound originally described as potent-inducer of IFN and other cytokines like TNF and IL-12 when given orally to mice and humans.

iii. *Transfer Factor*[85]*:* Transfer factor was first reported in 1949 by Lawrence and named it so because it was the factor that transferred tuberculosis immunity from a person who had an active immunity to tuberculosis to a naïve individual.[85] Later, it was discovered that this process in naturally accomplished between mammalian mothers and their newborns through mother's Colostrums.

Transfer factor products can be both dietary supplements and drugs depending on how they are prepared and marketed. Transfer factor preparations consist of three identifiable fractions:

- *Inducer fraction:* It triggers a general state of readiness in the immune system.
- *Antigen-specific fraction:* Is an array of critical tags used by immune system to identify the host of enemy microbes.
- *Suppressor fraction:* It keeps the immune system from focusing all its strength on a defeated infection while ignoring new microbial threat. It also control allergic reaction and block autoimmune disorder.

Originally, transfer factors were given through infection, later studies showed that transfer factor was equally effective orally.

iv. *Levamisole:* Mechanism of action for its immunostimulating effects is not well understood. It is believed that it restores cell-mediated immune function in peripheral T lymphocytes and stimulates phagocytosis by monocytes. The drug appears to restore depressed immune function rather than to stimulate response to above normal levels. Further studies are required for its effectiveness as immunomodulator in tuberculosis treatment.

Thus, immunotherapies have the potential to improve the outcome in all TB patients, including those with

TABLE 44.2: Immunoregulatory approaches for the treatment of TB

Agent	*Mechanism of action*	*Supportive studies*	*Results*
1. For which GMP manufacturing capacity exist			
i. High dose IVIg[60,61]	Anti-inflammatory action	Animal experiments	Marked therapeutic effect, and excellent safety
ii. HE2000 (16α Bromoepi-androsterone)[62]	Modified form of DHEA that cannot go into sex steroid pathway	Animal experiments	Well tolerated and safe and reduced the incidence of TB and significant decrease in viral load in HIV patient
iii. Multidose heat killed M vaccae)[63-65]	Induce regulatory T cells that inhibit Th2 response, a Th1 response that activate CTL that kill *M. tuberculosis* infected macrophages	Chinese DARDAR study	Effective as adjuctive therapy in MDR TB enhanced clearance of sputum and normalization of serum IL4 and TNFα Decrease in TB
iv. Neutralizing antibodies to IL-4 (PASCOLIZUMAB)[66]	It reduces IL-4 that causes a secondary decrease in TGFβ	Animal Experiments	Have a therapeutic effect and safe
2. For which GMP manufacturing capacity can be established			
DNA vaccine (HSP65)[67,68]	Enhance cytotoxic T cell while inhibiting IL-4 response, synergy with antibacterials with moxifloxacin	Animal experiment. Development of DNA vaccine, including three other antigens Ag 85B MPT–64 MPT–63, used together with antibac-terial	Downregulation of Th2 response. Significant reduction in CFU
3. Others			
i. Dzherelo[69]	Plant extract widely used in Ukraine	Need for definite GCP studies	
ii. SCV-07 SCICLONE (r-glutamyltryptophan)[70]	Immunostimulatory peptide with unknown mechanism of action	Small human TB study	Safe and use as an adjunct in MDR-TB, XDR-TB and in HIV-TB
iii. RUTI - A vaccine made of detoxified fragmented *Mycobacterium tuberculosis* delivered in liposome[71,72]	Trigger a strong Th1 and Th2 immunity against 13 known *M. tuberculosis* antigens. It enhances the CD8 and IFNγ	Animal experiment	In latent TB infection. It accelerates bacillary clearance

MDR-TB and XDR-TB. Immunotherapy for TB may shorten TB treatment and improve the immunity of individuals cured by chemotherapy, potentially preventing recurrence. Currently, none of the available agents have proof of efficacy for use. Further development and evaluation of existing immunotherapy agents is required to find effective agent.

TUBERCULOSIS AND NUTRITION

Introduction

Nutrition plays an important role in etiology, complications and therapy of tuberculosis. Although many are infected with tubercle bacilli, yet all do not develop the disease, tuberculosis recruits many of its candidates from amongst the undernourished, the under fed or residents of the centers of congestion of urban communities. "The death rates from tuberculosis in England rises and falls with the price of bread" was wisely said by Stewart. Young people who are both underweight and undernourished are choice of "candidates" for active tuberculosis.[86-89]

TB causes malnutrition, which further weakens immunity, thereby increasing the likelihood of active disease in latent TB. Wasting is associated with increased mortality in TB patients.[90] Reduced micronutrient intake, especially of vitamin B and minerals, such as vitamins A, E and C, zinc and selenium has been associated with impaired immune responses. [91-93]

Malnutrition and Immunity

It is well established that nutritional deficiency is associated with impaired immune functions.[94] Malnutrition limits cell-mediated immunity and increases susceptibility to infection, while infection can lead to nutritional stress and weight loss, thereby weakening the immune function and nutritional status.[95]

Malnutrition and TB

Malnutrition enhances the development of active TB, which makes malnutrition worse.[96] It has been suggested that generalized malnutrition by reducing the expression of gamma interferon, tumor necrosis factor alpha and other mycobactericidal substances may selectively compromise portions of the cell-mediated response that are important for containing and restricting TB.[97] During the wasting process, there is usually a loss of both fat and lean muscle tissue with the loss persisting for several months after the initiation of anti-TB therapy. [98,99]

During active TB, catabolic processes that cause wasting usually begin before the patient is diagnosed.[100] Utilization of amino acids and protein synthesis may be inhibited due to the presence of proinflammatory cytokines.[101,102] Cell-mediated immunity is the most important defense against TB. Malnourished individual is more likely to become infected with TB and latent infection is more likely to become active TB when the cell-mediated immune response is impaired in malnutrition.[103] In a larger study conducted in Norway, the incidence of smear- positive and smear-negative TB declined significantly with increasing BMI in all age groups.[104]

Nutritional Status Changes During TB Treatment

During drug treatment of active TB, nutritional status usually improves without supplementary nutrition. This happens due to a variety of reasons, including the improved appetite and food intake, reduced energy nutrient demands and improved metabolic efficiency. Most improvements, however are limited to increase in fat mass.[101,105,106] There are studies to show that the nutritional status may have an effect on relapse of active TB. So, the maintenance of good nutritional status in TB patients all though the life is important.

Low concentration of serum albumin less than 35 g/l, is an indicator of protein status at the time of TB diagnosis.[107] The concentration of micronutrients may have a role in host defense against TB.[92,93,95,104,108,109] In the era before drug management of active TB, administering cod liver oil rich in vitamins A and D was a common therapy to improve the host defense.[110]

Antioxidants

Antioxidants neutralize the free radicals. TB may induce oxidative substances, which in turn can promote tissue injury and inflammation. Reactive oxygen species (ROS) are highly toxic to lipids, fat cells causing peroxidation, resulting in damage to cell membranes and are also associated with the pathogenesis of lung fibrosis and dysfunction in pulmonary TB.[95,104,109,110]

Vitamin E: It protects cell membranes against lipid peroxidation and oxidative stress. Zinc is essential for DNA synthesis and cell differentiation. Zinc deficiency is associated with recurrent infection, decreased phagocytosis, decreased β and T lymphocytes production and depressed macrophage activity. Selenium is an essential part of antioxidative enzymes, such as glutathione peroxidase, which protects cells from oxidative damage.[108-111]

Studies of Micronutrient Status and TB

Vitamin A

Because of the acute phase response, serum retinal levels are generally lower in patients with active TB, particularly those who are TB/HIV coinfected and tend to improve with anti-TB therapy.[112]

Ascorbic Acid (Vitamin C)

Vitamin C, together with vitamin E and glutathione, are important for pulmonary antioxidant defense.[92,113] The levels of serum ascorbic acid in TB patients with history of smoking were significantly lower than in the controls.[92]

Pyridoxine (Vitamin B_6)

INH inhibits the phosphorylation of pyridoxine, which results in an increased excretion of vitamin B_6.[114,115]

Vitamin D

Susceptibility to TB and the severity of active TB may be increased by vitamin D deficiency.[96,97,116] It was hypothesized that immigrants from tropical countries, where latent TB is common, had a marked decrease in their serum vitamin D levels when they lived in cold and cloudy England, with considerably less opportunity for exposure to sunshine. Poverty was not considered the factor since these immigrants communities were generally prosperous.[117]

Effect of Micronutrient Supplementation on TB Outcomes

Vitamin A and zinc: The supplementation of vitamin A and zinc improves the effectiveness of the anti-TB treatment in the first-two months of therapy, with less improvement seen between two and six months of treatment. The major benefit is at the community level because the patient becomes less infectious sooner, with lesser opportunity to infect others.[118]

Anemia is common in patients with pulmonary TB, more so among TB/HIV coinfected patients.[119] However, iron loading may enhance the growth of *Mycobacterium tuberculosis* by impairing macrophage suppression of invading microorganisms. Elevated dietary iron may increase the risk of activating TB disease. In mild to moderately anemic TB patients, iron supplementation accelerated the normal hematopoiesis.[120]

Malnutrition and TB/HIV Coinfection in Adults

Coinfection may lead to poor appetite with decreased nutrient intake, which may interact with the altered metabolism associated with both infections as part of the immune and inflammatory responses.[94,119] The combination of TB/HIV coinfection and malnutrition has been termed "triple trouble". [120]

Nutritional Support within TB Programs

Food assistance is a potentially influential targeted means for increasing adherence to TB treatment, reducing the costs to patients of staying in treatment and improving the nutritional status. Food assistance may influence early case detection and promote full course of treatment. Both of these are important to decrease TB transmission.[121,122]

World Food Program (WFP): The goal of WFP is to improve nutrition, quality of life and self help of individual and communities.[94]

C-SAFE: The Consortium for the Southern Africa Food Security Emergency (C-SAFE) provides food assistance to patients with HIV/Acquired Immunodeficiency Syndrome (AIDS), including those coinfected with TB.[114]

Dietary Management in TB Patients

A TB patient requires more food for two reasons: First he has fever, which causes him to burn up his energy faster than in health. Second, he has a destructive process going on in his body, which he must seek to overcome by supplying ample repair material in the form of food.[86] A highly publicized diet is the Hermannsdörfer-Sauerbruch diet for tuberculosis given at the ratio of 1.15 gm protein, 2.7 grams fat; 4 grams carbohydrates.[86] Most TB patients have poor appetite, therefore, a meal should be made simple, easily digestable and tempting to encourage the patient to eat. All meals should have cereal-pulse combination with some amount of animal proteins. Some typical examples are: "Khichri" with curd; sweet dalia with milk; "paushtic chapattis" with curd and cheap sources of vitamin C, such as guava, amla, sprouted pulses should be given.[88]

A day's simple diet plan for TB patients (Tables 44.3 and 44.4) should be able to provide: Energy = 2,787 kcal; protein = 75 to 90 grams; vitamin A = 600 mg retinal; and calcium = 400 mg.

REHABILITATION IN TUBERCULOSIS

For many persons with tuberculosis, microbiological cure is just the beginning, not the end of their illness. Post-tuberculosis pulmonary impairment has emerged as a distinct clinical entity, which is almost indistinguishable from other forms.[122,123] Cavitation, extensive fibrosis, bulla formation and bronchiectasis have been implicated in the genesis of COPD caused by the destroyed lung.[124-126] A definite association between the type of healed lesions present and degree of impairment exist.[127] Pathological changes, such as "emphysematous change" on the radiograph could be considered as an important cause of obstructive ventilatory impairment. Effective chemotherapy decreases the likelihood of development of obstructive lung diseases.[128]

Lung function, such as Forced Vital Capacity (FVC) and post bronchodilator FEV_1 of post-tuberculosis patients were lower compared to those of COPD.[129] Thus,

TABLE 44.3: Food plan for tuberculosis patients in India

Meal	*Menu*	*Amount*
Early morning	Tea	1 cup
Breakfast	"Paushtic chapattis" (Besan, spinach, cabbage, onion, wheat, flour and oil)	2
	Curd	95 grams
	Tea	1 cup
Mid morning	Sprouted "moong chat"	1 bowl
	Tea	1 cup
Lunch	Scrambled egg	1
	Spinach and potato, vegetable	1 bowl
	"Chapattis"	2-3
	Peanut "chikki"	
	Amla	1
Evening tea	Tea	1 cup
Dinner	"Upma" (with vegetable)	1 bowl
	"Sâmbhar" (with brinjal and bottle gourd)	1 bowl
	Carrot "raita"	1.5 bowl
	Rice/ "chapattis"	cooked/2 to 3
	Guava	1

TABLE 44.4: Food choices for inclusion in a meal

Foods high in vitamin B_6 (pyridoxine): • Liver, chicken, meats, fish • Dried fruit (raisins, dates, figs) • Hazelnuts, walnuts, peanuts • Brussels sprouts, cauliflower, peas, broccoli • Chick peas, soybeans • Wheat germ, whole grain cereals, oatmeal • Bananas, cantaloupe, grapes	Foods high in iron: • Liver, kidney • Cream of wheat, whole grain cereals • Meats, veal, ham • Dried peas, beans and lentils • Prune juice, prunes, dates, dark green leafy vegetables Tip: Iron is taken up by the body best when eaten with foods high in vitamin C
Foods high in vitamin A: • Broccoli, carrots, squash, sweet potatoes • Spinach and other dark green leaf vegetables • Liver, dairy products, eggs • Cantaloupe, apricots	High protein foods: • Meats, lamb, veal, ham • Milk, yogurt, cheese • Poultry and fish • Dried peas, beans and lentils • Eggs Tip: Add skim milk powder to soups, milk and casseroles
Foods high in vitamin C: • Citrus fruit and juice • Tomato, baked potatoes • Broccoli, sweet peppers, kale • Cantaloupe, strawberries, cabbage, cauliflower Tip: Steam or cook vegetables in a small amount of water just until tender-crisp, will help to get the most amount of vitamin C from the vegetables.	Foods high in calcium: • Milk, yogurt, and cheese • Soyabeans, tofu • Broccoli, kale • Sardines and salmon with bones • Baked beans (canned)

pulmonary impairment associated with obstructive airway disease is recognized as a common complication of advanced tuberculosis. There is need of rehabilitation in patient of tuberculosis for the restoration of the disabled to maximum physical, mental, social, economic and vocational capacity of which they are capable.

Situation Needing Rehabilitation of TB Patients

- Chronically ill and drug failure patients, who continue to excrete TB bacilli inspite of treatment.
- Those patients, who have no source of steady income.
- Development of complication like emphysema, bronchiectasis or whose lung functions following surgical intervention is reduced to very low.

Tuberculosis continues to afflict the low-income groups. By the time they seek diagnosis and treatment, the disease is already in the advanced stage. Very often, they become untreatable and secrete drug-resistant bacilli. Some of them have little possibility of returning to work. Joint family system is fast disintegrating in India, but longevity is increasing. People have to rely on their own resources. Other members of the family are reluctant to bear the burden of the incapacitated person. There is thus, need for organized rehabilitation in these situations. Settlements and colonies for such handicapped people were established in the past. Papworth and Preston Hall in the United Kingdom, a township in Saranac Lake round the famous Trudeau Sanatorium in USA and Sheltered Work Centers like Altro shops in New York are some examples.

Rehabilitation is a field in which the Tuberculosis Association of India, other voluntary organizations and social service agencies can play an important role with the help of state governments and the Government of India.

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Prevention of Tuberculosis

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INTRODUCTION

Tuberculosis (TB) is endemic in many countries, including in India. Unsuspected TB cases contribute to TB transmission because they go unsuspected for days or weeks altogether. As soon as it gets detected, the patient should immediately visit a multiple health care facility or be admitted indoors in the wards. Unless TB is diagnosed (or at least suspected), its proper treatment and proper infection control measures are not put in place. In a community or a group with a high burden of disease, it is the responsibility of public health officials, to put preventive measures in place to alleviate the burden. There are multiple levels of prevention that are crucial in decreasing the mortality and morbidity of a disease: Primordial, primary, secondary and tertiary prevention.[1]

PRIMORDIAL PREVENTION

Adoption of proper lifestyle, especially in the early childhood is the basis of primordial prevention. For TB, it will involve the following measures:

- Nutritional interventions
- Environmental modifications (especially healthful housing and proper sanitation)
- Appropriate health education and behavioral changes.

PRIMARY PREVENTION

Primary prevention efforts aim at reducing an individual's susceptibility to the disease, illness or injury. Education, changes in lifestyle and behavior modification are components of primary prevention. Tuberculosis is infectious when it occurs in the lungs or larynx. TB that occurs elsewhere in the body in isolation is usually not infectious. A person who has TB disease in his/her lungs or larynx, can release many tiny particles called droplet nuclei into the air by coughing or sneezing; smaller numbers of droplet nuclei are released during normal activities like talking or spontaneously during breathing. Approximately 5,000 droplets are produced while talking, which may be increased four-fold or higher during coughing. These droplet nuclei particles are invisible to the naked eyes and approximately 1 to 5 microns in size. Droplet nuclei can remain airborne inside the room air for a long period of time, until they are removed by natural or mechanical ventilation or by exposure to direct sun light, which kills the *Mycobacterium* very fast.

Administrative Measures

The first line of defense for preventing the spread of TB in health care settings is to apply administrative control measures, which have greater impact on preventing TB transmission in health care setting. The aim of administrative interventions in any health care facility that manages patients with suspected tuberculosis is to reduce the total time period that such a patient stays in the health care facility, and reduce airborne transmission to other patients and health care workers in this limited time period.

Outpatient Area

Patients of TB, like any other patient, have to wait for long periods before they are actually examined by the physician. During this period, these patients are a constant source for airborne spread of disease to others. Reducing the overall stay of such patients in the health care facility is likely to prove the single-most effective measure of reducing airborne disease transmission in these areas. This can be achieved by fast tracking these patients, which can be accomplished by several measures that are not mutually exclusive. Fast-tracking will also depend upon the type of health care facility. At a chest center/hospital, most patients are chest symptomatics where fast-tracking has no real application, but the process will be more useful for general hospitals.

Inpatient Care Facilities

Need-based hospitalization of TB patients: One of the most effective means to reduce the risk of transmission of airborne pathogens, such as *M. tuberculosis* in hospital settings is to manage such patients in the outpatient setting whenever possible. Many patients can be managed entirely as outpatients, thereby avoiding hospitalization and the risk of exposing other patients and staff.

Establish separate rooms, wards or areas within wards for patients with infectious respiratory diseases: When hospitalization is required, TB patients should be physically separated from other patients so that others are not exposed to the infectious droplet nuclei that they generate. Policies on TB patients, separation inevitably generate concern about stigma, but with appropriate measures, such as training and public posting of separation rules helps to minimize stigma.

Administrative procedures should ensure that separation happens promptly, similar to the separation of men and women during inpatient admission. If sputum-smear microscopy or other relevant diagnostic tests are performed for patients with respiratory symptoms at the time of admission, then those who are smear-positive TB can be quickly identified for separation from other patients. Priorities for separation of TB patients are as follows:

- Separation of sputum-smear positive TB patients from immune compromised patients
- Separation of patients with known or suspected drug-resistant TB from immune compromised patients
- Separation of patients with known or suspected TB from all other patients.

The best choice for infectious or potentially infectious patients is to manage them in isolation rooms. Where such isolation rooms are not feasible, other options for physical separation include:

- Having a few small "airborne precaution rooms" for patients with infectious respiratory disease patients
- Having a separate ward designated for patients with infectious respiratory disease
- Keeping a designated area with better ventilation available for the placement of potentially-infectious patients
- When it is not possible to have a designated airborne precaution room, or area of a ward, there can at least be a designated area where TB inpatients can be preferentially placed.

Cough hygiene and adequate sputum disposal: Tuberculosis or multidrug resistant tuberculosis (MDR-TB) wards having infectious patients should display sign boards in the ward demonstrating cough hygiene. All patients admitted in the ward/area should be issued surgical masks and counseled on their proper use. Adequate measures for safe collection and disposal of sputum should also be undertaken.

Establish safe radiology procedures for patients with infectious respiratory disease, including smear-positive TB cases or TB suspects: When caring for an infectious TB case/suspect, the radiology departments should attempt to:

- Schedule inpatient chest radiographs on infectious and suspect TB patients for non-busy times, such as the end of the afternoon
- Provide coughing patients with a surgical mask to wear, or tissues or cloth to cover their mouths
- Provide priority service to potentially infectious TB patients to minimize the length of time spent in the department
- Restrict access to the radiology suite to patients and essential personnel only
- Use the room with the best ventilation for taking images of potentially infectious TB patients.

Environmental Controls

Environmental control measures are the second line of defense for preventing the spread of TB in health care settings. Environmental controls include ventilation (natural and mechanical), ultraviolet germicidal irradiation (UVGI), filtration and other methods of air cleaning. Environmental controls work on the same basic principle—dilution of infectious particles through real or "effective" air exchange. (One air change has occurred when the volume of air entering or exiting a room is equal to the volume of the room).

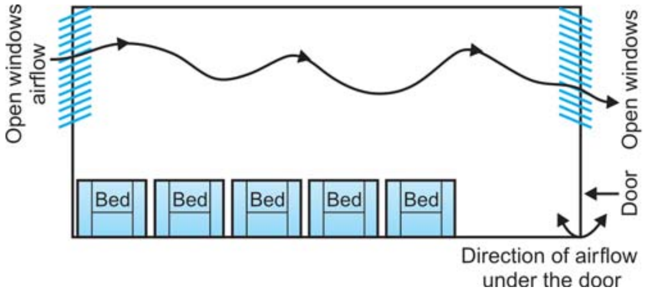

Fig. 45.1: Schema of a room with natural ventilation—Fixed unrestricted openings on both sides allow for adequate air exchange

Ventilation

In the case of ventilation, the dilution occurs through the introduction of fresh, uninfected air and removal of the infected air.

Natural ventilation: It refers to fresh air that enters and leaves a room or other area though openings such as windows or doors (Fig. 45.1). Natural ventilation is "controlled" when openings are fixed and unrestricted to maintain airflow at all times. Unrestricted openings (i.e. those that cannot be closed) on opposite sides of a room provide the most effective natural ventilation. In existing health care facilities that have natural ventilation, when possible, effective ventilation should be achieved by proper operation and maintenance of openings, and by regular checks to see that openings remain free of obstruction at all times.

Simple natural ventilation can be optimized by maximizing the size of the windows, opening up fixed window panes, by locating windows on opposing walls, and by the use of propeller "mixing fans". Types of mixing fans include ceiling fans, stand/desk mounted fans, or window/exhaust fans located in open windows. Mixing of air can disperse the pockets of high concentrations, such as in the vicinity of patients. The total number of infectious particles in the room will not change with mixing; the concentration of particles near the source may be reduced, and the concentration in other parts of the room may increase. In other words, unless adequate ventilation is present the mixing fan will not be useful in reducing infectious particles and the risk of transmission.

A common problem with reliance on natural ventilation is that patients or staff members close the windows during cold weather or at night. Further, there is likely to be variability of airflow patterns due to varying weather. In colder climates where rooms are closed to keep temperature adequately high especially in winter, natural ventilation can be implemented by airing via windows at frequent intervals. If natural ventilation of the room is inadequate, additional mechanical ventilation or other measures may be needed, especially in areas where risk of *M. tuberculosis* transmission is high.

Mechanical ventilation: It uses fans to drive the airflow through a building. Mechanical ventilation can be fully-controlled and combined with air conditioning and filtration systems as is normally done in some office buildings. Mechanical ventilation also includes "Mixed mode ventilation", in which exhaust and/or supply fans are used in combination with natural ventilation to obtain adequate dilution when sufficient ventilation rate cannot be achieved by natural ventilation alone.

The simplest form of mechanical ventilation is the use of "exhaust fans", placed for instance in windows to move air from inside a room to the outdoors. Exhaust fans also may be more acceptable to staff and patients than keeping windows consistently open. If exhaust fans are used, it is important to ensure that airflow is adequate, and airflows across the room (not in and out the same window or vent), and that exhaust fans and air intake (vents) should not be located side by side to avoid short-circuiting of air.

National Standards for Minimum Ventilation in Health Care Settings

Health care facilities should maintain a minimum amount of ventilation during all climatic conditions. This can be achieved by the fixed number of Air Changes per Hour (ACH). In settings relying on mechanical ventilation (either fan-assisted or closed systems) this can be calculated with the assistance of local engineers (Table 45.1).

Where ACH is not possible to measure, as is usually the case in rooms with natural ventilation

The following standards for ventilation should be followed to ensure that air exchange is safely greater than 12 ACH under all climactic conditions.

- Natural ventilation should be "controlled", with fixed, unrestricted openings that are insensitive to climatic conditions
- Openings should constitute greater than 20% of floor area
- Openings should be there on both the sides, preferably on opposite sides. For example, a 100 square feet, room should have greater than 10 square feet fixed, unrestricted openings on both sides, total of 20 square feet.

TABLE 45.1: Minimum air-changes per hour required for various health care settings

Type of health care setting	*Minimum air-changes per hour (ACH)*
Registration areas	>6 ACH[*]
Outpatient departments and their waiting areas	>6 ACH
Inpatients departments	>6 ACH
High-risk settings and their waiting areas	
ART centers	
TB/Chest departments (outpatient and inpatient)	
Bronchoscopy procedure rooms	>12 ACH[†]
MDR-TB wards and clinics	
Airborne isolation rooms	

[*] Equivalent to >40 liters/second (l/s) for a 4 m × 2 m × 3 m = (24 m^3) room.

[†] Equivalent to >80 l/s for a 4 m × 2 m × 3 m = (24 m^3) room.

Ultraviolet Germicidal Irradiation (UVGI)

Mycobacterium tuberculosis (MTB) is sensitive to germicidal radiation of ultraviolet rays found in the UV-C portion of the ultraviolet spectrum. The use of UVGI lamps is reserved for high-risk areas (laboratory, sputum collection area, poorly-ventilated spaces, etc.), where other environmental measures are not sufficient due to climatic or structural constraints.

Sputum collection area: This area must be settled outside in open air where bacilli will naturally be dispersed by wind and killed by sun rather than in a closed room where the concentration of bacilli will be high. In cold regions, assign a specific room of small size (1 m) with one single glass door to opening outside. Keep the door largely open for five minutes between each patient. The small volume of air in this room facilitates rapid ventilation.

Constraints on the use of UV lamps:

- Monthly checking and daily maintenance (dusting)
- Risk of mercury poisoning in case of broken or mishandled lamp; disposal of mercury from used lamps requires specific procedures
- May not work in humid areas.

Need to be replaced every 5,000 hours (as they begin to emit harmful wavelengths of light. A lamp working eight hours per day must be replaced every six months).Use only lamp-type UVC-254 µm, made from mercury and quartz

- Use only indirect lamps (portable lamps or those mounted high up and directed toward the ceiling), to avoid possible burns to the conjunctiva or skin from direct exposure. Ensure that the airflow crosses in front of the lamp
- Use direct UV lamps in empty rooms only (they can be switched on at night).

Personal Protection

Health staff: Tuberculosis is transmitted mainly via the respiratory route. Only anti-inhalation masks (high-filtration masks) are capable of preventing inhalation of the bacillus.

All members of the staff must wear these masks, whether caregiver or not under following conditions:

- When in contact with contagious patients
- When collecting sputum samples and preparing slides
- When collecting and disposing the sputum containers.

Patients and attendants: Contagious patients must wear a surgical mask (anti-projection mask) when they leave their rooms to go to another department or any other enclosed area (except outdoors). The mask is intended to prevent projection of *M. tuberculosis* by the carrier. Attendants and visitors must wear a high-filtration mask (like that worn by staff), when entering a contagious TB patient’s room. Inform patients, visitors and attendants about the risk of TB transmission and how to avoid it, or protect themselves: Ask patients to cover their nose and mouth when they cough or sneeze, and to use a sputum container; explain why, when and how to use masks; display posters of protective measures inwards, waiting rooms, etc.

Patient, visitor and attendants’ movement: Inside the TB department, circulation of patients and attendants should be controlled as follows:

- Limit the number of visits, duration of each visit, particularly for contagious patients
- Encourage visits outside the building, in the open air
- Before any visit, the nurse should provide information on the transmission risk.

In addition to wearing a mask, which is a specific protective measure, standard precautions (hand hygiene, gown, etc.) apply in TB wards, just as they do in any other hospital department.

Vaccines

The only vaccination for TB in the market is the Bacillus Calmette-Guérin (BCG) vaccine.[2] It has poor efficacy ranging from 0 to 80%. The BCG vaccine is routinely given in India to the newborn after birth. It is not recommended in the United States because secondary prevention techniques are greatly hindered by the BCG vaccine, which can interfere with the management of persons who are possibly infected with *M. tuberculosis*.

SECONDARY PREVENTION

Screening

Secondary prevention denotes the identification of people who have already developed a disease, at an early stage in the disease's natural history, through screening and early intervention. One can identify disease at the earliest stage, in its natural history. Hence, making intervention measures more effective. One can therefore, prevent mortality or complications of the disease and use less invasive or less costly treatment to do so.

Screening tests and preventive therapy accomplish secondary prevention efforts. This is particularly important for high risk population groups such as the Health care workers (HCW), prisoners and inmates of common living facilities.[3-5] Implementation of preventive therapy (treatment with antituberculosis drugs) reduces the risk that TB infection will progress to TB disease. Early identification and successful treatment of persons with TB disease remains the most effective means of preventing disease transmission.[6] Therefore, people who are likely to have infectious TB should be identified and provided treatment before they are able to widely transmit the *Mycobacterium*. Some of the screening methods applied for identification of high risk group populations are as given below:

Symptomatic Screening

Whenever possible, health care workers should undergo the initial screening. During their initial medical screening, they should be asked if they have a history of TB disease or if they have been treated for Latent tuberculosis infection (LTBI) or TB disease, previously. Documentation of any such history should be obtained from medical records, if possible. They should be observed for the presence of a cough or evidence of significant weight loss. All new recruits/inmates should be immediately screened for the symptoms of pulmonary TB. The index of suspicion should be high when pulmonary symptoms are accompanied by general, systemic symptoms of TB (e.g. fever, chills, night sweats, easy fatigability, loss of appetite and weight loss). Individuals, who have symptoms suggestive of TB disease should immediately receive a thorough medical evaluation, including a Tuberculin Skin Test (TST) or QuantiFERON-TB Gold (QFT-G), a chest radiograph, and if indicated, sputum examinations. Symptom screening alone is an unsatisfactory mechanism for TB, except in facilities with a minimal risk for TB transmission.

Chest Radiograph Screening

Screening with chest radiographs can be an effective means of detecting new cases of unsuspected TB disease. Radiographic screening requires fewer subsequent visits than a TST (i.e. only those with suspicious radiographs or TB symptoms require follow-up). However, such screening will not identify people with LTBI. Screening inmates with a chest radiograph doubled the TB case-finding rate and reduced the time from intake into the correctional facility to isolation substantially compared with TST testing (2.3 days and 7.5 days, respectively).[5] Digital radiographs (miniature or full size) provide enhanced imaging and improved storage and readability. A miniature radiograph can be performed in less than 1 minute and exposes the patient to approximately one-tenth the radiation dose of a conventional radiograph.

Screening with chest radiographs might be appropriate in certain jails and detention facilities that house substantial numbers of inmates for short periods and serve populations at high risk for TB (e.g. those with high prevalence of Human immunodeficiency virus (HIV) infection or history of injection-drug use and foreign-born persons from countries in which TB prevalence is high). Inmates who are infected with HIV might be anergic and consequently, might have false-negative TST results. Chest radiograph should be a part of the initial screening of HIV-infected patients and those who are at risk for HIV infection, but whose status is unknown. Persons who have radiographs suggestive of TB, should be isolated and evaluated further. Sputum-smear and culture examinations should be performed for inmates, whose chest radiographs are consistent with TB disease and it might be indicated for at least certain persons who are symptomatic, regardless of their TST, QFT-G or chest radiograph results.

Detection of Latent Tuberculosis Infection

The centers for disease control and prevention (CDC) recommends a strategy to identify those who have LTBI and, if indicated, the use of chemotherapy to prevent the latent infection from progressing to active TB disease. There are two tests that can be used to help detect LTBI.

a. *Tuberculin skin test:* Tuberculin skin testing using 0.1 ml of 5 tuberculin units (TU) of Purified protein derivative (PPD), tuberculin, is the most common method of testing for TB infection. In this test tuberculin is injected intradermally to see if there is a reaction to the test. Persons who have a documented history of a positive TST result, a documented history of TB disease, or a reported history of a severe necrotic reaction to tuberculin should be exempted from a routine TST. The TST sensitivity ranges from 75 to 90%.[7,8] Despite this limitation, skin testing, along with symptom review, frequently constitutes the most practical approach to screening for the TB disease.

b. *QuantiFERON-TB gold:* QFT-G is more sensitive than the TST. The test is highly specific and unaffected by BCG vaccination status, a major cause of false-positive TST response.

Chemoprophylaxis

Chemoprophylaxis is most often the treatment for primary infection in order to sterilize the lesions and prevent the development of active TB. It is more a treatment than chemoprophylaxis, in the literal sense of the term. It may reduce the risk of developing TB by up to 90% in a patient with primary infection. It usually consists of daily administration of isoniazid (INH) 5 mg/kg (maximum 300 mg/day) for six months, in both children and adults. The effectiveness of isoniazid prophylaxis depends on the sensitivity to isoniazid. The use of isoniazid is contraindicated in patients with severe or chronic active hepatitis. It should be administered with caution to patients who regularly consume alcohol.

i. *Chemoprophylaxis for newborn infant of sputum smear-positive mother:* In all the cases, where the mother is sputum smear-positive, at birth of child, chemoprophylaxis is administered to the child for six months; BCG vaccination is done afterwards (BCG vaccine should not be given during administration of isoniazid).

If a child immediately or subsequently develops signs of TB (in general, only evident after approximately two to eight weeks: Arrested growth, splenohepatomegaly, jaundice, sometimes pneumonia), she/he should receive complete anti-TB treatment after exclusion of other possible medical causes.

If a tuberculin skin test is possible, the approach is to administer isoniazid for three months, then do a tuberculin skin test.

If the tuberculin skin test is positive, isoniazid is continued for three more months.

If the tuberculin skin test is negative, stop isoniazid and administer the BCG vaccine.

- The child should not be separated from her/his mother unless she/he is severely ill. Breastfeeding should be continued. It is possible that isoniazid is not effective if primary resistance against this drug exists (varies according to the area) or if there is a problem of secondary resistance in the mother. The child must, therefore, be closely monitored in all cases.
- If a mother presents with TB during pregnancy or if the sputum becomes negative under treatment, it is sufficient to vaccinate the child at birth and to monitor him/her thereafter.

ii. *Children under five years of age in contact with Mantoux positive patients:* If suspicion of TB exists before administering chemoprophylaxis it is imperative to rule out active TB. If TB is suspected, the child should undergo complete curative treatment. If not, prophylaxis should be administered for six months. If the child is healthy, administer chemoprophylaxis for six months, regardless of the vaccination status of the child. If it is not possible to administer the prophylaxis, vaccinate and monitor the child.

The use of a tuberculin skin test may help to better specify indications for prophylaxis. In practice, it is simpler and prudent to systematically administer prophylaxis, when indicated.

iii. *Chemoprophylaxis in HIV patient:* The use of ART in HIV patients is the best TB prophylaxis, with up to 80% of risk reduction, without the use of isoniazid. The target population for chemoprophylaxis among HIV-seropositive includes all Mantoux (PPD) positive individuals who do not have active tuberculosis and could include PPD negative individuals living in high prevalence region for TB.

The optimal duration of preventive therapy with single drug isoniazid, daily or twice weekly, should be greater than six months to provide the maximum degree of protection against tuberculosis. The effectiveness of preventive therapy should be evaluated at regular intervals by monitoring patients for drug adherence, drug toxicity and for the development of tuberculosis. Though the impact of preventive therapy on an individual basis may be rather small, widespread implementation would have substantial impact on morbidity due to tuberculosis and some impact on mortality. Preventive therapy should be offered at voluntary counseling and testing centers, as part of a package of care that includes prophylaxis and treatment of opportunistic infections, nutritional support and counseling.

The CDC has recommended that preventive therapy for anergic HIV-infected persons should be considered if the patient has had known contact with an active TB case or belongs to a group in which the prevalence of TB infection is high.[9] In areas endemic for TB and HIV, Purified protein derivative (PPD) or tuberculin test may not be helpful in identifying persons who could benefit from INH prophylaxis. Among TB patients with HIV infection, up to 40% could be anergic. This further complicates the issue of tuberculosis preventive therapy among individuals infected with HIV.

Chemoprophylaxis in tuberculin negative HIV infected persons: Tuberculin skin test negative, HIV infected persons from high risk groups or from areas with a high prevalence of *M. tuberculosis* infection may be at increased risk of primary or reactivation tuberculosis. Combining the various studies on efficacy of preventive therapy in subjects with a negative PPD test, INH was found to be significantly better than placebo. Hence in HIV seropositive individuals, living in a high prevalence TB region, with negative PPD or in situations where tuberculin test cannot be performed, chemoprophylaxis with INH will reduce the risk of developing active TB in the short-term to around 60% of what it would have been without such a treatment.

Prerequisite to initiate preventive therapy: Prior to starting an individual on preventive treatment for tuberculosis, it is essential to ensure that he/she does not have active tuberculosis. This is done by a complete clinical examination along with a chest X-ray and sputum smear examination for Acid-fast bacilli (AFB). It is advisable that chest X-ray is done for every individual before considering preventive therapy. Any HIV-infected patient with fever, cough or abnormal chest X-ray should not be given preventive treatment until a full evaluation is done to confirm that active TB disease is not present. At times, it is difficult to exclude TB even when the chest radiograph is normal and three sputum smears are negative for AFB. Where mycobacterial culture facilities are available, sputum culture can be used to definitively diagnose TB. In general, it is safe to presume that completely asymptomatic individuals are unlikely to have TB.

Duration of preventive therapy: A multicentric trial conducted in USA, Mexico, Brazil and Haiti, demonstrated that the magnitude of protection obtained from a regimen of isoniazid (H) administered daily for 12 months was similar to that obtained from a regimen of rifampicin (R) and pyrazinamide (Z) administered daily for two months.[10] Moreover, it was noted that persons taking R and Z for two months were significantly more likely (80%) to complete therapy than those taking H for 12 months (69%). However, due to several cases of fatal hepatotoxicity reported among HIV-negative individuals on the RZ regimen, it is no longer recommended for preventive therapy.

There is evidence to suggest that preventive therapy is efficacious in HIV positive persons with tuberculin reactions greater than 5 mm, and that optimal duration of isoniazid preventive therapy (using a single drug) should be greater than six months to provide the maximum degree of protection against TB. Although the American Thoracic Society has recommended that isoniazid therapy should be continued for 12 months in persons with HIV infection, there are only a few studies comparing the efficacy of this approach with that of either shorter or longer courses.[11]

a. *Chemoprophylaxis in special situations:* Chemoprophylaxis in pregnancy: Chemoprophylaxis for tuberculosis is recommended during pregnancy for HIV-infected women, who have a history of exposure to active tuberculosis or after active TB has been ruled out. INH with pyridoxine (to reduce the risk of neurotoxicity) is the prophylactic agent of choice.[12] Some may choose to initiate prophylaxis after the first trimester to avoid teratogenicity.

   Chemoprophylaxis in children: Infants born to HIV-infected mothers should have a Mantoux test (5-TU PPD or 1-TU PPD RT23 with Tween 80) at or before age of 9 to 12 months, should be retested at least every 2 to 3 years.[12] Children exposed to those with active TB, should be administered preventive therapy after active TB has been ruled out. However, there have been no clinical trials of preventive therapy in HIV-positive children.

b. *Secondary prophylaxis:* The rate of recurrent TB is higher in HIV-1 positive individuals than in HIV-negative individuals with both reactivation and new infections contributing to recurrences.[13] It also showed that the absolute impact of secondary preventive therapy to reduce TB recurrence was highest among the individuals with low CD4 cell counts.

Current recommendations for preventive therapy against TB in HIV infected persons: WHO recommendation: Isoniazid is recommended drug (5 mg/kg to maximum 300 mg) to be taken daily, as self-administered therapy for six months. Individuals should be seen monthly and given only one month's supply of medication at each visit.

CDC recommendation: Isoniazid is chosen for prevention of tuberculosis in persons with HIV Infection. It is recommended for nine months rather than six months of rifampicin. Pyrazinamide may be offered daily for two months to contacts of patients with INH resistant, rifampicin susceptible TB.

American Thoracic Society: Isoniazid is recommended for 12 months as prophylaxis in person infected with HIV infection.[14]

iv. *Chemoprophylaxis and MDR-TB:* Among contacts of patients with MDR-TB, the use of INH is questionable.[15] Although alternative prophylaxis treatments have been suggested, there is no consensus regarding the choice of the drug(s) and the duration of treatment. Prompt treatment of MDR-TB is the most effective way of preventing the spread of infection to others. The following measures should be taken to prevent spread of MDR-TB disease:

- Early diagnosis and appropriate treatment of MDR-TB cases
- Screening of contacts as per Revised National Tuberculosis Control Programme (RNTCP) guidelines
- Further research into effective and nontoxic chemoprophylaxis in areas of high MDR-TB prevalence.

TERTIARY PREVENTION

The treatment of people who have already developed a disease is often described as tertiary prevention. The final strategy used for preventing and controlling TB is the identification and treatment of patients with active TB. An individual with active TB is infectious. Special precautions or isolation may be necessary to avoid transmission to others. Once the individual begins treatment and continues to follow the prescribed regimen, the individual becomes usually noninfectious within days or weeks.

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BCG Vaccine

PT James

INTRODUCTION

BCG vaccine is a live attenuated vaccine developed from a strain of *Mycobacterium bovis*. The vaccine is known after Albert Calmette, a bacteriologist and Camille Guérin, a veterinarian of Pasteur Institute. BCG vaccine has existed for more than 80 years and it is the most widely used amongst all current vaccines. It is administered to most of the neonates and infants in countries where it is part of the National Childhood Immunization Programme. More than three million doses of the vaccine have been used worldwide.[1]

History of BCG

Calmette and Guèrin while working at the Pasteur Institute, Paris were involved in the subculturing virulent strains of tubercle bacilli and testing different culture media. On seeing that a glycerine-bile-potato mixture grew bacilli that seemed less virulent, they changed the course of their research to see if repeated subculturing would produce a strain that could be attenuated for use as a vaccine. They started their experiment in 1908 to attenuate a virulent bovine strain of *Mycobacterium tuberculosis*. The strain was subcultured repeatedly every three weeks in media containing glycerin and ox-bile. Over a period of 13 years, 231 subcultures were made and finally the strain became attenuated, proved incapable of producing disease and not able to revert to its original virulence.[1]

Vaccination with BCG started from 1921 onwards. To begin with, it was administered orally and later, intradermally. In 1930, 251 infants were given BCG by mouth during the first 10 days of life in the Hanseatic city of Lübeck in Germany. Of them, 72 died of tuberculosis, most of them within two to five months. In addition, 135 developed tuberculosis, but eventually recovered; 44 became tuberculin positive, but remained well. There was an uproar against BCG all over the world. It was subsequently discovered that the BCG administered had been contaminated with a virulent strain that was being stored in the same incubator, which led to legal action being taken against the manufacturers of BCG. The incharge of the Lübeck laboratory was sentenced for 2 years imprisonment. Even though, BCG was exonerated from this disaster, the incident did cause a bad reputation for the vaccine. The value of BCG was re-established in 1928 by the Health Committee of League of Nations.

In most of the countries, vaccination is recommended for children and it is compulsory in many of them. In USA, BCG vaccination is not recommended routinely except in special circumstances, such as for those children exposed to multidrug-resistant tuberculosis. In UK, BCG is still given to school children, aged 13-14 years of age who show less than 5 mm in duration on tuberculin testing.[2]

In developing countries with the high incidence of tuberculosis, BCG is recommended to neonates at birth or as early as possible. In India, BCG was introduced in 1948 as a pilot project in two centers. In 1949, it was extended to schools in almost all the states in India. Dr Frimodt Moller had introduced BCG in Madanapalle under the aegis of International Tuberculosis campaign. A BCG-vaccine production center was established in Guindy, Madras in 1948 with the support of UNICEF and WHO.[3]

The Vaccine

BCG vaccine is available in two forms—liquid form and freeze-dried form (lyophilized). The liquid vaccine has to be freshly prepared and used within 14 days. Freeze-dried form can be stored for longer periods when kept below 6°C. All BCG strains in the world are derived from the original strain maintained at the Pasteur Institute, Paris. For vaccine production, a seed lot system is maintained to minimize the variation, which may occur on the repeated subculturing of the strain. The bacterial strain in the uniform composition is maintained in the dried form and stored below 6°C. Culture material for vaccine production is taken from this seed lot. All BCG laboratories keep their strains in the freeze dried form to prevent these strains from reverting back to their virulent forms.

The common strains used for vaccine production are Pasteur 1173pz, Tokyo 172, Danish 1331 and Glaxo 1077. In India, Danish 809 was used earlier, but later Danish 1331 is being used for both liquid and freeze-dried vaccine production. BCG Laboratory, Guindy, manufactures freeze-dried BCG vaccines. The vaccine was available initially in 50 dose ampoules, later changed to 20 dose ampoules in order to avoid wastage.[4] The Staten Serum Institute, Copenhagen used to supply BCG seed to the Madras laboratory, but later in 1993, Madras laboratory prepared their own seed lot, the Madras Working Seed Lot (MWSL). The initial capacity of the laboratory was 40 million doses when the country needed 55-60 million doses. From 2,000 onwards, India is self-sufficient in vaccine production and even capable of exporting it.

Vaccination

BCG is administered as intradermal injection at the lower deltoid area, because the site has the lowest complication rate. The dose is 0.1 ml for children and 0.05 ml for infants below 3 months old; 0.1 ml vaccine contains 0.1 mg of moist weight of BCG.

BCG vaccine can be adversely affected by exposure to light, so it should be stored in the dark except when the doses are actually being withdrawn from the vial.[5] The vaccine should be used immediately after reconstitution, any reconstituted vaccine not used within eight hours must be discarded. Any reconstituted product, which exhibits flocculation or clumping that cannot be dispersed with gentle shaking, should not be used. The reconstituted vaccine should be maintained at 2 to 8°C (35 to 46°F). BCG vaccine (Freeze-dried) contains viable attenuated mycobacteria and should be handled as an infectious agent at all times. After use, any unused vaccine and all equipment, packaging and materials exposed to the product should be immediately placed in a container for biohazardous materials and disposed off as biohazardous waste.

The recommended schedule of vaccination differs widely among countries.[6] The United States and Netherlands have not used BCG on a national scale. Single dose in infancy is the recommendation of the Expanded Program of Immunization of WHO. In UK, single dose in adolescence was followed, but routine vaccination was withdrawn in 2005 as it was not cost-effective. India introduced BCG in 1948—the first non-European country to do so. Brazil introduced universal BCG immunization in 1967, which continues till date. In Brazil, BCG is repeated in health professionals and people in close contact with patients of TB and leprosy. The recent Brazilian studies confirm that a second dose of BCG does not increase the protective efficacy.[7] BCG is given regularly throughout life in the countries of former USSR. In South Korea, Singapore, Taiwan and Malaysia, BCG is given at birth and again at 12 years. In Singapore, this policy was changed to single dose at birth from 2001, onwards. Repeated vaccination throughout childhood is followed in the Eastern European countries. Depending on Tuberculin negativity or the absence of BCG scar, repeated vaccination is given in Poland. In developing countries with the high incidence of tuberculosis, WHO has recommended the administration of BCG to infants, or as early as possible to children. These policy differences reflect differences in the pattern of tuberculosis among countries, their health services and the differences in opinion about the protective efficacy of BCG.

Postvaccination Reactions

After the administration of BCG vaccination intradermally to an individual who is not infected with tubercle bacilli, the bacilli start to multiply at the site and reach the regional lymph glands through the lymph channels. About two to three weeks after a correct intradermal injection, a papule develops at the site. Within five weeks, the size reaches about 4-8 mm, which then subsides or breaks into a shallow ulcer, usually covered with a crust (Fig. 46.1). Spontaneous healing occurs usually within 6-12 weeks leaving a permanent tiny scar. In the case of subjects naturally infected with tubercle bacilli or with previous BCG vaccination, the local reaction may develop sooner and be exaggerated. This accelerated form is known as Koch's phenomenon. After BCG vaccination, the individual becomes tuberculin positive after a period of eight weeks normally, but may take up to 14 weeks (Figs 46.2A and B).[8]

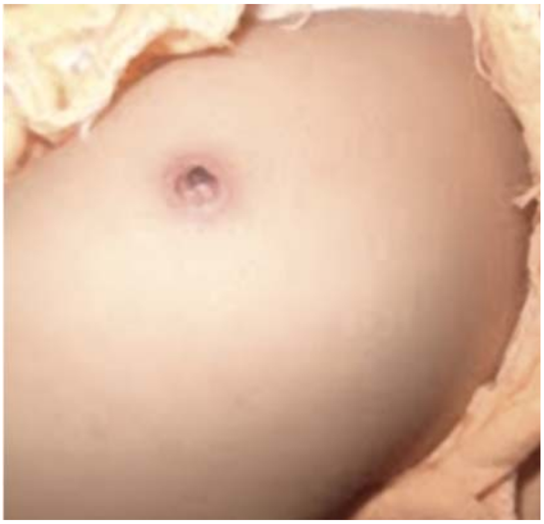
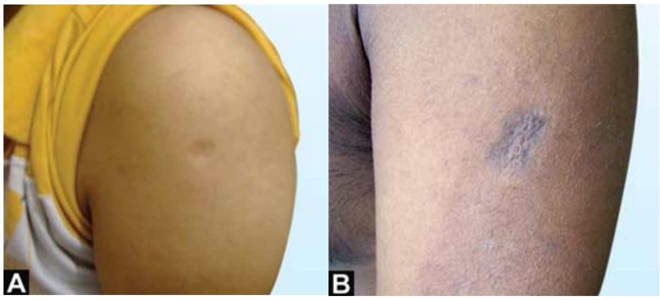


Fig. 46.1: The shallow ulcer–five weeks after BCG vaccination



Figs 46.2A and B: (A) Normal BCG scar, (B) BCG scar with keloid

Efficacy of BCG Vaccination

Protective efficacy is a measure of the proportion of people who would have developed the disease, if they had not undergone vaccination. Trials of the vaccine have been undertaken, since it was first developed in 1920s. Despite of this, controversy persists from the very beginning. There are about 20 controlled trials from different countries with highly inconsistent results. Variability in protective efficacy has been observed not only in different trials, but also between the sites of the same trial.[9]

The earlier BMRC trials of 1950s showed that BCG, when given to teenage school-children, gave about 75% protection for 15 years.[10,11] From 1955 to 2005, the national policy in UK was to vaccinate all children aged 12-13 years. As the rates of tuberculosis in teenagers and young adults had declined, the policy was changed since BCG was no longer a cost-effective proposition. The rate of disease in the vaccinated group was so low that about 10,000 vaccinations were needed to prevent one single case, which was relatively easy to treat. Moreover, the adverse effects from the vaccination may outweigh the preventive benefit.[12] This remains the current scenario in many of the developed countries where the rates of tuberculous infection are very low.

Indian Scene

In India, the efficacy of BCG vaccination has been controversial from 1948 onwards since when it was first introduced.

Chingleput Trial

The National Tuberculosis Institute was also concerned with the efficacy of BCG. In 1968, the "Tuberculosis prevention trial"—the largest ever conducted BCG trial was initiated under the auspices of the Indian Council of Medical Research (ICMR), World Health Organization (WHO) and United States Public Health Service (USPHS) with the technical assistance of the National Tuberculosis Institute (NTI). The Chingleput district of Tamil Nadu was selected for the study as this area had a high prevalence of tuberculosis, as well as that of leprosy and this was a vaccination free zone.

Objectives of the Chingleput trial were:

i. To asses the protective effect of BCG vaccination in the noninfected persons.
ii. Effect of BCG vaccination in infected persons.
iii. Protective effect of different strains of BCG.
iv. Epidemiological data on tuberculosis in the community.

The entire population of 3,60,000 persons was registered during the intake and 2,70,000 were administered vaccine and placebo. The study population was divided as three different groups who were given: 1. Madras vaccine; 2. Paris vaccine; 3. Placebo. All the individuals were tuberculin tested; those above 10 years were X-rayed; for those with X-ray shadows: Sputum smear examination and culture were done to detect new cases occurring in the community.

The tuberculosis prevention trial was completed as scheduled. The twelve and a half year report of the trial was rather shocking for the scientific community. It showed that BCG vaccination did not offer significant protection to the adult bacillary type of tuberculosis.[13,14] Some had termed the results as the "great Madras failure" while others called it the "great BCG hoax." Editorials in the newspapers questioned the continued inclusion of BCG in the immunization program. Several expert committees examined all the procedures followed up in the study and came to the conclusion that the study had been meticulously carried out with the best available vaccines.

Even though the study results showed that BCG offered no protection to adult type tuberculosis, the childhood forms of tuberculosis were not studied. A committee of ICMR and WHO studied the epidemiological aspects of the causes of TB in India and concluded that BCG could provide substantial protection against the childhood forms of TB, such as the tubercular meningitis and miliary TB. It is precisely because of the beneficial effects that the continued use of BCG among infants in the immunization program has been recommended.[14]

Two meta-analysis on summary estimates of BCG efficacy have shown a very high rate of protection against meningeal and miliary TB, with the rates being as high as 86% in one clinical trial. It was concluded that BCG offered 51% overall protection and 50% protection against pulmonary tuberculosis.[9,13,14]

Many different theories have been put forward to explain the varying efficacy of the different trials.[6,10]

- Variation in methodology employed in different trials;
- Usage of different strains of vaccine;
- Tuberculin reactivity status of the subjects are different in different trials;
- Mycobacterial strains causing infection may be different in different areas of the world;
- Genetic susceptibility to tuberculosis may vary in between populations;
- Different nutritional states may vary the susceptibility to disease;
- Partial protection by environmental mycobacteria.

Another important issue affecting BCG vaccination is the duration of protection. BCG gives good initial protection, but this may wane off with time.[15] Published data do not provide the evidence of the protective effect of BCG beyond ten years after the vaccination. There is also no evidence to suggest that repeat BCG vaccination or a booster dose increases the protection.[16]

BCG and Leprosy

There is an indirect evidence that BCG vaccine protects against leprosy as well. The range of efficacy varied from 20% in Burma to 80% in Uganda. Even though, there is no significant difference in the pattern of different types of leprosy in BCG vaccinated and non-vaccinated groups, there is reduction in the incidence of reactions, as well as of deformities and disabilities in BCG vaccinated cases. In one of the meta-analysis, protective effect was shown to be 26% in the 7 experimental studies, while the other 19 observational studies had overestimated the protective effect.[17] An additional dose of BCG was more protective in the prevention of leprosy, so a booster dose of BCG is warranted for the contacts of leprosy in areas where leprosy continues to be a public health problem.[8] On the basis of another meta-analysis, which included published data of up to June 2009, there is a strong argument for more emphasis on the role of BCG vaccination in leprosy control and research.[18,19]

Other Uses of BCG

BCG is also used for a number of other conditions, such as for immunotherapy in various forms of cancers. When used in the treatment of superficial forms of bladder cancer, it prevented recurrence in up to 67% of cases. Interstitial cystitis and painful bladder syndrome are treated with intravesical instillation of BCG. It is also used for immunotherapy in colorectal cancer. BCG may protect against the onset of Buruli ulcer. In veterinary medicine, it is used for the treatment of equine sarcoid in horses.

BCG induces the production of TNF-α, which can kill the T-cells responsible for Type-I diabetes. The recurrence of symptoms in patients with multiple sclerosis is reduced with the BCG vaccination.

COMPLICATIONS OF BCG VACCINATION

Adverse reactions to BCG vaccination are rare, provided that correct immunization techniques are used. Vaccination of children with active atopic dermatitis should be deferred until remission since the vaccine may exacerbate the skin condition. Malignancy, corticosteroid treatment, fever, generalized septic skin conditions and immunosuppressive disorders are other relative contraindications. The World Health Organization recommends that people known to be infected with Human Immunodeficiency Virus (HIV) should never be given BCG, but that routine immunization of infants should continue in areas where the incidence of tuberculosis and HIV infection is high.[20] In UK, it is advised that BCG should not be given to infants born to mothers known or suspected to be HIV infected, unless the infants are subsequently confirmed to be HIV negative.[21,22]

There are two major categories of adverse reactions to BCG vaccination: Noninfectious and infectious. Local adverse reactions usually occur at a rate of 0.1 to 0.5 per 1,000 vaccinations. On the other hand, serious, disseminated complications may occur in less than one in one million vaccinations.[23] Most complications (70.8%) are likely to occur at the injection site or in the form of suppurative lymphadenitis. Lesions at the injection site included the formation of ulcers, subcutaneous abscesses, or necrotic lesions due to excessive delayed hypersensitivity reactions. In some reports, abscesses at the injection site occurred more commonly in comparison to lymphadenopathy.[24] Localized or generalized non-fatal persistent BCG infection (10.5%), fatal disseminated BCG infection (0.3%) and post-BCG syndromes, principally keloid scarring (18.2%) are also reported. Keloid scarring is the commonest of the late noninfectious complications. The risk of such scarring is minimized by giving the injection in the skin overlying the lower deltoid area. Injections higher up on the arm are more likely to lead to keloid scarring. Local abscesses and ulcers usually present between one and five months after vaccination, but some may present even later. Lymphadenopathy occurs in the drainage area of the vaccinated site, thus the commonest site is the axilla. Cervical lymph nodes may be affected if the vaccine is given in the upper deltoid region. Most of the BCG complications can be managed with local treatment (Table 46.1).

TABLE 46.1: Various complications of BCG vaccination and their management[21]

Complication	*Management*
Local hypersensitivity reaction	None or topical dressing
Abscess or ulcer at injection site	Drainage or needle aspiration, if indicated. INH or Erythromycin
Regional lymphadenitis	Surgical if there is excessive enlargement, overt suppuration, or sinus formation
Distant lesion, e.g. osteitis	Chemotherapy
Disseminated BCG infection (BCG-osis)	Chemotherapy
Disseminated BCG infection with cardiovascular effects following intravesical instillation of BCG	Chemotherapy with intravenous corticosteroids

Generalized life-threatening hypersensitivity reactions have occurred following the intravesical instillation of BCG. These hypersensitivity reactions are treated with isoniazid (300 mg daily) for three months. BCG therapy is resumed only if benefits exceed the risks.

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Extrapulmonary Tuberculosis

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INTRODUCTION

Tuberculosis when involves organs other than the lungs, is termed as Extrapulmonary Tuberculosis (EPTB). Around 85% of all types of tuberculosis are of pulmonary type, the remaining 15% are EPTB cases.[1-9] In Human Immunodeficiency Virus (HIV)-infected tuberculosis cases, around 50% have EPTB disease.[10] Based on the Indian data from the Revised National Tuberculosis Control Program (RNTCP) of Government of India, it has been suggested that 18% of all cases of tuberculosis are due to EPTB disease. The proportion of EPTB has shown an upward trend in the recent years both in the developed and the developing countries. In the developed countries like UK and USA, it is mainly due to the immigration of significant number of people from high burden countries, while the increase in the incidence of EPTB in the developing countries of sub-Saharan Africa and South Asia, it is due to HIV coinfection.[3,4,11,12] In the presence of HIV coinfection, lymph node or Central Nervous System Tuberculosis (CNS-TB) are commonly seen.[13]

EPTB cases constitute a bigger chunk in tertiary care hospitals and institutions. Of all the EPTB cases, tuberculosis of the lymph node and the pleura together contribute around 75% of the total number followed by bone and joint tuberculosis, Genitourinary Tuberculosis (GUTB), Tuberculous Meningitis (TBM), abdominal and miliary tuberculosis. Various other organs affected in a decreasing order are: Skin, pericardium, brain parenchyma, larynx, liver, pancreas, eyes, ears, adrenal glands, and pituitary and thyroid gland.

DIAGNOSIS

Diagnosis of EPTB is more difficult than that of pulmonary tuberculosis. Reasons for the same are multifold viz, the difficulties in obtaining the tissue and to isolate mycobacteria from the pathological tissue, uneven distribution of disease, an insidious onset, atypical presentation and limited clinical experience of individual experts from different disciplines. These problems are further compounded by the paucibacillary nature of EPTB, making it imperative to depend on investigations other than on the gold standard for the diagnosis, like the demonstration of Acid-fast Bacilli (AFB) on microscopy. The constitutional clinical features like low-grade evening pyrexia, loss of appetite and weight, malaise and fatigue are also not regular manifestations. Sometimes, the disease may even present with the pyrexia of unknown origin.[14,15] However, clues specific to the involved organ are often helpful to reach to the diagnosis. Nevertheless, physicians must have awareness about various risk factors for EPTB to enable them to have a high index of suspicion for the timely and accurate diagnosis.[16]

In general, EPTB manifestations are nonspecific, not significantly different in the HIV-infected or the non-infected patients, but extensive disease, inadequate or delayed TB treatment and HIV coinfection have been found associated with increased mortality.[17] For the diagnosis of EPTB, all efforts must be exhausted to isolate of tubercle bacilli from the body fluids or the biopsy specimens. Role of Adenosine Deaminase (ADA) estimation in tuberculous fluid collections in various types of EPTB is helpful in reaching the diagnosis. Application of molecular methods, such as Polymerase Chain Reaction (PCR) assay targeting IS6110, multiplex PCR and RT-PCR have been reported useful in the diagnosis of EPTB, particularly where there is strong clinical suspicion, and conventional techniques are not helpful.[18-20]

LYMPH NODE TUBERCULOSIS

Tuberculosis of lymph nodes, caused by both typical *Mycobacterium tuberculosis* and nontuberculous mycobacteria is the most common type of EPTB encountered in the developing world, including in India.[21-23] In USA, nontuberculous mycobacteria are responsible for lymph node disease in children of less than 5 years of age; typical *Mycobacterium tuberculosis* remains the cause of tuberculous lymphadenitis in the higher age group.[24] Lymph node tuberculosis is more commonly seen in the Asians, Hispanics and African-Americans. The disease was historically named as King's Evil and the divine touch of the King was considered as remedy for the illness. Scrofula was another popular Latin name for the entity, meaning glandular swelling. The cervical or supraclavicular nodes are affected in about 70% of the cases, the other sites being the axillary, inguinal or chest wall nodes.[25,26] About 10% cases may have concomitant mediastinal lymph node disease, which occurs due to the retrograde spread from the mediastinum to cervical region.[27,28] Hilar or mediastinal lymph nodes are frequently involved in primary tuberculosis and HIV-infected patients.

Pathogenesis

Lymph node tuberculosis is often a localized manifestation of systemic spread of tuberculous infection. Initially, at the time of primary infection, tubercle bacilli get entry into the lungs and form primary complex. During this stage there occurs hematogenous and lymphatic spread of infection to the rest of the body where bacilli remain dormant. Later, whenever the host defenses get weakened due to local or systemic factors, the dormant foci get reactivated. The systemic nature of the disease is further substantiated by the fact that 1/3rd cervical node tuberculosis cases are associated with current or past pulmonary tuberculosis. Sometimes, in primary lymph node disease, the tubercle bacilli get entry through the tonsils, thereby reaching to cervical nodes resulting in lymphadenitis. Contrary to the lymph node tuberculosis due to typical tubercle bacilli, the atypical mycobacterial lymphadenitis is a highly localized disease. In the atypical mycobacterial lymphadenitis, infection reaches the lymph nodes through tonsils, conjunctiva, gingival or oropharyngeal mucosa, hence, surgical excision is the modality of choice.

The lymph nodes are small, discrete and grow very slowly, but occasionally they grow faster and become tender or painful (Fig. 47.1). Subsequently periadenitis develops, which causes matting and fixation of lymph nodes**.** With the increasing size, there occurs caseation necrosis and liquefaction in the diseased lymph nodes. This leads to the perforation of deep fascia and formation of collar stud abscess. The absence of warmth and redness on the overlying skin earns it a peculiar "cold abscess" name, which is almost synonymous with tuberculous etiology of the abscess. Sometimes, in an immunocompromised host or in HIV infection, the abscess grows very fast making overlying skin warm, erythematous and painful, mimicking an acute pyogenic abscess. Such abscesses may burst and form chronic discharging sinuses or ulcers. The sinuses characteristically have thin, bluish, undermined edges while the discharge is usually watery (Fig. 47.2). The garlanding of neck by multiple lymph nodes, abscesses and discharging sinuses, which used to be a common sight in specialty clinics, is now a thing of past due to an early treatment with effective tuberculosis drug therapy.

Clinical Features

Lymph node tuberculosis is the disease of children and young adults. In the developing countries with high burden of tuberculosis, it is more common in children,

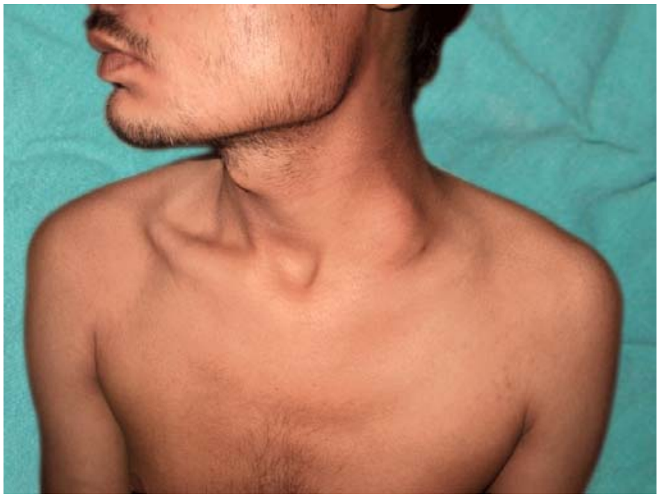

Fig. 47.1: A typical case of tuberculous cervical lymphadenitis

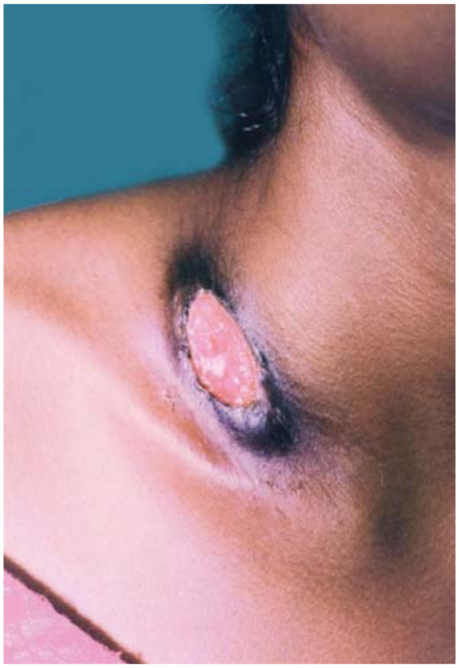

Fig. 47.2: Typical chronic tuberculous ulcer over right cervical region

while in developed countries its peak incidence occurs in age group of 20–40 years. In immunocompetent patients, only a single group of lymph nodes are involved in two-third cases, while multiple groups are affected in remaining one-third cases, around 90% of HIV-infected cases have involvement of multiple groups of nodes. Also, concomitant intrathoracic or intra-abdominal lymph node involvement and pulmonary tuberculosis are common in HIV-infected cases.[22,29-31] Apart from the main symptom of the local visible swelling, enlarged nodes may result in other signs and symptoms due to obstruction or pressure on adjacent viscera, e.g. mediastinal lymphadenopathy can cause dysphagia, tracheoesophageal or esophagomediastinal fistula. Chylothorax, chyluria or chylous ascites may develop as a result of pressure on thoracic duct due to upper abdominal or mediastinal lymphadenopathy. Although rare, obstructive jaundice has also been reported due to the obstruction of biliary duct by enlarged lymph nodes at porta hepatis.[32]

Diagnosis

It usually presents as slowly enlarging swelling in cervical region in children without causing much pain or discomfort. Concomitant mediastinal and hilar nodal enlargement is seen in around 5 to 12% cases. The incidence of concomitant pulmonary tuberculosis is highly variable. Ultrasonography (USG), Computed Tomography (CT) scanning and Magnetic Resonance Imaging (MRI) help to demarcate the extent of disease, whenever nodal involvement in mediastinum and abdomen is suspected. Enlarged nodes with hypodense areas, calcification, peripheral rim enhancement and central necrosis are the common imaging findings (Fig. 47.3). The gold standard for diagnosis of tuberculous lymphadenitis is the excision biopsy. Demonstration of AFBs in Fine Needle Aspiration Cytology (FNAC), pus or biopsy specimens from the affected glands constitute the most authentic diagnosis. Although, AFB positivity rate is not very impressive, larger biopsy sample may show positivity rate up to 50 to 70%.[32-36] Infrequent demonstration of bacilli on direct smear examination is due to the paucibacillary nature of the disease. In selected cases, endoscopic ultrasound-guided FNAC can be used for assessing mediastinal and abdominal lymphadenopathy. The modality is a safe, minimally invasive and accurate outpatient diagnostic technique in suspected EPTB cases.[37]

Treatment

Antituberculosis drug therapy alone is quite adequate to achieve cure in the majority of cases caused by typical tubercle bacilli. The recommended treatment for

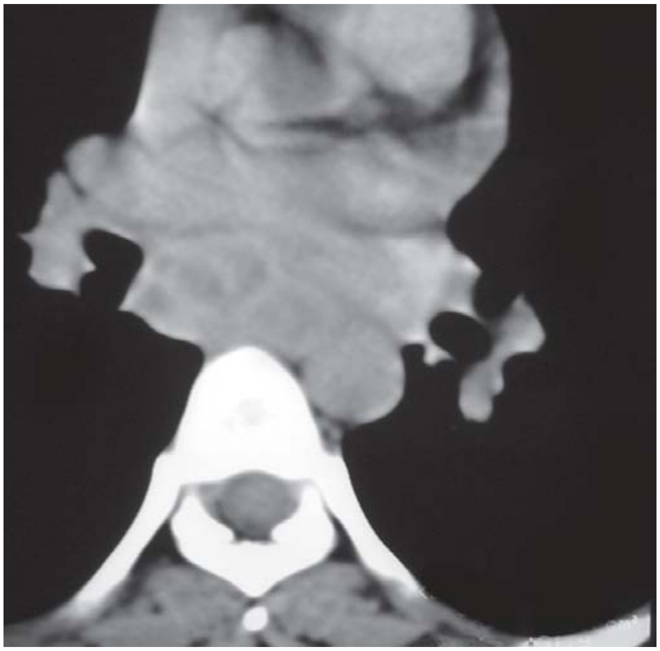

Fig. 47.3: CT imaging showing enlarged mediastinal lymph nodes with hypodense areas, peripheral rim enhancement and central necrosis

previously untreated lymph node tuberculosis consists of short-course chemotherapy regimens of six months duration, in which four drugs, i.e. isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) are given for the initial two months in the intensive phase followed by two drugs (HR) for four months in the continuation phase. The Revised National Tuberculosis Control Programme (RNTCP) of the Government of India, and several other Similar National Control Programs elsewhere follow the WHO recommended Directly Observed Therapy Short Course (DOTS) strategy under which drugs are administered intermittently thrice a week. Under RNTCP, the lymph node tuberculosis has been considered a milder and paucibacillary form of tuberculosis, hence, has been placed in category III treatment regimen. Recent studies have demonstrated that the DOTS strategy is an effective treatment modality with treatment completion and success rate of 95 to 97%.[38,39]

While treating lymph node tuberculosis, a paradoxical phenomenon is encountered during the ongoing drug therapy in some cases. There occurs the enlargement of existing nodes or even new lymph nodes may appear ipsilaterally or contralaterally in the same group of nodes, or otherwise. Biopsy samples or aspirate of these nodes do not grow TB bacilli, the phenomenon does not represent the relapse or treatment failure. These lymph nodes tend to regress spontaneously on the continuation of the same drug regimens without any alteration. There is no need of changing the drug regimen in such situations. This phenomenon is mostly attributed to hypersensitivity to tuberculoproteins released due to the bactericidal action of drugs or the disrupted macrophages. The phenomenon of paradoxical response to tuberculous chemotherapy is also termed as Immune Reconstitution Inflammatory Syndrome (IRIS). Sometimes, the response is highly exaggerated when lymph nodes get significantly enlarged, become painful or lead to abscess formation. When located in the mediastinum, such enlarged nodes tend to mechanically press the esophagus or tracheobronchial tree, thereby causing dysphagia or respiratory difficulty respectively (Fig. 47.4). In such situations, addition of a short course of corticosteroid is recommended, after the exclusion of other usual causes of treatment failure.[40]

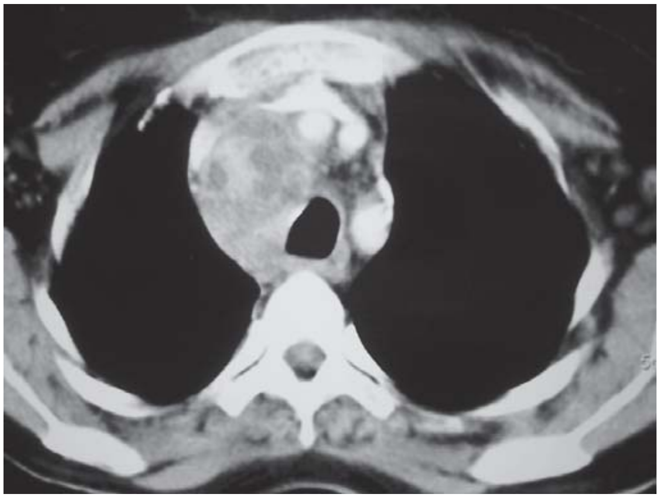

Fig. 47.4: CT image showing enlarged mediastinal lymph node compressing tracheobronchial tree

PLEURAL EFFUSION

Tuberculous pleural effusion is the second most common type of EPTB. Nearly 20% of all EPTB cases in both HIV-infected and non-infected patients have pleural effusion. Also, tuberculous pleural effusion is the most common cause of lymphocytic exudative type of effusions in high tuberculosis burden countries like India. Although the fluid collection is intrathoracic in the pleural cavity intimately covering the lung, the entity is generally classified as extrapulmonary disease.[35,41-44] (See details in the chapter on TB Pleural Effusion).

Tuberculous Empyema Thoracis

Tuberculous empyema represents a chronic, active infection of the pleural space resulting into the collection of frank pus loaded with large number of tubercle bacilli. The condition is uncommon than tuberculous pleural effusion.[45] Tuberculous empyema commonly develops as a sequel to thoracoplasty, artificial pneumothorax or inadequately treated pleural effusion. The onset is usually gradual with the symptoms of mild fever, fatigue, weight loss, chest pain, dyspnea and cough. Skiagram chest shows pleural effusion, but often with the thickening of pleura, pleural calcification, loculation or encystment. Finger clubbing, intercostal narrowing with tenderness or empyema necessitatis may be seen on examination. Treatment consists of pleural pus drainage and antituberculosis chemotherapy. Problematic treatment issues include the inability to reexpand the trapped lung and difficulty in achieving therapeutic drug levels in pleural fluid, which can lead to drug resistance. The treatment may require decortication or thoracoplasty, should an adequate tuberculosis drug therapy coupled with repeated pleural tappings fails. Surgery should be undertaken by experienced thoracic surgeons.[45]

BONE AND JOINT TUBERCULOSIS

Spinal Tuberculosis (Pott's Disease)

It is the most common type of osseous tuberculosis, nearly half of the bone and joint cases are due to spinal involvement, other site being the hip joint. Usually, weight-bearing joints are affected by tuberculosis.

Pathogenesis and Clinical Features

Usual constitutional symptoms may be seen well before the localizing signs become actually perceivable. Often, local signs at the involved site or at the site of extended disease are more prominent. In spinal tuberculosis, lower thoracic and upper lumbar vertebrae are commonly affected, followed by middle thoracic and cervical region vertebrae. Usually, more than one adjacent vertebra is involved and the body of the vertebrae is preferentially affected rather than its other elements. The tubercle bacilli reach skeletal tissue as a result of hematogenous spread during primary tuberculous infection. The disease originates in the cancellous area of bone close to the superior or the inferior end-plates and extends into intervertebral disc after penetrating the subchondral bone plate and thence to the body of adjacent vertebra. With further progression, there occurs the demineralization of end plates and softening of body leading to vertebral collapse or anterior wedging (Fig. 47.5). This is responsible for typical angulation or gibbus deformity in the spine seen in Pott's disease patients. The spread of disease may also follow sub-anterior longitudinal ligament route. The subligamentous spread of tuberculous abscess downward away from the primary involved vertebra can cause the destruction of anterior surface of other vertebral bodies.

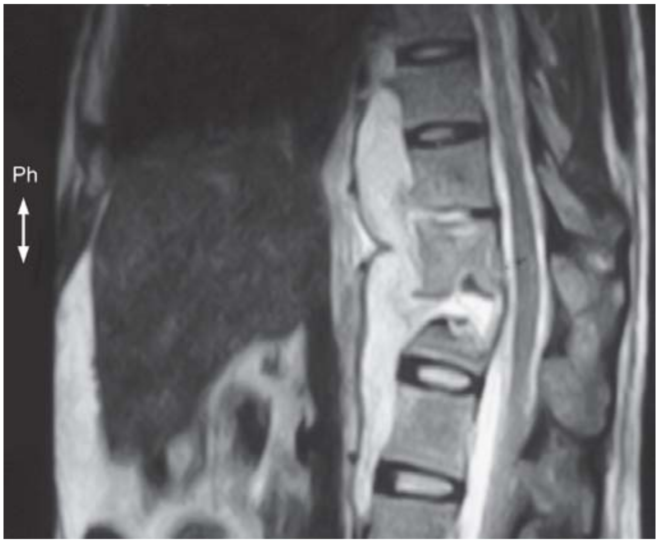

Fig. 47.5: MRI image of young male suggests partial collapse of D12 vertebra with the involvement of intervening disks and prevertebral abscess suggesting spinal tuberculosis

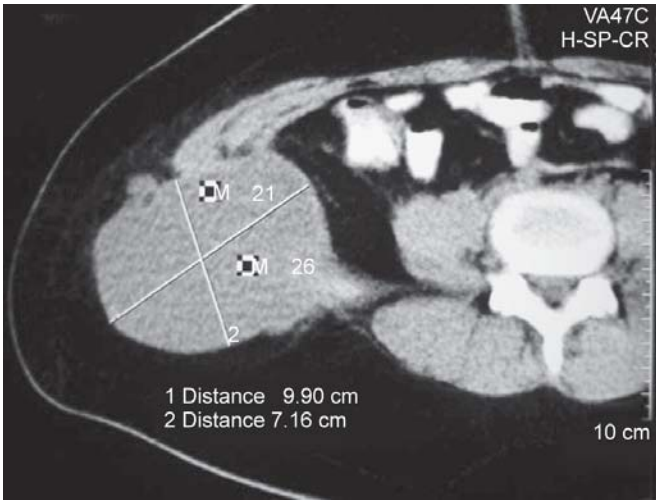

Fig. 47.6: CT scan pelvis reveals abscess in the right iliac fossa. There was pus collection both medial and lateral to right iliac bone. About 300 ml of pus was aspirated under ultrasound guidance and the pus was found positive for tubercle bacilli

These exudates tend to spread following the path of least resistance along with fascial planes, vasculature and nerves, and present as cold abscesses elsewhere. Commonly, such an abscess is seen as a paravertebral abscess, psoas abscess in lumbar region, or abscess in iliac fossa (Fig. 47.6), some even gravitate below the inguinal ligament on medial side of thigh. Sometimes, it spreads laterally from the iliac fossa to appear over the iliac crest. Rarely, it tracks with gluteal or femoral vessels to form gluteal or Scarpa's triangle abscess.[46] If the cervical spine is involved with tuberculosis, the exudates track down in prevertebral area as a retropharyngeal abscess, which may mechanically cause deglutition and respiratory difficulty or hoarseness of voice. Accumulation of pus in the mediastinum may present as posterior mediastinal mass from where it can spread to the pleural cavity, esophagus or trachea.

Paraplegia (Pott's paraplegia) develops in about 30% cases of Pott's disease.[46,47] Commonly, it is the mechanical pressure on the cord, sometimes nonmechanical causes are responsible for such neurological complications. Generally, paraplegia develops during the course of active disease, but rarely it may occur years after cure, even without any TB reactivation, possibly due to the formation of a ridge of bone anterior to cord, fibrosis of dura mater or gliosis of cord.

Diagnosis

Plain radiography reveals narrowing or disappearance of disk space, area of destruction in the body and wedging or collapse of the vertebral bodies. The bony changes become perceivable on plain radiograph only about five to six months after the onset of pathology. However, CT and MRI scans may pick up such lesions quite early, also, the extent of associated complications is demarcated better with these investigations. The CT and MR imaging are particularly useful to study the status of the spinal cord or the canal and to pick up the involvement of posterior elements of vertebrae. Some of the complications, such as the prevertebral abscess in neck region and the typical fusiform abscess in the dorsal spine area, can also be appreciated better with such imaging. Healed psoas abscess may show calcification too. Often, typical clinicoradiological or MRI is quite adequate to diagnose spinal tuberculosis. However, in atypical presentation, differentiation is required from conditions like pyogenic osteomyelitis, mycotic infection, syphilis, neoplasia, multiple myeloma, lymphoma, chondroma, metastasis, traumatic fracture or sarcoidosis, and others. In such situations, biopsy of the affected vertebrae and culture of the contents would be necessary to clinch the diagnosis.

Tuberculous Arthritis

Tuberculous arthritis is typically a monoarticular disease, although multiple joint involvement has been described in literature.[46,48] About 15% of all skeletal tuberculosis cases are constituted by hip joint and about 10% cases by knee joint TB, shoulder joint is rarely involved. Involvement of joint may occur as a result of direct extension from adjacent tuberculous osteomyelitis or through hematogenous spread during primary tuberculosis. Clinicopathological staging of joint tuberculosis usually decides the clinical features for that stage. Pain and circumferential limitation of joint movements are typical clinical features. Osteolytic areas and tuberculous sequestra are encountered along with the loss of the definition of articular margins. In advanced stages, periarticular osteoporosis, peripheral bony erosions and gradual reduction in joint space constitute a radiological triad suggestive of joint tuberculosis. Pyogenic, fungal and rheumatoid arthritis may need differentiation from joint tuberculosis.

Poncet's Disease

This is defined as parainfective polyarthritis in which active tuberculosis is located anywhere in the body, not necessarily in the affected joints, AFBs are never isolated from the involved joints. Commonly, the extra-articular site of active tuberculous disease is the lymph node.[48-50] This is basically a tuberculous hypersensitivity phenomenon, commonly accompanied by strongly positive tuberculin skin test or erythema nodosum. Mostly seen in children or young adults, it commonly involves knee, ankle, wrist, elbow, metacarpophalangeal and proximal interphalangeal joints. Constitutional features, including fever, pain, swelling and tenderness of the involved joints are generally present. Synovial fluid is exudative type, but fluid is sterile, negative for AFB and even PCR is negative for mycobacterium. The condition responds very well to the drug treatment of basic active tuberculous disease.

Tuberculosis Osteomyelitis

Osteomyelitis is usually seen in the bones of extremities involving small bones of hands and feet, like phalanges, metacarpals and metatarsals. Although tuberculosis can involve any bone, the long bone disease is rare. The disease commonly presents with clinical features, such as pain, swelling with raised temperature, tenderness and boggy soft tissue at the involved site. An abscess or sinus may also be encountered. The condition needs differentiation from chronic pyogenic osteomyelitis and neoplasia. The typical radiographic picture reveals honey combing, sequestration of diaphysis and subperiosteal new bone formation.

Treatment of bone and joint tuberculosis: Overall consensus is that spinal tuberculosis without neurological involvement and without unsightly deformity is a medical condition. Combined management, the modality of choice consists of orthopedic intervention by surgeon and tuberculosis drug therapy under supervision of physician. The basic principles of tuberculosis drug therapy regimens essentially remain the same as for pulmonary tuberculosis. There have been some difference of opinion regarding the duration of therapy, the orthopedicians favored a larger 18–24 months duration of drug therapy in the past.[51,52] However, the latest evidence suggests that short course chemotherapy of nine months duration is quite adequate.[53,54] It is also recommended that six-month short-course regimen with four drugs (HRZE) in the intensive two months phase and two drugs in the subsequent four months maintenance phase is sufficient for the cure.[54] Latest WHO guidelines have also endorsed that pulmonary and EPTB should be treated with same regimens, but because there are technical difficulties in the assessment of treatment response of bone and joint tuberculosis, the nine-month treatment is recommended for such cases.[55]

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

Only about 5% of all extrapulmonary tuberculosis cases are contributed by CNS-TB, but the CNS-tuberculosis has a high morbidity and mortality. In developing country like India, the prognosis of disease had been poor due to inadequate availability of diagnostic and treatment facilities. Human immunodeficiency virus has compounded the risk for the development of CNS-TB. In one study its occurrence was found in up to 2 cases of 100 HIV-infected persons.[13]

Pathogenesis

Tubercle bacilli reach the brain parenchyma and the meninges during the stage of hematogenous spread of primary complex formation. Thereupon, these bacilli form tiny lesions during primary complex stage prior to the development of delayed hypersensitivity or cell-mediated immunity. In more than 95% cases, these lesions get healed by natural healing with the appearance of cell mediated immunity. Later in life, such lesions may get reactivated and present with different clinical variants of CNS-TB (Table 47.1).

TABLE 47.1: Different clinical forms of CNS tuberculosis

- Meningitis (TBM)
- Tuberculoma
- Arachnoiditis
- Encephalitis
- Arteritis or vasculitis
- Tuberculous abscess
- Radiculomyelitis
- Behavioral abnormalities
- Demyelination

Once reactivated, the foci may rupture into the subarachnoid space leading to arachnoiditis or grow intracranially as tuberculomas. Frequently, CNS-TB is the part of disseminated tuberculosis, about 20% of such patients have concomitant miliary tuberculosis. Occasionally, direct extension from tuberculosis of contiguous parts would lead to CNS-TB, like from skull bone disease, tuberculous otitis or spondylitis. Rarely, extradural tuberculous abscess may occur with vault tuberculosis.[56] When tubercle bacilli enter the Cerebrospinal Fluid (CSF), there occurs intense inflammation of meninges, i.e. tuberculous meningitis, the meninges get covered with thick gelatinous grey exudates. The latter get extended to brainstem affecting the cranial nerves. Exudates further track down the spinal cord and spinal roots of the nerves. The thick gelatinous material also interferes with CSF drainage system, thereby causing hydrocephalus, quite frequently.

Clinical Features

The TBM usually develops as a complication of primary tuberculosis, hence commonly seen in early childhood, but may occur at any age. The initial symptoms of disease are nonspecific in the form of loss of appetite, irritability, malaise, vomiting, headache, changed behavior, drowsiness or even convulsions. These features usually mark the prodromal stage of the disease, which may last for two to eight weeks. Neck retraction or rigidity may be accompanied at this stage due to meningeal inflammation. In infants, fontanelle may be bulging. Around 50% cases have papilledema, but usually without the loss of vision. Increasing hydrocephalus is responsible for decreasing consciousness and brain damage. Choroid tubercles may also be seen in some cases. Tuberculous meningitis patient can be classified in different clinical stages depending upon the level of consciousness and presence of neurological deficits.[57]

Diagnosis

TBM often needs to be differentiated from other types of meningitis like bacterial, fungal, viral, carcinomatous or neurosyphilitic. The diagnosis is easy in the presence of suggestive clinical features and associated pulmonary or miliary tuberculosis, the conditions seen in more than half of such cases. In HIV infected persons, the concomitant EPTB is more common. Suggestive features on CT and MRI scan, such as hydrocephalus, tuberculomas, gyral enhancement, infarcts and basal exudates, also help in making the diagnosis. MRI images are particularly useful in differentiating tuberculosis from fungal, viral and bacterial disease.

CSF findings play a vital role in the diagnosis of CNS-TB. Although CSF pressure is found elevated and papilledema is present, lumbar puncture can be performed safely because it is a chronic type of meningitis. White cell counts are raised with polymorph predominance initially, but lymphocytes take over in later stages. The counts are not elevated more than 500/cmm. Usually, CSF is clear and its glucose level is less than 40% of the corresponding blood glucose level. Proteins in CSF are in the range of 100–200 mg/dl usually, may exceed 1 gm/dl in the event of spinal block due to coexisting spinal meningitis. If allowed to stand, one can see the cobweb formation in CSF. Chloride estimation in CSF is not helpful in differentiating TBM from viral or bacterial etiology. In about 5% TBM cases, CSF may be normal. In the presence of HIV infection, CSF remains unremarkable and not helpful in making diagnosis. Nevertheless, CSF must be sent in HIV-infected patients for AFB culture, it may come out to be positive in up to 50% cases. Sterile CSF culture for bacteria, fungi and negative Gram staining are supportive of TBM diagnosis. A cut off level of more than 10U/L, CSF-ADA has sensitivity of 92.5% and specificity of 97% for the diagnosis of TBM.[58] Values more than 8U/l (sensitivity <59% and specificity >96%) improved the diagnosis of TBM ($p < 0.001$).[59] PCR test for *M. tuberculosis* among Indian patients had sensitivity of 44.5% and specificity 92% in the most likely TBM cases.[58]

CT scan and MRI imaging often demonstrate findings in CNS-TB, such as thickening and enhancement of basal meninges, small granulomas, infarction and hydrocephalus, periventricular edema, tuberculous abscess and tuberculoma (Fig. 47.7). These are quite helpful in reaching the diagnosis as well as for following the progress of treatment. Serial CT scans performed for assessing the course may sometimes reveal new tuberculomas or accentuation of those pre-existing during tuberculosis drug therapy, the phenomenon recognized as paradoxical response.[60,61] However, such accentuated lesions get resolved gradually with the continuation of the same chemotherapy. A substantial series has recently described the radiological features of paradoxical neurological TB-IRIS in HIV-infected patients with tuberculoma.[62]

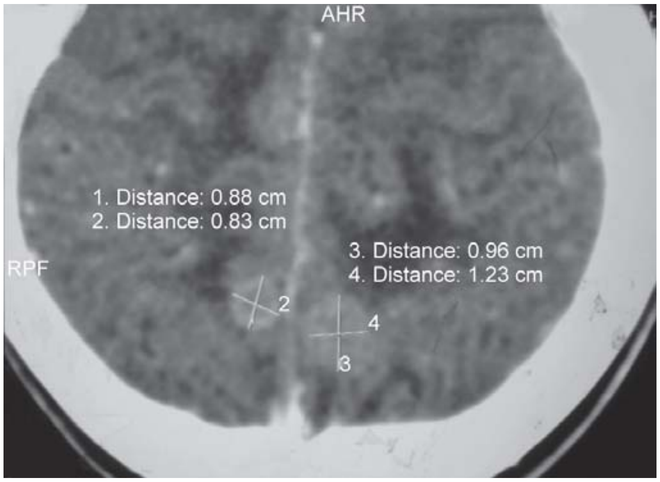

Fig. 47.7: CECT head showing hypodense lesions with rim shadow in a typical case of tuberculoma

Treatment

Tuberculous meningitis is a serious form of tuberculosis in the terms of morbidity and mortality, hence a better prognosis can only be anticipated if the disease is detected at an early stage and right treatment is initiated without wasting any time. Isoniazid, pyrazinamide and ethionamide penetrate the Blood Brain Barrier (BBB) adequately; rifampicin enters poorly while streptomycin and ethambutol cross BBB adequately only when meninges are inflamed. Four drugs [HRZS/E] should be included in the intensive phase. Ethambutol is avoided in comatose patients because vision cannot be monitored. Therefore, streptomycin should be substituted for ethambutol accordingly. Intrathecal streptomycin is no longer used. The optimum duration of TB drug therapy is still debatable. Even in the absence of randomized controlled trials to compare the efficacy of 6 months verses 12 months regimens, the meta-analysis of available literature suggests that six-month regimens are as affective as longer duration regimens provided the bacteria are fully susceptible to first line drugs.[63] However, chemotherapy for 9–12 months of treatment is recommended for TBM, because of the serious risk of mortality and morbidity.[63,64]

The use of corticosteroids is somewhat controversial. Although its use does not benefit stage I, but it improves prognosis in stage II and III disease. Therefore, if nothing is suggestive of drug resistance and fungal etiology is ruled out, corticosteroid should be used as adjuvant to tuberculosis drug therapy in stage II and III TBM.[64] A recent Cochrane review supports the routine use of corticosteroids in HIV-negative patients with TBM to reduce mortality and disabling residual neurological deficits, however, not adequate evidence is yet available in favor or against a similar conclusion for those who are HIV positive.[65] Surgery is sometimes necessary for the management of hydrocephalus, an early drainage improves the outcome.[66] Surgical drainage of intracranial or extradural abscess will also be necessary.[67] Tuberculomas usually regress with chemotherapy; therefore, a trial of at least two months drug therapy must be given before surgery.

ABDOMINAL TUBERCULOSIS

Abdominal tuberculosis, which encompasses tuberculosis of Gastrointestinal Tract (GIT) anywhere from esophagus to anus, peritoneum, mesentery, omentum, mesenteric lymph nodes, hepatobiliary system, spleen and of pancreas, accounts for 3% of all EPTB cases, concomitant pulmonary lesions are found in about 25% of such cases. The incidence is expected to increase with an increase in the HIV incidence, EPTB is more commonly encountered in HIV-infected cases. A pre-chemotherapy era autopsy series of pulmonary TB cases had revealed intestinal involvement in 55 to 90% cases, the disease was more common in the presence of extensive pulmonary involvement.

Pathogenesis

The tuberculosis infection reaches the abdominal organs through hematogenous spread during primary infection stage, from swallowing of sputum loaded with tubercle bacilli in pulmonary tuberculosis patients, through direct extension from adjacent organ tuberculosis and occasionally through lymphatics. Intake of milk infected with *Mycobacterium bovis* causing tuberculosis is not common these days due to the universal practice of pasteurization or boiling of milk before consumption. The intestinal disease in India is primarily caused by *M. tuberculosis* and not by *Mycobacterium bovis*.[68] The most common site for abdominal TB is the ileocecal region possibly due to the abundance of lymphoid tissue in the Peyer's patches, physiological stasis and minimal digestive work undertaken in this part of intestine allowing more contact time to bacilli for invasion. The disease spreading from lymph nodes, intestine or from fallopian tubes usually leads to peritoneal tuberculosis. In about 30% cases, lymph node and peritoneal tuberculosis may be seen even without the intestinal disease.[69]

When the bacilli reach the intestine, they are trapped in the Peyer's patches, consequently granuloma formation takes place therein. These granulomas grow and get confluent with each other. The inflammation spreads to the submucosa, and the mucosa overlying the inflamed Peyer's patches ulcerate. These ulcers are superficial, do not penetrate beyond muscularis propria.[70] The ulcers are transversely placed covering a ring of the intestinal mucosa and so, appropriately named as girdle ulcers. The ulcers may be single or multiple, the mucosa in between the girdle ulcers is quite healthy, termed as skip lesion. Stricture formation ensues when these ulcers heal by fibrosis. The strictures called "napkin ring strictures", are often responsible for intestinal obstruction. Other areas in intestine may show no granuloma formation, but for chronic inflammation. Sometimes, there occurs excessive inflammation and fibrosis causing adhesions of gut, mesentery and lymph nodes assuming altogether a shape of a mass, which may erroneously appear as neoplasm.

Grossly, intestinal tuberculosis is classified as ulcerative, ulcero-hyperplastic and hyperplastic. While ulcerative and hyperplastic forms (stricture form) are seen in small intestine, ulcero-hyperplastic form is found in colon and ileocecal region. Tuberculous peritonitis occurs in different forms: Ascetic, encysted and fibrinous, sometimes felt as an abdominal mass comprising of a mesentery and thickened omentum. Gross examination on laparotomy/laparoscopy exhibits straw colored fluid, multiple yellow-white tubercles scattered over peritoneum or greater omentum; the peritoneum lacks its usual shine and hyperemia.[71] The involved abdominal lymph nodes may be enlarged and matted with or without caseation. Granulomas are commonly seen in the lymph nodes.

Clinical Features

Clinical presentation of abdominal tuberculosis is quite protean, may mimic many acute or chronic intestinal ailments. Nearly two-third cases of abdominal tuberculosis are young adults of 20 to 40 years of age with slight preponderance for female gender. The onset of symptoms may be acute, chronic or acute on chronic. Often, about one-third present as acute abdomen with pain in right iliac fossa mimicking acute appendicitis or as acute intestinal obstruction, while the remaining two-third have insidious onset with symptoms like pain in abdomen. Constitutional symptoms of low grade fever, malaise, anorexia and weight loss are often present. Pain in abdomen is seen in around 80 to 95% cases, while alternate constipation and diarrhea are seen in about 9 to 20% cases. Other features like a moving ball of wind in abdomen, nausea, vomiting and malena may also be seen. Features of malabsorption are also encountered in some cases. No characteristic signs are described for abdominal tuberculosis, the popular classical "doughy" feel of the abdomen has been observed in 6 to 11% cases in Indian series, however, not reported in some large series.[72] Right iliac tenderness like that in acute appendicitis or lump in this region mimicking carcinoma or appendicular abscess may be felt. The signs of acute or subacute small intestinal obstruction like abdominal distension, vomiting and absolute constipation with or without a palpable mass may be encountered as per the pathological stage of the disease. Many other clinical features ensue depending upon the involved organ or the site and type of involvement.

Diagnosis

Clinical presentation of abdominal tuberculosis is quite nonspecific and usually overlapping with malignant or inflammatory bowel diseases. Nevertheless, a high index of suspicion particularly arises for persons hailing from high burden countries with suggestive constitutional symptoms and evidence of pulmonary or EPTB lesions. Anemia, reduced serum albumin (<3.5 gm/dl) or raised C-reactive proteins and positive tuberculin skin test are usually present, but not deciding investigations. Thus, the only disease site specific clinical features, radiological and Ultrasonography (USG) findings, pathological lesions (both gross plus microscopic) and isolation of mycobacteria, altogether are necessary for clinching the authentic diagnosis in the majority of cases. The following radio imaging techniques are substantially helpful in arriving at the diagnosis of abdominal tuberculosis:

1. *Chest radiograph:* Concomitant pulmonary lesions either healed or active, have been reported in 25 to 80% of abdominal tuberculosis cases.[70,73,74] There may be features suggestive of pulmonary TB, pleural effusion or mediastinal lymphadenopathy. In such situation, effort should be made to demonstrate tubercle bacilli in sputum, Bronchoalveolar Lavage (BAL) or gastric lavage in children. The presence of tuberculous lesion elsewhere in the body supports the diagnosis of abdominal tuberculosis.
2. *Plain abdominal radiograph:* The presence of certain findings, such as multiple air fluid levels with distended bowel loops (intestinal obstruction), ascites, perforation or intussusception and calcified nodes indirectly support the diagnosis.
3. *Small bowel barium study:* Hypersegmentation of barium column also called as chicken intestine, stiffened and thickened folds, luminal stenosis with smooth and stiff contours (hour glass stenosis), and multiple strictures with the segmental dilatation of intestinal loops are various suggestive signs. Similar findings may be encountered in Crohn's disease.
4. *Barium enema:* The thickened ileocecal valve gives a broad triangular picture having base towards cecum, popularly known as "inverted umbrella" sign. Extreme irritability due to ulceration causes the rapid movement of barium, hence no barium contrast is visualized in inflamed segments of the ileum, cecum and ascending colon with normal column of barium on other side, also described as "Stierlin's sign". Whenever there is stenosis in the gut, a very narrow string of the contrast is visualized, known as "string sign". Both Stierlin's and String's signs may also be positive in Crohn's disease, hence are not specific for tuberculosis.
5. *Ultrasonography:* Ultrasound is helpful in picking up the ascites (either loculated or free), thickened omentum, retroperitoneal or mesenteric lymphadenopathy. Ultrasonographic guidance for investigations like FNAC or fluid tapping always adds to the diagnostic yield.
6. *CT scan:* There occurs circumferential thickening of the wall of cecum and terminal ileum. Also, the ulceration and nodularity in terminal ileum along with narrowing and proximal dilatation may be visualized. Other abnormalities like obstruction, perforation and abscess can also be seen on CT scan. In tuberculous ascites, fluid density is usually very high, i.e. around 25–45 HU due to high protein content of the fluid. Peritoneal thickening and nodules may also be seen.

To confirm the diagnosis, we need to demonstrate AFB in peritoneal fluid or typical histopathological picture in the biopsy taken through laparotomy. Blind percutaneous needle biopsy of peritoneum can also be performed. However, biopsy under direct visualization is always safer as it averts complication like gut perforation and gives a high diagnostic yield. Laparoscopy is the procedure of choice for biopsy, but mini laparotomy would be preferable in the presence of intense plastic peritonitis and extensive adhesions. Colonoscopic FNAC may be taken from the ileocecal lesions to improve its yield. Ascitic fluid is straw-colored exudative type with total cell count of around 150–4000/cmm, lymphocytes being more than 50%. Ascitic fluid AFB positivity rate is usually less than 20%. The culture positivity could be improved up to 83%, when at least 1 liter fluid was centrifuged and subjected to culture for tubercle bacilli.[75] Ascitic fluid ADA level of more than 40 U/L is highly supportive of tuberculous etiology. High level of interferon-gamma in ascitic fluid is also suggestive of tuberculous etiology. The role of immunological investigations for diagnosis of tuberculosis is still undefined.

Treatment

The treatment is essentially same as for pulmonary tuberculosis. All patients of abdominal tuberculosis should be treated with short course chemotherapy for six months duration. The standard regimen includes four drugs (HRZE) in the initial two-month intensive phase followed by two drugs (HR) in the four-month continuation phase. Six months short-course chemotherapy compared with 12 months chemotherapy regimen, achieved cure in 99% cases.[76] Six-month regimen is the standard regimen for the treatment of abdominal tuberculosis as per the recommendation of the Joint Tuberculosis Committee of the British Thoracic Society.[54] The routine use of adjuvant corticosteroid is not advisable in such cases.[72]

Surgery in the form of intestinal resection and end-to-end anastomosis, is occasionally required, only if there is mechanical obstruction.[72,77,78] It is particularly indicated for strictures of longer than 12 cm with involvement at multiple sites. Obstructive intestinal lesions may respond to chemotherapy alone, without surgery. In one report, 91% patients had clinical improvement and 70% had complete radiological resolution while only 8% required surgery at the completion of chemotherapy.[79] Sometimes, the obstructive symptoms may increase initially, but only to regress ultimately. On an average, it takes around six months for the amelioration of obstructive symptoms.

GENITOURINARY TUBERCULOSIS

Genitourinary tuberculosis is a significant problem in the developing world, around 9% of all EPTB cases in India are estimated as of GUTB.[10] Often, the disease continues to progress since the diagnosis is not made until it is too late.[14] Most patients present with renal failure, bladder and or ureteric strictures, which could have been easily averted, had an early diagnosis and treatment made available to them. Three to four percent cases of pulmonary TB also have concomitant GUTB, commonly involving the kidneys, bladder, urethra, and male or female genital tract.[1,10]

Pathogenesis and Clinical Features of Urological TB

The mycobacterial infection reaches the kidneys and other urogenital organs during the stage of hematogenous spread of primary tuberculosis. These bacilli form tiny lesions as tubercles in these organs, which heal either spontaneously or with treatment, only to get activated after the years of dormancy. The disease usually occurs during the second and fourth decade of life. The most common clinical presentation of urological tuberculosis is sterile pyuria and painless hematuria. Patient may present with the symptoms of dysuria, hematuria, frank pyuria and renal mass. The features are quite suggestive of recurrent urinary tract infections with fever, but for any isolation of common bacterial growth on culture. The granulomas formed in the kidneys enlarge and rupture leading onto bacilluria. The infection spreads downward to the calyces, pelvis, ureter and bladder. Ureteric stenosis may develop particularly in the distal region giving rise to obstructive uropathy, which may result in tuberculous pyonephrosis. The bladder involvement causes features of cystitis and bladder wall fibrosis. The latter results in the marked reduction of bladder capacity, commonly termed as thimble bladder deformity. The reduced bladder capacity is responsible for the frequency of micturition and nocturia.

Pathogenesis and Clinical Features of Gynecological TB

Infertility, either primary or secondary is a common presentation in female genital tuberculosis. In India, one-third cases of tubal disease infertility are attributed to tuberculosis.[80] Alterations in menstrual pattern (menorrhagia, amenorrhea or postmenopausal bleeding) are common features in such patients. Female genital tuberculosis may be mistaken for ovarian malignancy. The differentiation is further complicated by the presence of high levels of CA-125, which are also described in gynecological tuberculosis. Primary female genital tuberculosis is rare, usually seen when the male partner suffers from active genitourinary tuberculosis.[81,82] Mostly, genital TB is almost always secondary to tuberculosis elsewhere in the body. Commonly the infection spread directly from active abdominal tuberculous pathology.

Diagnosis

Sterile pyuria should raise the suspicion of GUTB. Urine culture for mycobacteria, particularly the collected early morning samples of three consecutive days give better yield. The intravenous pyelography is an important investigation for the diagnosis of urological tuberculosis. The pyelogram may reveal abnormalities, such as the calyceal clubbing and pelviureteric junction stenosis with pelvic dilatation. Calcification in urinary tract and prostate may support the diagnosis of tuberculosis. Hydronephrosis, and sometime small kidney may be seen on ultrasonography. Urinary tract and kidney abnormalities can also be picked on CT scanning. Sometimes, perinephric or psoas abscess may also be encountered. In males, the involvement of vas deferens will give a beaded feel on palpation and a draining scrotal sinus can also be seen. Diagnosis is confirmed by growing AFB from urine or biopsy tissue culture. Urine for tubercle bacilli is usually not rewarding. Moreover, the positive microscopy may also raise the suspicion of contamination either by *Mycobacterium smegmatis*, a saprophytic mycobacteria or of environmental mycobacteria in laboratory reagents. Diagnosis of female genital tuberculosis is made with the help of multiple criteria, including the menstrual blood culture. FNAC, endometrial curettage and laparoscopic biopsy as per an algorithm defined for use in the developing countries.[83] Recently, PCR has also been shown as an important diagnostic test.[84]

Treatment

Six-month tuberculosis chemotherapy is advised, although controlled clinical trials are lacking for short course chemotherapy in GUTB.[85] Adjuvant corticosteroids are recommended to avert ureteric strictures. Steroids have also been found helpful in the treatment of tuberculous interstitial nephritis.[86] Sometimes, surgery such as nephrectomy is required for the destroyed nonfunctioning kidney; partial nephrectomy ureteric stricture dilatation and bladder reconstruction may be done as per appropriate indication. A full course of chemotherapy is essential in addition to surgery.

SKIN TUBERCULOSIS

Skin tuberculosis contributes 1 to 2.5% share of all skin disease cases, the ailment is more commonly found in poor socioeconomic populations.[87-89] The skin may be involved by tuberculosis through different modes of spread.

Clinical Features

There are three main classes of skin tuberculosis determined by the presence of previous sensitization to tubercle bacilli, immune response of the host and route of inoculation by tubercle bacilli. In order of frequency, these are lupus vulgaris, tuberculosis verrucosa cutis and scrofuloderma. These three types are seen in persons, who had previously been infected with tubercle bacilli and have delayed hypersensitivity to the tubercle bacilli. In absence of previous sensitization, the disease may occur in the form of tuberculous chancres and miliary tuberculosis of skin. Tuberculids are the hypersensitivity lesions of skin, which occur as a result of tuberculosis elsewhere in the body.

Lupus vulgaris: It is the most common variety of skin tuberculosis, which is present with firm plaques that exhibit central clearing and activity on margins (Fig. 47.8). The active margins show erythematous translucent papules, popularly described as apple-jelly nodules. Most often, the lesions are dry, but sometimes seropurulent discharge and crust formation may be seen. Long-standing lesions may occasionally get complicated with squamous cell carcinoma. Usually, the lesions are encountered over the face, buttocks and lower limbs. Sometimes, underlying tuberculosis may extend in the skin as lupus vulgaris. BCG vaccination may rarely get complicated as lupus vulgaris. Often, patients do not have constitutional symptoms, and tuberculin skin test is usually positive in such cases. Typical clinical features, demonstration of mycobacterium in the smear or biopsy, classical tuberculosis granuloma and response to the therapeutic trial authenticate the diagnosis. Skin TB can be adequately treated with six-month short-course chemotherapy.[90]

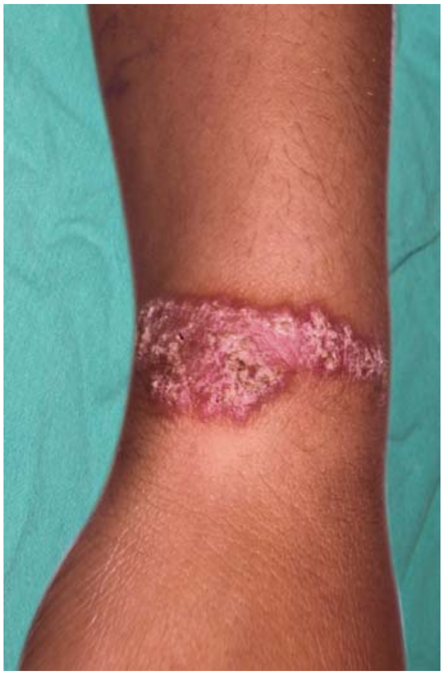

Fig. 47.8: Lupus vulgaris lesion showing central scarring and peripherally active lesion in upper limb just above the wrist

Scrofuloderma: It is the commonest form in which tuberculosis involves the skin as a direct extension of the underlying tuberculous pathology of lymph nodes, bones or urogenital tract.[91,92]

Chancre: This is a primary infection of skin, which occurs as a result of accidental inoculation of the abraded or injured skin by tubercle bacilli. Commonly, seen in the children of the family with member/s having sputum-positive pulmonary tuberculosis. Lesions are often seen on the limbs. At the outset, a papilla or a nodule develops locally, which subsequently ulcerates. Simultaneously, there occurs regional lymph node enlargement. The cutaneous lesion and regional lymphadenopathy together constitute the primary complex. Lesions usually heal spontaneously or may progress into lupus vulgaris. The biopsy of the early lesion shows neutrophils and tubercle bacilli, typical tuberculous granulomas are seen later.

Miliary TB of skin: Skin lesions, consequent upon hematogenous spread of tubercle bacilli during primary infection, often go dormant or get healed with the development of immunity. These lesions get reactivated in the form of pustules and papules, later in life whenever there occurs immunosuppression, e.g. during measles or viral infections. Usually, constitutional symptoms of tuberculosis are present along with such lesions.

Tuberculids: Four diagnostic criteria must be fulfilled to qualify for the confirmed diagnosis of tuberculids:

1. On biopsy, the lesion should have tuberculoid granuloma
2. *Mycobacterium* should not be seen in the lesion
3. Mantoux test is strongly positive
4. Treatment of underlying tuberculosis should ameliorate the tuberculid skin lesions.

There are four types of tuberculids described; lichen scrofulosorum, erythema induratum, papulonecrotic tuberculids and erythema nodosum with different morphological features (Fig. 47.9).

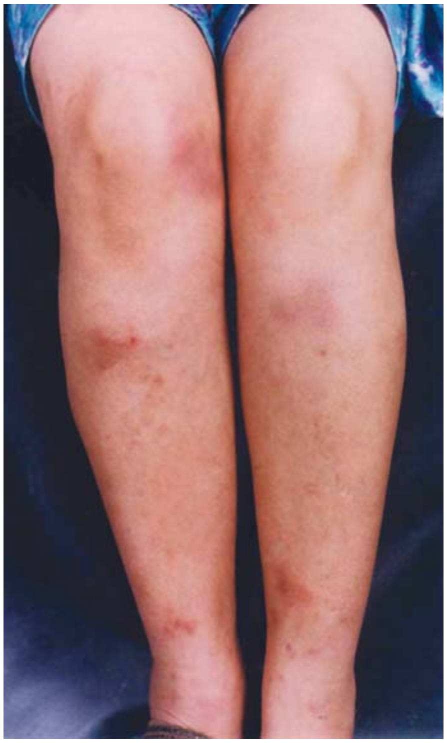

Fig. 47.9: Erythema nodosum over shin area in a 16-years-old girl suffering from tuberculous lymphadenitis

DISSEMINATED MILIARY TUBERCULOSIS

Miliary tuberculosis is a disseminated disease with discrete millet seed size tuberculous foci found homogeneously distributed in the lungs and other viscera.[15,93-96] Classical miliary mottling on chest radiograph is the familiar picture, which supports the diagnosis. It is the cryptic variant, which poses a diagnostic dilemma even in the endemic area. Sometimes, the disease may present as Acute Respiratory Distress Syndrome (ARDS), therefore, the tuberculous etiology must be kept in mind, particularly when no obvious cause is available for the same.

Pathogenesis

Commonly during the stage of hematogenous spread of primary tuberculosis, the AFB get disseminated to various viscera particularly the highly vascularized organs like the lung, liver, spleen, bone marrow and brain. The bacilli initiate the discrete tuberculous foci in these viscera. With the development of immunity and delayed hypersensitivity, these foci heal in majority of the subjects. In a few, they fail to heal and progress to acute miliary tuberculosis. In the endemic areas, the miliary TB is seen in young children, however, in the developed countries, majority of such patients are seen in the elderly patients. Miliary TB can also come up later in life when healed primary foci, after getting reactivated with caseation necrosis, erode into the blood vessels. The erosion of active focus in the blood vessel causes hematogenous embolization of tubercle bacilli giving rise to disseminated tuberculous foci all over the body. Microscopically, in an immunocompetent person, each focus represents a typical tubercle with caseation in the center comprising of Langhans type of giant cells, epithelioid cells, lymphocytes, fibrocytes and AFB. However, in immunosuppressed subjects or elderly persons, the appearance is often of nonreactive type lesions, which show necrosis teaming with tubercle bacilli, but without typical granuloma formation.

Clinical Features

The miliary tuberculosis has slight preponderance for male gender. Symptoms develop gradually, include generalized constitutional features along with spiky fever and chills. Nearly 6 to 8% of all EPTB cases are miliary TB cases. There are two main clinical variants of miliary TB viz. acute miliary and cryptic miliary.

Acute miliary TB: Over and above the constitutional features, headache may be encountered, possibly due to

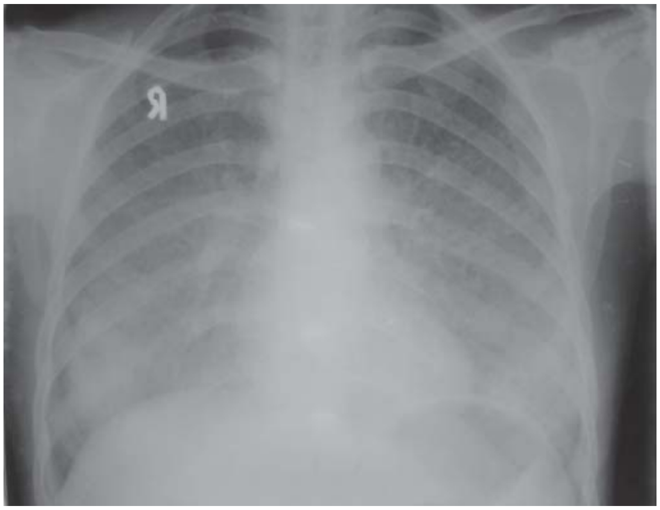

Fig. 47.10: The chest radiograph posterior-anterior view showing typical miliary tuberculosis in a young female

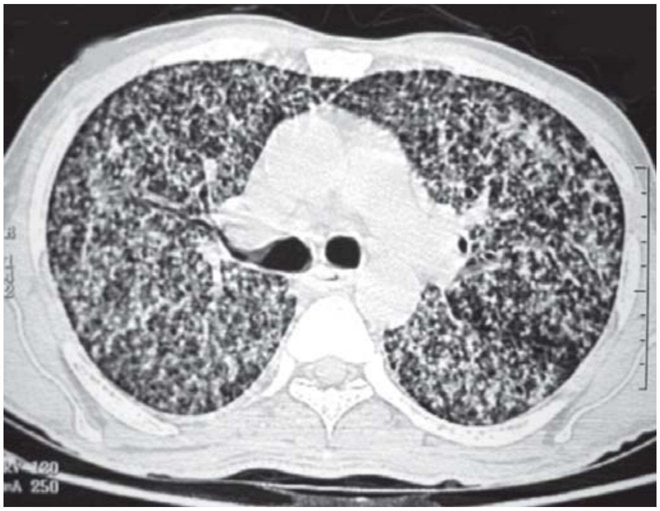

Fig. 47.11: High-resolution CT thorax shows extensive miliary nodules in both lungs

coexisting TBM, thus a lumbar puncture must be performed in patients with headache. Hemoptysis and dyspnea are not frequently seen in such cases. Hepatosplenomegaly and icterus may be present. Chest examination is unremarkable. However, minimal pleural and pericardial effusions may be seen. Fundus should be looked for choroid tubercles. The latter are seen as pale, grayish white, oblong patches frequently bilateral. In one series, they were encountered in 7.2% cases only.[97] Demonstration of choroid tubercle is highly supportive of the diagnosis of miliary tuberculosis; however, the finding is more common in children. Tuberculomas may commonly complicate miliary tuberculosis. Adrenal insufficiency has also been commonly described. The chest radiograph reveals typical miliary pattern, i.e. homogeneously distributed discrete uniform size (1–2 mm) millet-shaped lesions in all lung zones (Figs 47.10 and 47.11).

Cryptic miliary TB: Cryptic is an atypical presentation of miliary tuberculosis in which chest radiograph does not show classical miliary mottling. Usually seen in elderly patients of over 60 years of age, but may be seen in the younger age group, particularly in the endemic areas. The symptoms usually appear insidiously, include the presence of weight loss, intermittent fever, malaise and mild hepatosplenomegaly. Meningitis and choroid tubercles are very uncommon features in this variant of miliary tuberculosis. Maintaining a high index of suspicion is the only way for its timely diagnosis.

Diagnosis

Classical miliary mottling on chest radiograph is most helpful to make the diagnosis of miliary tuberculosis, the same may not be seen in early stages or in the cryptic miliary variant. In such situations, characteristic picture on HRCT is very helpful. Sometimes, chest radiograph picture like that seen in ARDS or acute lung injury and shadows larger than usual miliary mottling are also encountered. For confirmation of diagnosis, all efforts must be made to isolate tubercle bacilli from various specimens such as sputum, pleural fluid, CSF, urine, BAL fluid, blood and histopathological samples. Tuberculin skin test is often negative. In one series, tuberculin anergy was reported in 68% cases of miliary TB.[98]

Blood dyscrasias like pancytopenia and leukemoid reactions are commonly seen in the cryptic form of miliary tuberculosis. Sometimes, bone marrow examination is required, particularly in the presence of leukemoid reaction. Bone marrow aspiration may reveal granulomas or even *Mycobacterium tuberculosis*. Liver biopsy provides the highest yield, granulomas have been reported in up to 75% cases. In unconfirmed cases, particularly when the patient is not willing for invasive procedure, therapeutical trial with antituberculosis drugs must be given. With the initiation of tuberculosis drugs, fever usually subsides within 7–10 days, over all clinico-radiological improvement is appreciated in four to six weeks of treatment. Early diagnosis is imperative for favorable outcome of treatment of miliary tuberculosis, which is uniformly fatal, if untreated.[98,99]

Treatment

In principle, the standard six-month treatment for pulmonary tuberculosis is adequate for miliary tuberculosis also. The standard regimens comprise of initial two month intensive phase of isoniazid, rifampicin, pyrazinamide and ethambutol (or streptomycin) followed by four months continuation phase of isoniazid plus rifampicin. Nine-months regimen is recommended in infants and children.[100] Unequivocal evidence is lacking for the use of corticosteroid in the treatment of miliary tuberculosis.

PERICARDIAL TUBERCULOSIS

Tuberculous involvement of pericardium is usually secondary to tuberculosis elsewhere in the body. Nearly 1 to 8% of pulmonary tuberculosis patients have concomitant pericardial tuberculosis. Of all acute pericarditis, about 4% in developed countries and 60 to 80% cases in the developing countries are in fact tuberculous in origin.[101,102]

Pathogenesis

Direct extension from tuberculous mediastinal lymphadenitis is the commonest route for the involvement of pericardium. The infection may also reach pericardium through lymphatic and hematogenous routes from tuberculosis of the lungs, kidneys, bones or other organs. Pericardial tuberculosis has following four pathological stages: 1. dry pericarditis; 2. effusive pericarditis; 3. absorptive, and 4. constrictive pericarditis stage. Patient may present during any stage of pathological progress. Invariably, the pericardial fluid is straw colored and exudative type; very rarely there could be frank pus in the pericardium due to intense inflammation. The pericardium may contain somewhere between 15 ml and 3500 ml of fluid. When the fluid collection occurs at very rapid rate, the patient may develop cardiac tamponade. With in a few weeks of development of pericardial effusion, there occurs thickening especially of the visceral pericardium resulting into effusive constrictive pericarditis. In the absence of effective antituberculous therapy, continued fibrosis may lead to chronic constrictive pericarditis. Complete obliteration of pericardium due to fibrosis interferes with the proper cardiac functioning. Sometimes, the disease may involve the myocardium, ultimately leading to myonecrosis and muscle atrophy. Around 15% of patients show pericardial calcification, but it is reported in around 75% in some studies.[103,104]

Clinical Features

The disease is usually seen during third to fifth decades of life. Gradual onset tuberculous toxemia with anorexia, weight loss, malaise, low-grade evening temperature, and early fatigability is usually present. In around 20% cases, pericardial effusion may present as acute cardiac tamponade with tachycardia, high jugular venous pressure and feeling of retrosternal compression. Shortness of breath, chest pain and edema feet may be seen in around 40 to 70% cases.[105-107] Cardiac auscultation reveals muffled heart sounds and pericardial rub. Echocardiography is an important aid to confirm the diagnosis. Effusive-constrictive pericarditis patients usually show cardiomegaly, edema feet and elevated jugular venous pressure. In chronic constrictive pericarditis, there occurs the impediment of venous return due to tough encasement of the heart; however, heart shape and size remain normal. This causes pulmonary and systemic congestion leading ultimately to shortness of breath, orthopnea with edema, ascites and pulsus paradoxus. Long-standing elevation of venous pressure may cause protein-losing enteropathy and resultant hypoproteinemia. Ascites is more prominent, called ascites praecox.[108]

Diagnosis

Idiopathic or viral pericarditis is a common condition, which needs to be distinguished from tuberculous pericarditis. The former conditions are usually acute in onset, have minimal or no effusion, and are self-limiting in two to three weeks. On the contrary, more prolonged course and large effusions are frequent in tuberculous pericarditis. Chest radiograph may reveal cardiomegaly, pericardial calcification and pulmonary disease. Whenever associated with pulmonary tuberculosis, sputum must be examined for tubercle bacilli. ECG changes of acute pericarditis, such as ST elevation were seen in only 10% cases in some studies.[106,109] Echocardiography is a good test for detecting effusion and cardiac tamponade, although, not very accurate in picking up pericardial thickening. CT and MRI are other important adjuncts in helping the diagnosis.[110] Pericardiocentesis is performed for diagnostic tests of the fluid as well as for therapeutic purpose in cardiac tamponade. Pericardiocentesis should preferably be done under echocardiography employing apical approach. Pericardial fluid characteristics are exactly the same as encountered in tuberculous pleural effusion as far as physical, cellular, tubercle bacilli isolation, or ADA level are concerned, the same diagnostic standards are applicable.[111] Pericardial tissue taken by open biopsy may reveal typical granulomas with caseation necrosis in around 60% cases.

Treatment

If not treated, the disease is almost always fatal; even with treatment the mortality is 3 to 14%. Medical treatment using standard six-month short-course tuberculosis chemotherapy is successful in achieving the cure.[103,112] Addition of corticosteroids has been found associated with reduction in the frequency of pericardiocentesis and mortality.[103,112,113] Therefore, all patients of tuberculous pericarditis, barring contraindications should get 40–60 mg of prednisolone daily for four to six weeks with subsequent tapering over a five-week period. Pericardiocentesis is life-saving in cardiac tamponade, but recurrent effusion may require pigtail catheter placement. Some cases may require pericardiotomy, cardiopulmonary bypass may be necessary in cases with extensive calcification.[37]

HEPATIC TUBERCULOSIS

Hepatic tuberculosis is relatively uncommon form of extrapulmonary tuberculosis. It is secondary to pulmonary or gastrointestinal tuberculosis. Hepatic involvement has been reported in 10 to 15% of patients with pulmonary tuberculosis, and commonly found in patients with disseminated tuberculosis.[114] Hepatic tuberculosis generally occurs due to the reactivation of an old tuberculous focus, or on rare occasions as a result of a primary hepatic infection.[115,116] Tubercle bacilli reach the liver by way of hematogenous dissemination; the portal of entry in case of miliary tuberculosis is through the hepatic artery whereas in the case of focal liver tuberculosis, it is via the portal vein. The tuberculous liver abscess is an uncommon presentation in patients with hepatic tuberculosis.[115]

The clinical diagnosis of hepatic tuberculosis is difficult. Usually, symptoms and signs in this condition are nonspecific. Other than the constitutional symptoms, abdominal pain is present in 65 to 87% and jaundice in 20 to 35% patients. The jaundice may be caused by extra- or intrahepatic biliary obstruction.[117] Hepatomegaly is frequently encountered. The laboratory investigations frequently reveal increase in alkaline phosphatase with normal transaminases.[118] Ultrasonography finding of tuberculous liver abscess consists of a hypoechoic mass lesion in the liver, CT scan findings show a hypodense lesion with peripheral enhancement and central nonenhancing necrotic area.[114] The definitive diagnosis of tuberculous liver abscess needs microbiological and pathological examination of the specimen from the abscess. Aspiration of the liver lesion under the guidance of USG or CT can provide a precise specimen for confirmation.

Hepatic tuberculosis is treated with similar six-month regime (2HRZE/S, 4HR) as for other forms of tuberculosis. It is only occasionally that drainage is required for a large abscess. Most of the lesions, including the abscess will resolve with chemotherapy, provided an early treatment is instituted.

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Multidrug-Resistant Tuberculosis

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INTRODUCTION

Tuberculosis (TB) is the leading cause of death among curable infectious diseases.[1] TB remains a significant global health concern, despite the substantial progress made over the past decades in TB control activities in various countries.[2, 3] The number of TB cases that occurs each year in the world are still growing, although the rate of increase is slowing.[2] One of the most worrisome elements of the TB pandemic is the global emergence and spread of drug-resistant strains of TB.[4,5] The emergence of Multidrug-resistant TB (MDR-TB) and Extensively drug-resistant TB (XDR-TB) have dampened all enthusiasm in controlling and eliminating TB globally. Drug-resistant TB commonly arises through the selection of mutant strains, usually due to inadequate chemotherapy.[6] Treatment of drug-resistant TB requires prolonged and expensive chemotherapy using second-line drugs that are more toxic and less efficacious. The only way to control and eventually eliminate TB is through a concerted attempt by health care providers, health administrators, funding agencies and commitment of the individual clinicians treating those patients.[7]

EPIDEMIOLOGY

There were an estimated 9.2 million new cases of TB in the world in 2006 (139 per 1,00,000 population) and out of these, 4.1 million cases were of sputum-positive pulmonary TB (44% of the total).[8] It is estimated that 4,89,139 cases of MDR-TB emerged in 2006 and the global proportion of MDR-TB among all TB cases was 5.3%.[9] It is ironical that drug resistance develops and flourishes in those settings that are least able to deal with it. China and India carry approximately 50% of the global burden and the Russian Federation carries a further 7%.[9] In terms of proportion, the countries of the former Soviet Union are facing a serious and widespread epidemic, where almost half of all TB cases are resistant to at least one drug and every fifth case of TB have MDR-TB.

Studies conducted in India have found MDR-TB rates of 0.14 to 5.3% among new cases[10-21a] and 12.8 to 49% among previously treated cases.[15,22-28a] The fourth global report of the World Health Organization (WHO) states a prevalence of 2.8% among new cases and 17.2% among treated cases in India.[9] These data, although not representative of the entire population, provide a fairly decent estimate of the rate of drug-resistance among new and previously-treated TB cases in India. Tables 48.1 and 48.2 show the prevalence of MDR-TB, reported in various studies from India among new and previously treated cases, respectively.

The XDR-TB outbreak in KwaZulu-Natal, South Africa, in 2006 caught global attention on this deadly form of TB.[29] As of June 2008, 49 countries have reported confirmed XDR-TB cases to the WHO; XDR-TB has been found in all areas wherever it has been tested.[30] The situation is grim because the facility for second-line drug susceptibility testing (DST) is available only in few centers across the world and the real burden of XDR-TB is unknown. It has been estimated that 10% of all MDR-TB strains identified across six continents were actually XDR-TB.[31] XDR-TB has also been reported from different parts of India. The prevalence of XDR-TB among MDR-TB has varied from 1.5 to 33% in various studies from different parts of India[32-37] (Table 48.3).

DEFINITION

MDR-TB is defined as TB caused by bacilli showing resistance to isoniazid and rifampicin with or without resistance to other antituberculosis drugs. XDR-TB is defined as TB caused by bacilli showing resistance to isoniazid and rifampicin, in addition to any of the fluoroquinolones and to at least one of the three following injectable drugs, viz amikacin, kanamycin or capreomycin.[38]

Drug-resistance in TB may be broadly classified as primary or acquired.[39] When drug-resistance is demonstrated in a patient who has never received antituberculosis treatment previously, it is termed as primary resistance. Acquired resistance is one that results due to specific previous treatment. However, the WHO and the International Union Against Tuberculosis and Lung Diseases (IUATLD) have replaced the term primary resistance by the term "drug resistance among new cases" and acquired resistance by "drug-resistance among previously treated cases".[40]

CAUSES OF DRUG RESISTANCE

Previous treatment for TB is the most important risk factor for the development of MDR-TB.[6] Inadequate previous treatment exerts selection pressure and favors the multiplication of resistant tubercle bacilli, which eventually become the dominant population. Bacilli, which initially had resistance to only one drug may soon develop resistance to two drugs and then sequentially to many drugs. The potential causes of inadequate drug treatment are summarized in Table 48.4 and the mycobacterial genes involved in drug resistance are shown in Table 48.5. In addition to these, bacterial virulence factors (e.g. W-Beijing genotype[41]) and host

TABLE 48.1: Prevalence of MDR-TB among the new cases of pulmonary TB in India

Location	*Period of study*	*No. of isolates*	*MDR-TB (%)*
Bangalore[10]	1980s	436	1.1
Wardha[11]	1982-89	323	5.3
North Arcot[12]	1985-89	2779	1.6
Pondicherry[12]	1985-91	1841	0.8
Kolar[13]	1987-89	292	3.4
Jaipur[14]	1989-91	1009	0.9
New Delhi[15]	1990-91	324	0.6
Pune[16]	1992-93	473	1.0
Tamil Nadu[17]	1997	384	3.4
North Arcot[18]	1999	282	2.8
Hyderabad[19]	2001-03	714	0.14
Ernakulam[20]	2004	305	2
Gujarat[21]	-	1571	2.4
Delhi[21a]	2008-09	177	1.1

TABLE 48.2: Prevalence of MDR-TB among the previously treated cases of pulmonary TB in India

Location	*Period of study*	*No. of isolates*	*MDR-TB (%)*
Gujarat[22]	1983-86	1259	30.2
Delhi[15]	1990-91	81	33.3
Haryana[23]	1991-95	196	49
Tamil Nadu[24]	1996	162	20.3
Delhi[25]	1996-98	263	14
Bangalore[26]	1999-2000	226	12.8
Ahmadabad[27]	2000-01	822	37
Delhi[28]	2006	2880	47.1
Delhi[28a]	2005-08	196	20.4

TABLE 48.3: Prevalence of XDR-TB among MDR-TB in India

Study	*Setting*	*No. of MDR-TB patients*	*No. of HIV-infected patients*	*Prevalence of XDR-TB, n (%)*
Mondal et al[32]	Tertiary care centre, Lucknow	68	Not reported	5 (7.4%)
Jain et al[33]	Tertiary care centre, Mumbai	326	Not reported	36 (11%)
Singh et al[34]	Tertiary care centre, New Delhi	12	All HIV infected	4 (33%)
Thomas et al[35]	Field trial, Chennai	66	Not reported	1 (1.5%)
Sharma et al[36]	Tertiary care centre, New Delhi	211	All HIV negative	5 (2.4%)
Paramasivan et al[37]	Tuberculosis research centre, Chennai	1498	Not reported	69 (4.6%)

HIV: Human immunodeficiency virus

TABLE 48.4: Causes of inadequate treatment of tuberculosis

Causes	*Description*
Providers/Programs: Inadequate regimens	Inappropriate guidelines Noncompliance with available guidelines Absence of guidelines Poor training No monitoring of treatment Poorly organized or funded TB control programs
Drugs: Inadequate supply/quality	Poor quality Unavailability of certain drugs (stock-outs or delivery disruptions) Poor storage conditions Wrong dose or combination
Patients: Inadequate drug intake	Poor adherence (or poor direct observation of treatment) Lack of information Lack of money (No free treatment available) Lack of transportation Side effects Social barriers Malabsorption Substance abuse disorders

TABLE 48.5: Antituberculosis drugs and genes involved in their resistance

Drug	*Genes involved in drug resistance*
Isoniazid	Enoyl-acyl carrier protein (ACP) reductase (InhA) Catalase-peroxidase (katG) Alkyl hydroperoxide reductase (AhpC) Oxidative stress regulator (oxyR) β-ketoacyl-acyl carrier protein synthase (kasA)
Rifampicin	RNA polymerase subunit B (rpoB)
Pyrazinamide	Pyrazinamidase (PncA)
Streptomycin	Ribosomal protein subunit 12 (rpsL) 16s ribosomal RNA (rrs) Aminoglycoside phosphotransferase gene (strA)
Capreomycin	Hemolysin (HlyA)
Ethambutol	Arabinosyltransferase (emb A, emb B and emb C)
Fluoroquinolones	DNA gyrase (gyr A and gyr B)

genetic factors[42] may also contribute to drug resistance. The presence of HLA-DRB1*14, DQB1*0503 and DQB1*0502 alleles were found to be significant risk factors for the development of MDR-TB.[42]

Another important concern is that the nation-wide emergence of MDR-TB has led to the widespread use of second-line drugs, mainly by the private sector. Second-line drugs are freely available over the-counter and there is no control on the purchase and use of these drugs by patients or practitioners. No data exist regarding treatment practices in the private sector or medical colleges for patients with diagnosed or suspected cases of drug-resistant TB. This has already led to the development and spread of XDR-TB in India.

DIAGNOSIS OF DRUG-RESISTANT TB

MDR-TB and XDR-TB are pure laboratory diagnoses. The diagnosis of drug-resistant TB requires isolation and culture of the tubercle bacilli followed by DST in a quality-assured, accredited laboratory. The laboratory capacity is limited in regions like India, Sub-Saharan Africa and South-East Asia where the burden of MDR-TB and XDR-TB is high, resulting in serious diagnostic challenges. The Supranational reference laboratory network (SRLN) was formed in 1994 to ensure optimal performance and quality assurance of the laboratories engaged in DST of anti-TB drugs. The network has expanded since 2004 and now includes 26 laboratories in six WHO regions and is coordinated by the Prince Léopold Institute of Tropical Medicine in Antwerp, Belgium.[9]

Lack of Adequate Laboratory Infrastructure

DST for antituberculosis drugs is highly prone to laboratory errors and hence requires laboratories that are subjected to continuous internal quality control and periodic external quality assurance.[43] Otherwise, overdiagnosis may impose unnecessary financial burden on the country and drug toxicity on the patient, whereas underdiagnosis may lead to undertreatment of the patient leading to further drug resistance, treatment failure and spread of resistant strains to others. Till date, there are serious laboratory constraints due to lack of adequate infrastructure, technical manpower and finances. In India, the SRLN is located at Tuberculosis Research Centre (TRC), Chennai and this is the only laboratory in India that is accredited to perform second-line DST.[43] There is an urgent need for rapid scaling up of the laboratories to ensure proper diagnosis and management of MDR- and XDR-TB.

Delay in Diagnosis

Field diagnosis of MDR-TB is not possible at present and requires transportation of the patient's sputum to the

Intermediate reference laboratory (IRL) for diagnosis. In the IRL, culture is done on Lowenstein-Jensen medium and DST is carried out using the proportion method, which is considered to be the gold standard.[43] Cultures are very slow growing and often take 6 to 8 weeks to complete. Preliminary results from DOTS plus program in Gujarat and Maharashtra show that the average time delay for processing the sputum sample and getting back the DST results is at least three months.[44] During this time, patients may be inappropriately treated, drug-resistant strains may continue to spread and amplification of resistance may occur. In Gujarat, 20 out of 175 MDR-TB patients died prior to initiation of category IV regime while waiting for the DST results. Alarming reports of potential nosocomial transmission and rapid mortality in patients with HIV coinfection[29] have highlighted the need for rapid screening methods.

The Hain GenoType® MTBDR plus assay is a multiplex PCR line-probe assay that detects mutations in the rpoB gene for rifampicin resistance, the katG gene for high-level isoniazid resistance and the inhA gene for low-level isoniazid resistance, directly from smear-positive sputum. Results are available within one day.[45,46] This molecular assay is a highly accurate screening tool for MDR-TB and achieves a substantial reduction in diagnostic delay.

MANAGEMENT

No randomized controlled trial exists to address the issue of optimal management strategy for MDR-TB. The management of MDR-TB and XDR-TB is associated with numerous challenges.[47]

Pretreatment Evaluation and Counseling

Once the diagnosis of MDR-TB or XDR-TB is confirmed, the first challenge is to disclose the diagnosis to the patient and counsel the patient. Various issues need to be discussed like the nature of the disease, the nature of treatment he/she is about to undergo, the duration of treatment, the possibility of Adverse drug reactions (ADR), the need for strict adherence to treatment, the need for daily injections for at least 6 to 9 months and need for initial/subsequent hospitalization if needed. It is advisable to involve close family members during the counseling, since family support is an essential component in the management. Female patients should receive special counseling on family planning. The patients should be screened for comorbidities like diabetes mellitus, liver disease, renal insufficiency, drug or alcohol use, HIV, mental illness, thyroid disorders, pregnancy and lactation.

Treatment Strategy

Three different strategies can be used in the management of drug-resistant TB, viz: i. standardized treatment, ii. empirical treatment, or iii. individualized treatment.[48] Standardized treatment refers to the use of a fixed combination of drugs for treating all patients. The regimen is usually based on the DST profile of the population at large. Empirical treatment, on the other hand, uses those drugs to which the individual has not been previously exposed or received for less than one month and hence, presumed to be effective. Individualized treatment, on the other hand, is based on individual DST results and uses only those drugs with proven in vitro susceptibility. Initiation of an empirical regimen till DST results are available and then switching over to an individualized regimen is probably the best strategy to achieve the highest cure rates. Table 48.6 summarizes the basic differences between standardized and individualized regimes.

TABLE 48.6: Difference between standardized and individualized regimen

Standardized regimen	*Individualized regimen*
Same treatment regimen for all cases	Individualized regimen for each case
Based on representative DST of whole population	Based on previous H/O ATT and individual DST results. Uses the most effective drugs against the particular strain
Easier to implement on a programmatic scale	Difficult to implement on a programmatic scale
Low cure rates	Better cure rates
Cost and duration predictable	Expensive and duration may be extended based on lack of response

Designing an Appropriate Regimen

The exact number of drugs that are needed to cure MDR-TB and prevent the creation of further drug resistance is unknown.[4] Most studies had used regimens containing four to six second-line drugs, a prudent approach has given the high bacillary burden and chronic lesions among patients and the poor potency and penetration of second-line drugs.[49,50] The recommended duration of treatment is guided by smear and culture conversion. The minimal recommendation is that treatment should lasts for at least 18 months after culture conversion. Extension to 24 months may be indicated in patients with extensive pulmonary damage.[48]

The DOTS plus recommends the use of Standardized Treatment Regimen (STR) under the RNTCP program, comprising of 6 drugs (kanamycin, ofloxacin, ethionamide, pyrazinamide, ethambutol and cycloserine) during 6 to 9 months of the intensive phase and 4 drugs (ofloxacin, ethionamide, ethambutol and cycloserine) during the 18 months of the continuation phase.[43]

P-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (K, Ofl, Z and Eto) or any 2 bacteriostatic (E and Cs) drugs are not tolerated, but one must remember that extrapolating this standardized regimen to complicated, individual cases may result in treatment failures. The DOTS-plus program has been initiated in pilot phase in Gujarat and Maharashtra. Preliminary data from Gujarat shows encouraging results. Of 116 patients who have been placed on Category IV regime, 60 patients had completed nine months of treatment. In this cohort of 60 patients, 88.3% had achieved smear conversion and 68.3% had achieved culture conversion at the end of nine months.[44]

Studies that have achieved cure rates of more than 75% highlight the importance of using sufficient number of drugs at the highest possible dosages for the maximum duration.[49,50] An aggressive approach right from the start can help in achieving better outcomes. Table 48.7 summarizes the lessons learnt from these studies. These principles have to be adhered, when designing regimens for MDR or XDR-TB, to achieve the best possible outcomes.

TABLE 48.7: Lessons learnt from previous studies on MDR and XDR-TB that had achieved high cure rates

- Treat aggressively
- Use at least four drugs presumed to be effective
- Use the highest possible doses, limited only by adverse drug reactions
- Give drugs for the maximum possible duration
- Include as many first-line drugs as possible (especially in XDR-TB), even if *in vitro* susceptibility is absent
- Fluoroquinolones and aminoglycosides should be a part of any regimen
- Use later-generation fluoroquinolones, if there is resistance to earlier fluoroquinolones
- Use capreomycin if there is resistance to amikacin or kanamycin
- Use adjuvant drugs if there is inadequate response/marked drug resistance
- Use resective thoracic surgery in patients with inadequate response or treatment failure associated with limited disease and good pulmonary reserve.

Drugs for MDR-TB and XDR-TB

Table 48.8 gives a list of drugs available to treat MDR- and XDR-TB. Currently available second-line drugs used to treat MDR and XDR-TB are four to ten times more likely to fail than standard therapy for drug susceptible tuberculosis.[4] Many health care providers have little or no experience with second-line drugs and their side effects, especially in combinations of 4 to 6 at a time. Most second-line drugs have a short shelf life, global production of quality assured drugs is limited and drug registration may be a lengthy and costly process that is not always attractive to drug manufacturers.[43] In addition, drugs may need to be changed often due to side effects, delayed DST results and poor response to treatment. After the introduction of rifampicin, no worthwhile antituberculosis drug with new

TABLE 48.8: Drugs to treat MDR and XDR-TB and their recommended dosages

Drug	*Daily dosage*
Aminoglycosides	
Streptomycin	15 mg/kg (750–1,000 mg)
Kanamycin	15 mg/kg (750–1,000 mg)
Amikacin	15 mg/kg (750–1,000 mg)
Capreomycin	15 mg/kg (750–1,000 mg)
Thioamides	
Ethionamide	10–20 mg/kg (500–750 mg)
Prothionamide	10–20 mg/kg (500–750 mg)
Pyrazinamide	20–30 mg/kg (1,200–1,600 mg)
Fluoroquinolones	
Ofloxacin	7.5–15 mg/kg (600- 800 mg)
Levofloxacin	500–1000 mg
Moxifloxacin	400 mg
Ethambutol	15–20 mg/kg (1,000–1,200 mg)
Cycloserine†	15–20 mg/kg (500–750 mg)
Terizodone†	15–20 mg/kg (600 mg)
Para-aminosalicylic acid	150 mg/kg (10–12 g)
Adjuvant drugs	Dosages not standardized
Amoxicillin-Clavulanate	
Rifamycin derivatives	
Rifapentine	
Rifabutin	
Macrolides	
Clarithromycin	
Telithromycin	
Oxazolidinediones	
Linezolid	

†Pyridoxine should be administered at a dose of 50 mg/250 mg of cycloserin or trizodone

Table 48.9: Newer antituberculosis agents currently under development

Diarylquinoline
TMC207 (Previously R207910)
Nitroimidazopyran
PA-824
Nitro-dihydroimidazo-oxazole
OPC 67683
Pyrrole
LL3858, LL3522
Macrolides
Clarithromycin
Telithromycin
Oxazolidinones
Linezolid
PNU-100480
Diamine
SQ109
Ring-substituted imidazoles

mechanism(s) of action has been developed in over thirty years, but many newer agents are under development and some are already in clinical trials. Table 48.9 gives a list of these newer antituberculosis agents. Among these, the nitroimidazopyran PA-824 and the diarylquinoline TMC207 (previously R207910) are promising new agents.[51,52]

The diarylquinoline TMC207 offers a new mechanism of antituberculosis action by inhibiting mycobacterial ATP synthase. A recent phase II randomized placebo-controlled trial compared the efficacy and safety of this agent in combination with standard five-drug, second-line antituberculosis regimen.[53] The addition of TMC207 to standard therapy for MDR-TB reduced the time to conversion to a negative sputum culture, as compared with placebo and increased the proportion of patients with conversion of sputum culture (48% vs 9%). Most adverse events were mild to moderate and only nausea occurred significantly more frequently among patients in the TMC207 group than among patients in the placebo group (26% vs 4%). Another multicenter international trial, involving our center, is ongoing to evaluate the safety and efficacy of TMC207 in MDR-TB (NCT00449644).

The role of linezolid in drug-resistant, TB has evoked considerable interest. Although *in vitro* studies have shown the good activity of linezolid against different species of mycobacteria, clinical experience with the use of linezolid in the management of mycobacterial infections is still sparse. Some case series have reported good efficacy of linezolid against MDR and XDR-TB.[54,55] Studies have shown that linezolid (600 mg twice daily in adults) is safe and generally well tolerated for courses of therapy of less than 28 days, but long-term linezolid use has been associated with reversible hematopoietic suppression, primarily thrombocytopenia and neuropathy.[56,57] Undoubtedly, linezolid is a valuable drug to the armamentarium of antituberculosis agents, but long-term studies are required to conclusively prove the efficacy and safety of linezolid in MDR and XDR-TB.

Adverse Drug Reactions

Adverse drug reactions are an important cause of poor compliance and default.[58] Adverse drug reactions sometimes warrant stoppage of the offending drug and further curtail drug options. Even in short-course chemotherapy for drug sensitive TB, side-effects, such as hepatitis, dyspepsia, skin reactions and arthralgia were responsible for the termination of therapy in up to 23% of patients during the intensive phase.[59] The side-effect profile of TB chemotherapy is magnified in patients with concurrent HIV infection or prior history of hepatitis,[60] and those being treated with second-line drugs for MDR-TB, during which as many as 86% of patients may develop medication side-effects.[61] Table 48.10 gives a list of the common adverse-drug reactions encountered during treatment of MDR and XDR-TB.

To minimize the adverse impact of medication side-effects in treatment adherence, it is important that TB health staffs are adequately trained on their recognition and management. It is also important that medications for managing side-effects should be ordered concurrently with the ordering of anti-TB chemotherapy to facilitate timely and adequate treatment of such side effects.

Follow-up and Monitoring

Close follow-up and monitoring is mandatory for patients with MDR and XDR-TB to ensure strict compliance to the regime, prompt identification and management of adverse drug reactions and early detection and treatment of treatment failure. Directly Observed Treatment (DOT) is integral for close follow-up and monitoring.[43] Monitoring of patients on MDR- and XDR-TB treatment requires not only careful clinical examination, but also appropriate laboratory investigations like chest radiographs, renal and liver function tests, serum electrolytes and thyroid profile at appropriate time intervals for prompt identification of adverse reactions.

Follow-up sputum smear and culture schedule during treatment is as follows: Four sputa are to be

TABLE 48.10: Common adverse events of drugs used in MDR and XDR-TB

Drug	*Adverse event(s)*
Aminoglycosides	
Streptomycin	Pain at injection site, ototoxicity (vertigo and deafness), nephrotoxicity, hemolytic anemia, aplastic anemia, agranulocytosis, thrombocytopenia, and lupoid reactions
Kanamycin	
Amikacin	
Capreomycin	Hypokalemia, hypocalcemia and hypomagnesemia, cutaneous reactions and occasionally hepatotoxicity
Thioamides	
Ethionamide	Epigastric discomfort, anorexia, nausea, metallic taste and sulfurous belching, vomiting and excessive salivation; psychotic reactions including hallucinations and depression; hypoglycemia, hypothyroidism and goiter; hepatotoxicity; gynecomastia, menstrual disturbance, impotence, acne, headache and peripheral neuropathy; tolerance varies with ethnicity; usually well tolerated in Africa and Asia
Prothionamide	
Pyrazinamide	Hepatotoxicity, GI intolerance, hyperuricemia and arthralgias
Fluoroquinolones	
Ofloxacin	Uncommon GI disturbance (e.g. anorexia, nausea, vomiting), CNS symptoms (e.g. dizziness, headache, mood changes and rarely convulsions), QT interval prolongation
Levofloxacin	
Moxifloxacin	
Ethambutol	Dose-dependent optic neuritis and peripheral neuritis
Cycloserine	Dizziness, slurred speech and convulsions
Terizodone	Headache, tremor, insomnia, confusion, depression and altered behavior, suicide risk, generalized hypersensitivity reaction or hepatitis
Para-aminosalicylic acid	GI disturbance (e.g. anorexia, nausea, vomiting, abdominal discomfort and diarrhea), general skin or other hypersensitivity, and hepatic dysfunction, hypokalemia, hypothyroidism and goiter; best avoided in renal failure as it may exacerbate acidosis; sodium salt should not be given when a restricted sodium intake is indicated
Linezolid	Hematological (anemia, thrombocytopenia), peripheral neuropathy
TMC207	Nausea, QT interval prolongation

collected and examined by smear and culture at least thirty days apart from 3rd to 7th month of treatment (i.e. at the end of the months 3, 4, 5, 6 and 7) and at 3-month intervals from the 9th month onwards till the completion of treatment (i.e. at the end of the months 9, 12, 15, 18, 21 and 24).[43] The importance of the sputum examination during treatment needs to be emphasized, since the most important objective evidence of improvement is the conversion of sputum smear and culture to negative.

Patients will be considered culture converted after having two consecutive negative cultures taken at least one month apart. Patients who remain culture positive despite nine months of regular treatment are suspects of treatment failure and DST for second-line drugs should be done. An MDR-TB patient who has completed treatment and has been consistently culture negative with at least five consecutive negative results in the last 12 to 15 months is considered to be cured. If one follow-up positive culture is reported during the last three quarters, patient will still be considered cured, provided this positive culture is followed by at least three consecutive negative cultures, taken at least 30 days apart, provided that there is clinical evidence of improvement.[43]

ROLE OF IMMUNOTHERAPY

Various modalities have been tried to enhance the immune system of the body to fight off the tubercle bacillus. Favorable results were observed when immuno-enhancement using *Mycobacterium vaccae* vaccination was used to treat drug-sensitive pulmonary TB patients in Africa,[62] but very few studies have been conducted in drug-resistant TB patients to support its use.[63] Studies have shown that adjuvant therapy with *Mycobacterium welchii* vaccination along with anti-TB drugs was well-tolerated and facilitated early sputum conversion.[64,65] Aerosolized IFN-gamma, granulocyte-macrophage colony-stimulating factor, aerosolized IFN-alpha and low-dose recombinant human interleukin-2 have all been used as adjunctive therapy in the treatment of MDR-TB with conflicting results.[4] Although no definite recommendations are possible at this juncture, trials are ongoing and immunotherapy stands as a promising agent of the future.

RESECTIVE THORACIC SURGERY

The use of resective thoracic surgery alone or as a part of comprehensive treatment strategy has been shown to be associated with improved outcomes in drug-resistant TB.[66,67] Various surgical procedures have been performed in patients with MDR-TB ranging from segmental resection to pleuropneumonectomy. A combined medical and surgical approach is increasingly being used to treat patients with MDR-TB. The cure rate with surgical resectioning as an adjunct to medical therapy approximates 83 to 93% in some published series.[68,69] The principle behind surgical treatment is that it reduces the bacterial burden by resecting cavitary lesions or destroyed lobes. It is important to note that at least three months of treatment should be given before surgery, if feasible.

Indications for surgery in patients with MDR-TB include: (i) persistence of culture-positive MDR-TB despite extended drug retreatment, (ii) extensive patterns of drug resistance that are associated with treatment failure or additional resistance, (iii) local cavitary, necrotic/destructive disease in a lobe or region of the lung that is amenable to resection without producing respiratory insufficiency and/or severe pulmonary hypertension.

Surgery for TB requires highly experienced surgeons, as well as appropriate preoperative and postoperative care, trained support personnel and specialized facilities with the availability of safe blood transfusion services. Specialized facilities should also include stringent infection control measures since infectious substances and aerosols are generated in large quantities during surgery and during mechanical ventilation and postoperative pulmonary hygiene manipulations.

NUTRITIONAL SUPPORT

In addition to cause malnutrition, MDR-TB can be exacerbated by poor nutritional status, low body mass index and severe anemia.[48] Without nutritional support, patients can become enmeshed in a vicious cycle of malnutrition and disease. The second-line drugs may also further decrease the appetite, making adequate nutrition a greater challenge. Vitamin B_6 100 mg/day should also be given to all patients receiving cycloserine or terizidone to prevent adverse neurological effects.

Vitamin D has been shown to be involved in the host immune response towards *Mycobacterium tuberculosis*. Vitamin D was used for the treatment of TB in pre-antibiotic era.[70,71] Observational studies have found an association between vitamin D deficiency and active TB.[72,73] Vitamin D is a low-cost intervention that is easy to administer in resource-poor settings. The possible postulated mechanisms are that 1, 25-dihydroxy vitamin D induces anti-mycobacterial activity in macrophages by triggering antimicrobial peptides, such as cathelicidin,[74] but a recent randomized controlled trial has shown that vitamin D does not improve clinical outcomes or mortality in patients with TB.[75]

SPECIAL SITUATIONS

TB-HIV coinfection, pregnancy, breastfeeding, renal insufficiency, and liver, CNS, psychiatric and substance abuse disorders complicate the management of drug-resistant TB.

TB-HIV Coinfection

It is estimated that in India, almost 50% of individuals with HIV will develop TB during their disease course making it the most common opportunistic infection in our country.[76] HIV infection per sec does not appear to predispose a person to MDR-TB. Studies have shown that drug-resistant TB, including MDR-TB is not more common among HIV-infected persons compared to the general population.[77,78] Despite this, theoretically speaking HIV-infected individuals have a greater chance of developing MDR-TB due to the following reasons (i) increased susceptibility to TB, (ii) increased risk of nosocomial transmission, (iii) increased risk of treatment failure due to lack of compliance, drug interactions and malabsorption.

On the other hand, the mortality of drug-resistant TB in HIV-infected individuals is much higher than that of non-HIV infected individuals. The complexity and lethality of drug-resistant TB-HIV coinfection was shown in a recent study in South Africa, in KwaZulu-Natal province where 52 out of 53 HIV patients with XDR-TB died with a median survival of only 16 days from the time of diagnosis.[29]

Pregnancy

All female patients of childbearing age should be tested for pregnancy upon initial evaluation. Birth control is strongly recommended for all non-pregnant women receiving therapy for drug-resistant TB. Hamedeh and Glassroth reviewed the literature concerning over 2,000 pregnancies in mothers with TB and found no significant difference in side-effects in these women compared with non-pregnant subjects and no higher incidence of fetal abnormalities.[79] TB in pregnancy poses special challenges due to three issues. First is the use of chest radiography for diagnosis or follow-up risks radiation exposure to the developing fetus. Second, active TB per sec can lead to adverse outcomes in both mother and fetus. Third, the fetus is at the risk of teratogenic effects. Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester, considering the severity of the underlying disease. Aminoglycosides can be toxic to the developing fetal ear and should be avoided. Ethionamide has been shown to be teratogenic in animals and should be avoided.

Breastfeeding

In lactating mothers on treatment, most antituberculosis drugs will be found in the breast milk in concentration that would equalize only a small fraction of the therapeutic dose used in an infant. However, any effects on infants of such exposure during the full course of MDR-TB treatment have not been established. Therefore, when resources and training are available, it is recommended to provide infant formula options as an alternative to breastfeeding. The mother and her baby should not be completely separated. However, if the mother is sputum smear-positive, the care of the infant should be left to family members until she becomes sputum smear-negative, if this is feasible. When the mother and infant are together, this common time should be spent in well-ventilated areas or outdoors. In some settings, the mother may be offered the option of using a surgical mask or an N-95 respirator until she becomes sputum smear-negative.

Tuberculosis in Prisons

Since early 1990s, TB outbreaks in prisons have been reported in many countries in Eastern Europe and TB strains transmitted in prisons are more likely to be drug-resistant or associated with HIV coinfection. A recent survey found a mean TB notification rate of 232 per 1, 00,000 prisoners in Europe, the highest rates being in Kazakhstan (17,808) and Azerbaijan (3,944).[80] A higher proportion of TB patients among prisoners had MDR strains than those outside prison. A cross-sectional survey was undertaken of 600 patients in Russia (309 civilians, 291 prisoners) with pulmonary TB from 2001-2002. Prevalence of MDR-TB was 37% in new prison cases and 55% in previously treated cases compared to that of 20% and 46% in civilian cases, respectively.[81]

Prisons are high-risk environments for TB transmission because of overcrowding, poor nutrition, poor ventilation and limited access to often insufficient health care. Moreover, prisoners do not represent a mere cross-section of society in general. Prisoners who are overwhelmingly male, are typically aged 15–45 years and come predominantly from poorly educated and socioeconomically deprived sectors of the population where TB infections and transmissions are higher.[82] Prisoners are also more likely to suffer from other debilitating diseases and have additional health problems such as drug addiction, alcoholism and liver disease. All these pose challenges to management and lead to poor outcomes in TB in prisons.

Tuberculosis and Air Travel

There is increasing concern among public health agencies and the public about the potential transmission of TB during air travel. The WHO guidelines recommend the tracing and screening of passengers exposed to people with pulmonary TB who sat in adjacent rows for longer than 8 hours and prohibit air travel in patients with pulmonary TB unless the patient has two consecutive negative sputum smears for drug-susceptible TB and two consecutive cultures for MDR-TB.[83] A recent systematic analysis of 13 studies involving TB during air travel found no evidence of transmission in majority of the studies.[84] Only two studies reported reliable evidence of transmission. The analysis suggests that there is a reason to doubt the value of actively screening air passengers for pulmonary TB. The resources that would be spent in such screening could be used for addressing other priorities in TB control.

PREVENTION OF NOSOCOMIAL TRANSMISSION OF MDR-TB

Numerous nosocomial outbreaks of TB have been reported and have often involved MDR strains of *Mycobacterium tuberculosis*.[85,86] In the outbreak in KwaZulu-Natal, South Africa, 85% of cases had a similar genotypic strain denoting nosocomial transmission of resistant TB strains. Table 48.11 lists the characteristics in a TB patient that increases the risk of infectiousness.

The CDC, Atlanta in 1990 made recommendations to try to prevent such nosocomial transmission.[87] These include isolation in a single room with negative pressure relative to the outside, with six air exchanges per hour,

TABLE 48.11: Characteristics in a TB patient that increases the risk of infectiousness

- Presence of cough
- Cavitation on chest radiograph
- Positive Acid-fast Bacilli (AFB) sputum smear result
- TB of the larynx (substantially infectious)
- Failure to cover the mouth and nose when coughing
- Incorrect, lack of or short duration of antituberculosis treatment
- Undergoing cough-inducing or aerosol-generating procedures (e.g. bronchoscopy, sputum induction and administration of aerosolized medications).

the room to be exhausted to the outside; consideration of ultraviolet lamps or particulate filters to supplement ventilation; use of disposable particulate respirators for persons entering the room and during cough inducing procedures. The CDC then published a draft guideline[88] proposing new measures to prevent nosocomial TB, including the use of respirators with high-efficiency particulate air filters (HEPA respirators) in isolation rooms for patients with possible tuberculosis.

Airborne Infection Isolation (AII) Room

Patients with suspected or confirmed TB disease should be placed in airborne infection isolation (AII) room, if available or in a separate room with the door closed, apart from other patients and not in an open waiting area. AII rooms should be single-patient in which environmental factors and entry of visitors and Health Care Workers (HCWs) are controlled to minimize the transmission of *M. tuberculosis*. All HCWs who enter an AII room should wear at least an N-95 disposable respirator. Visitors may be offered respiratory protection (i.e. N-95) and should be instructed by HCWs on the use of the respirator before entering an AII room. AII rooms have specific requirements for controlled ventilation, negative pressure and air filtration. Each inpatient AII room should have a private bathroom. AII rooms in existing healthcare settings should have an airflow of ≥6 air exchanges per hour. In future, new construction or renovation of health care settings should be designed so that AII rooms achieve an airflow of ≥12 air exchanges per hour.

High-Efficiency Particulate Air (HEPA) Filters

HEPA filters can remove at least 99.97% of airborne particles, 0.3 µm in diameter. Particles of this size are most difficult to filter and are thus considered the Most Penetrating Particle Size (MPPS). HEPA filters should be used; (1) when discharging air from local exhaust ventilation booths or enclosures directly into the surrounding room or area; and (2) when discharging air from an AII room (or other negative-pressure room) into the general ventilation system.

While AII rooms and HEPA filters are recommended by the CDC for preventing nosocomial spread of *M. tuberculosis*, it is questionable whether these recommendations could be adapted to our setting due to logistic and financial constraints.

Prophylaxis of MDR-TB Contacts

For contacts thought to be infected with *M. tuberculosis* that is resistant to both isoniazid and rifampicin, no satisfactory chemoprophylaxis is available.[89] There is no consensus regarding the choice of the drugs and the duration of treatment. The CDC has put forth guidelines for the management of persons exposed to MDR-TB.[90] The two suggested regimens for MDR-TB preventive therapy are as follows:

1. Pyrazinamide (25 to 30 mg/kg daily) plus ethambutol (15 to 25 mg/kg daily); or
2. Pyrazinamide (25 to 30 mg/kg daily) plus a quinolone with anti-TB activity (e.g. levofloxacin or ofloxacin). The recommended duration of therapy is 12 months for the patients with underlying immunosuppression and at least 6 months for all other patients. All patients should be closely observed for at least 2 years and a low threshold for referral to a center with experience in managing MDR-TB should be maintained. However, the WHO does not recommend chemoprophylaxis for contacts of MDR-TB due to uncertain efficacy and possibility of aggravating further drug resistance.

FINANCIAL BURDEN OF MDR-TB

The annual financial burden of TB to our country is at least US $ 3 billion (i.e. more than Rs 13,000 crore).[91] The use of second-line drugs on a large programmatic scale will further impose a heavy financial burden. The cost is also increased by the need for improved laboratory capabilities, rigorous follow-up and monitoring of adverse events. This huge challenge was addressed by the WHO in 2000, when the Green light committee (GLC) was formed to successfully negotiate prices of drugs with manufacturers and provide quality assured second-line drugs at concessionary prices to financially burdened countries. In 2002, the GLC was adopted by the newly established Global Fund to Fight Acquired Immunodeficiency Syndrome (AIDS), Tuberculosis and

TABLE 48.12: Cost of treatment with second-line drugs

Type of DR-TB (Resistance to)	*Regimen*	*Estimate using the lowest prices*[#]	*Estimate using the highest prices*[#]
MDR-TB (HRS)	3KEtZOE/18EtOE 3CaEtZOE/18EtOE	20,863.00 32,387.00	77,277.00 88,674.00
MDR-TB (HRSE)	3KEtZOCy/18EtOCy 3CaEtZOCy/18EtOCy	26,533.00 38,057.00	1,70,643.00 1,82,040.00
MDR-TB	6KOEtCyZE/18OEtCsE*	1,30,860.00	2,73,060.00

Ca = capreomycin; Cy = cycloserine; E = ethambutol; Et = ethionamide; K = kanamycin; O = ofloxacin; Z = pyrazinamide

* DOTS plus recommended standardized regimen

# Drug prices obtained from Current Index of Medical Specialities (CIMS) and Advance Drug Review (ADR), 2008.

Malaria (GFATM) and today it is the leading financial mechanism supporting the management of MDR-TB in resource-constrained settings. While the standard short-course chemotherapy with isoniazid, rifampicin, pyrazinamide and ethambutol may cost Rs 1900/-, the cost of treatment with second-line drugs works out to be several times more (Table 48.12).

There is no data from India on the feasibility and cost-effectiveness of using second-line drugs to treat patients with drug-resistant TB. A feasibility and cost-benefit analysis was conducted as a part of the national program to treat chronic TB in Peru in 1997.[92] The regimen used was a directly observed standardized 18-month daily regimen, consisting of kanamycin (3 months only), ciprofloxacin, ethionamide, pyrazinamide and ethambutol. The program resulted in a cost of US $ 06 million per year, i.e. 8% of the national tuberculosis program budget and US $ 2381 per patient for those who completed treatment. In the highest cost scenario, in which individualized treatment was assumed to cost US $ 1,00,00 per patient, total annual costs were between US $ 13 million and US $ 20 million and around one-quarter to one-third of the national tuberculosis program budget. Thus, standardized regimes are relatively much cheaper compared to individualized regimes albeit at a price of lower efficacy.

CURE RATES IN MDR-TB AND XDR-TB

Treatment of drug-sensitive TB with traditional first-line agents is associated with excellent cure rates. Short course chemotherapy has been shown to cure 94 to 97% of patients with resistance to streptomycin, isoniazid or to both drugs.[93] On the contrary, the outcome of treatment of MDR-TB with short-course chemotherapy is extremely poor. Studies conducted at TRC, Chennai, had shown that 35 out of 38 patients with MDR-TB failed to respond to conventional regimens.[94] Table 48.13 shows the cure rates achieved in various studies on MDR-TB and XDR-TB.[95]

CONCLUSION

The global TB epidemic has been complicated by the emergence of multidrug and extensively drug-resistant strains of TB. Indiscriminate use of second-line drugs for treating MDR-TB has already given rise to the development of XDR-TB and if this practice goes uncurbed, it may soon emerge as the dominant TB strain throughout the world. Since drug resistance is a man-made phenomenon, every effort should be made to diagnose and treat drug-sensitive TB effectively at the grassroot level and prevent the development of drug resistance. MDR-TB and XDR-TB are pure laboratory diagnoses and therefore, require quality laboratory support for timely and accurate diagnosis. The treatment of MDR-TB is lengthy and costly and requires excellent patient compliance for prolonged periods for achieving acceptable cure rates. Studies in the recent past have shown that MDR-TB and even XDR-TB can be treated effectively with the currently available drugs and achieve a satisfactory outcome. Control of drug-resistant TB requires a strong health infrastructure to ensure delivery of effective therapy coupled with surveillance and monitoring activities, to enable timely intervention to limit transmission and spread of the disease.

TABLE 48.13: Treatment outcome in MDR-TB and XDR-TB

Study, year of publication	*Type of DR-TB*	*Treatment outcome*
Goble et al, 1993	MDR-TB [n = 171]	Cured = 65% Treatment failure = 35%
Sharma et al, 1996	MDR-TB [n = 19]	Sputum smear conversion = 18/19 (94.7%)
Park et al, 1998	MDR-TB [n = 107]	Cured = 82.5% Treatment failure = 17.5%
Yew et al, 2000	MDR-TB [n = 63]	Cured = 81% Treatment failure = 14.3%
Kim et al, 2001	MDR-TB [n = 1011]	Cured = 48% Treatment failure = 8.1% Default = 39%
Tahaoglu et al, 2001	MDR-TB [n = 158]	Cured or completed treatment = 77% Treatment failure = 8%
Mitnick et al, 2003	MDR-TB [n = 75]	Cured = 83% Death = 8%
Nathanson et al, 2006	MDR-TB [n = 1047]	Cured or completed treatment = 69.7% Treatment failure = 6.7%
Gandhi et al, 2006	XDR-TB [n = 53]	Death = 52/53 (98.1%) HIV positive = 44/44 tested
Sharma, 2007	MDR-TB [n = 172] XDR-TB [n = 1]	Cured = 41.6% Treatment failure = 38.7%
Dhingra et al, 2008	MDR-TB [n = 27]	Cured = 48% Default = 37%
Shean et al, 2008	MDR-TB [n = 491]	Cured or completed treatment = 49% Treatment failure = 5% Default = 29%
Masjedi et al, 2008	MDR-TB [n = 43]	Cured/completed treatment = 67.5% Death = 18.6%
Mitnick et al, 2008	XDR-TB [n = 48] MDR-TB [n = 603]	Cured or completed treatment = 60.4% of XDR-TB; Treatment failure = 10.4% of XDR-TB;Cured or completed treatment = 66.3% of MDR-TB; Treatment failure = 2.1% of MDR-TB
Bonilla et al, 2008	XDR-TB [n = 43]	Cured or completed treatment = 49% Death = 19%
Kwon et al, 2008	XDR-TB [n = 27] MDR-TB [n = 128]	Cured or completed treatment = 65% of XDR-TB Cured or completed treatment = 66% of MDR-TB Treatment failure = 14% overall
Banerjee et al, 2008	XDR-TB [n = 18] MDR-TB [n = 406]	Completed treatment = 41.2% XDR-TB Death = 29.4% XDR-TB
Keshavjee at al, 2008	XDR-TB [n = 29] MDR-TB [n = 579]	Cured or completed treatment = 48.3% of XDR-TB; Treatment failure = 31% of XDR-TB; Cured or completed treatment = 66.7% of MDR-TB; Treatment failure = 8.5% of MDR-TB

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Revised National Tuberculosis Control Programme in India—DOTS and DOTS Plus*

D Behera

INTRODUCTION

Tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, and rarely by other organisms of the "tuberculosis complex".

Tuberculosis is most commonly transmitted by inhalation of infected droplet nuclei, which are discharged in the air when a patient with untreated sputum-positive TB coughs or sneezes. If the bacillus succeeds in infecting a person, only about 5 to 10% of such infected persons (primary infection) develop active disease. In the remaining 90 to 95% of infected persons, initial infection usually goes unnoticed. Tuberculin sensitivity appears within a few weeks of infection and initial lesions commonly heal leaving no residual changes except occasional pulmonary or tracheobronchial lymph node calcifications (primary complex). Infection occurs almost exclusively through the respiratory route. The infection may then spread from the primary lung lesion to any part of the body via the blood stream, lymphatic and bronchial systems.

Postprimary TB (active TB disease) arises from endogenous reactivation of latent foci, which remained dormant since the initial infection or exogenous reinfection. Postprimary TB usually affects the lungs (more than 85%), but can involve any part of the body. Pulmonary TB which is sputum smear-positive is highly infectious and should receive topmost priority for treatment. Cases which are smear-negative are much less infectious than those, which are smear-positive. Extrapulmonary TB can affect the lymph nodes, pleura, bones and joints, the genitourinary tract, the nervous system (meningitis), intestines, etc. The precise diagnosis of some of the severe forms is a challenge to physicians as they present a symptom complex with extraordinary diversity. However, patients with extrapulmonary TB (without concomitant pulmonary TB) hardly ever spread the disease to others. If untreated, TB leads to death within two to three years in at least half the patients. About 20 to 25% have natural healing and 25 to 30% remain positive and continue to spread the disease in the community.

Extent of the Tuberculosis Problem

One-third of the global population is estimated to be infected with TB bacillus. The annual incidence of new cases of all forms of TB (pulmonary and extrapulmonary) worldwide is estimated to be approximately 8.8 million, of which about 95% occur in developing countries. Globally, it is estimated that 1.8 million people die from TB each year—the majority of them in developing countries.

Tuberculosis remains a major public health problem in India. About 40% of the population in India is estimated to be infected with TB bacillus. Every year approximately 1.8 million people develop TB and nearly 400,000 die from it. The annual incidence of smear-positive TB is estimated to be 75 per 100,000 population [based on Annual Risk of Tuberculous Infection (ARTI) study done for the four zones of the country from 2000 to 2003] India accounts for one-fifth of global incidence of TB and tops the list of 22 high TB burden countries.

TB kills more adults in India than any other infectious disease.

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*SK Jindal, R Agarwal. Oxygen Therapy. In: D Behera (Ed.) Revised National Tuberculosis Control Programme in India—Dots and Dots Plus, 2nd edition. New Delhi: Jaypee Brothers Medical Publishers; 2008. pp. 585-623.

In India, everyday:

- More than 5,000 develop TB disease
- More than 1,000 people die of TB (i.e. 1 death every 1.5 minutes).

Tuberculosis is a barrier to socioeconomic development. It is estimated that the annual cost to society and the country due to TB amounts to nearly US$ 3 billion in indirect costs and US$ 300 million in direct costs. The greatest burden of tuberculosis incidence and mortality in India is in adults aged 15 to 60 years, which include the most productive members of society. TB affects more men than women, but still kills more women than all causes of maternal mortality put together.

Every Year due to TB (As per Estimates Made in 1997)

- More than 170 million work-days are lost
- Nearly 300,000 school children dropout from the schools
- More than 100,000 women are rejected by their families.

The Human Immunodeficiency Virus (HIV) epidemic has the potential to worsen the TB situation, increasing the number of TB cases and accelerating the progression of TB infection to active disease. It is estimated that 50 to 60% of HIV-infected people will develop TB disease in their lifetime when compared to 10% of HIV-negative persons infected with TB.

Another challenge to TB control in India is MDR-TB. Fortunately the data available to date shows that the levels of MDR-TB remain relatively low, at around 3%, amongst new patients and 12% in retreatment cases. However, these relatively low percentage figures translate into large absolute number of MDR-TB cases, who can transmit their drug resistant disease to others and require effective treatment.

Childhood TB is a reflection of the prevalence of sputum smear-positive Pulmonary Tuberculosis (PTB) and the extent of transmission of TB infection in the community. The incidence of TB in children is less compared to adults, but they are likely to suffer from more serious forms of TB and may die if not treated properly.

TB Control in India

The National Tuberculosis Programme of India (NTP) was initiated in 1962, based on the research by Tuberculosis Research Centre, Chennai and National TB Institute, Bengaluru. The national program was designed for domiciliary treatment using self-administered standard drug regimens. A large network of District TB centers were created with trained staff and infrastructure. Despite the existence of the NTP, there was little impact on the TB burden till 1992. A combined review of the program in 1992 concluded that the NTP could not achieve the objectives because of low priority, managerial weaknesses, over dependence on X-rays for diagnosis and inadequate funding. Incomplete treatment was the norm rather than exception due to the low rates of treatment adherence and lack of supervision.

On the recommendations of an expert committee, a revised strategy to control TB was pilot-tested in 1993 in a population of 2.35 million and thereafter increased in phased manner. A full-fledged program was started in 1997 and rapidly expanded with excellent results. This Revised National Tuberculosis Control Programme (RNTCP) uses the Directly Observed Treatment Short-Course (DOTS) chemotherapy strategy, which is based on results of tuberculosis research done in India. By June 2005, the RNTCP had covered more than 1 billion population (more than 90% of the country was covered) and whole of the country was expected to be covered by 2005 end. Since the inception of RNTCP and up to June 2005, more than 4.5 million patients were initiated on treatment and about 750,000 additional lives were saved.

REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME

Objectives of the RNTCP

The Goal of the RNTCP is to decrease mortality and morbidity due to TB and reduce the transmission of infection until TB ceases to be a major public health problem. The goal is achieved through the following objectives. The Objectives of the RNTCP are:

1. To achieve and maintain a cure rate of at least 85% among newly detected infectious (new smear-positive) cases.
2. To achieve and maintain detection of at least 70% of such cases in the population.

Effort should be made to first achieve the objective 1 and then make additional efforts to meet the objective 2.

TB can be controlled by early detection and effective treatment of infectious pulmonary TB cases who act as the sources of infection. Thus the basic curative as well as preventive strategy is the treatment of infectious TB patients until cure. The priority for treatment are newly diagnosed, sputum-positive pulmonary tuberculosis cases, as they are the main sources of infection and are more likely to die unless effectively treated.

The RNTCP is based on the DOTS strategy, which is the internationally recommended strategy of choice for

TB control. The DOTS strategy has the following five components:

- **Sustained political commitment** to increase human and financial resources and make TB control a nation-wide activity integral to national health system.
- **Access to quality-assured TB sputum microscopy** for case detection among persons presenting with, or found through screening to have, symptoms of TB (most importantly prolonged cough).
- **Standardized short-course chemotherapy** to all cases of TB under proper case management conditions, including direct observation of treatment—proper case management conditions imply technically sound and socially supportive treatment services.
- **Uninterrupted supply of quality-assured drugs** with reliable drug procurement and distribution systems.
- **Recording and reporting system enabling outcome assessment** of each and every patient and assessment of the overall program performance.

Directly Observed Treatment, in which a trained peripheral health worker or community volunteer watches as patients swallow all medicines, is fundamental to ensuring cure. DOT should be ensured for every dose in the intensive phase of treatment and at least the first dose of the week in the continuation phase. DOT is one of the five components of the DOTS strategy.

The diagnosis and treatment of TB are functions of the general health services and hence a part and parcel of Primary Health Care. At the District Level, the District Tuberculosis Centre (DTC) acts as the nodal center for planning, training, logistics, quality control, monitoring and supervision.

Early detection of disease should be done in all symptomatic patients reporting to the general health services with cough of duration of three weeks or more by the examination of three sputum smears for AFB. Contacts of smear-positive cases should also be evaluated. Sputum examination and treatment of TB, including anti-TB drugs are provided free of charge under the program. The outcome of treatment is evaluated by the analysis of the results of quarterly cohorts of all registered cases.

Organizational Structure and Functions

The structure of RNTCP comprises of five levels: National level, state level, district level, subdistrict level and peripheral health institution level.

National Level

At the central level the Revised National TB Control Programme is managed by Central TB Division of Directorate General Health Services, the technical arm of the Ministry of Health and Family Welfare (MoHFW). A National Programme Manager, Deputy Director General TB (DDG TB), is in charge of the tuberculosis program for the entire country. The Joint Secretary from the administrative arm of the MoHFW looks after the financial and administrative control of the program. The Central TB Division (CTD) is assisted by three national tuberculosis institutes, namely, National Tuberculosis Institute (NTI), Bengaluru; Tuberculosis Research Centre (TRC), Chennai; and Lala Ram Sarup (LRS) Institute of Tuberculosis and Respiratory Diseases, New Delhi.

Organizational structure at central level is shown in Flow chart 49.1.

Central TB Division has five units to manage various program activities. These units are headed by the Chief Medical Officer (CMO) of the rank of Deputy Program Manager (DPM) and assisted by other technical and secretarial staff. The five units are as mentioned below:

1. Supervision, monitoring and epidemiological surveillance unit
2. Human resource development unit
3. Procurement, supply and logistic unit
4. Finance unit
5. Advocacy and IEC unit.

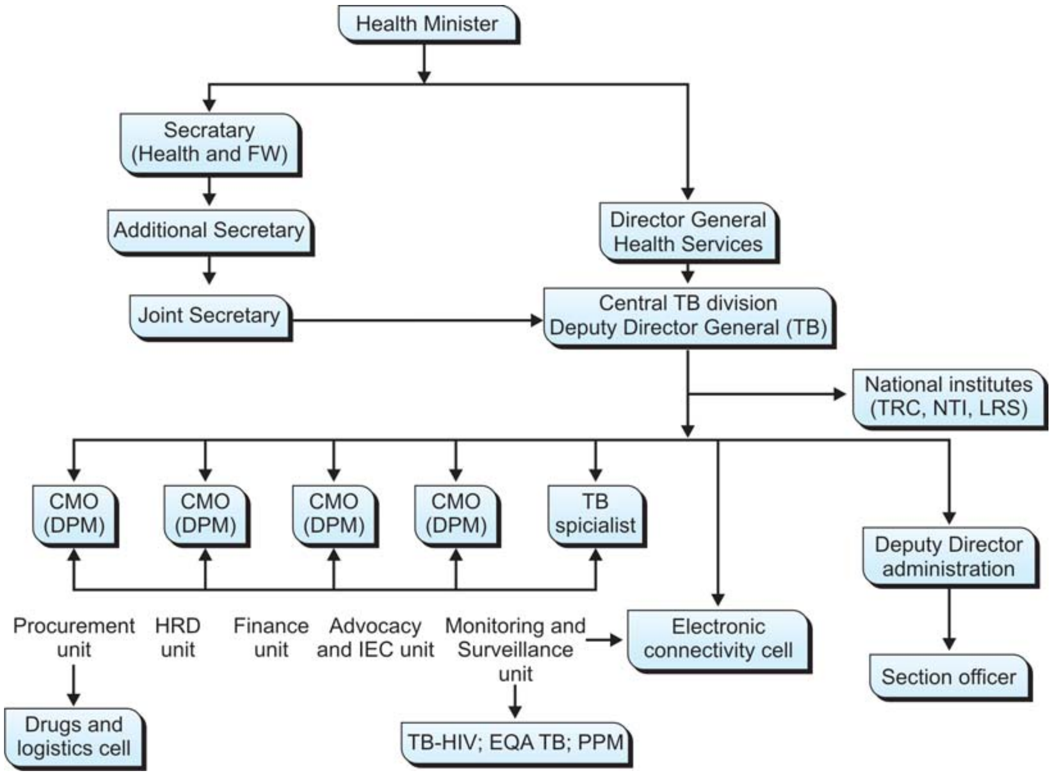
State Level

At the State level, the State Tuberculosis Officer (STO) is responsible for planning, training, supervising and monitoring the program in their respective states as per the guidelines of the State TB Control Society or its equivalent (STCS or its equivalent). The STO based at the State TB Cell is administratively answerable to the State Government and technically follows the instructions of the CTD, and coordinates with CTD and the districts for executing the duties mentioned above. There should be a full-time STO trained in RNTCP for each state.

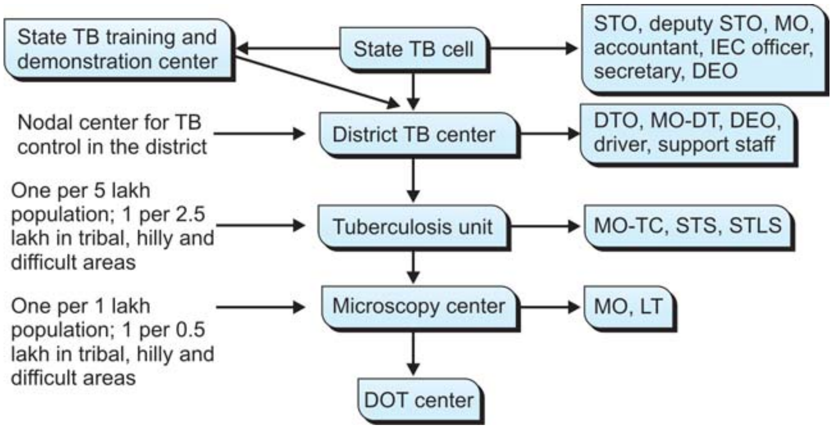
With the rapid expansion of the program, MoHFW has restructured and strengthened the functions of the STCS or its equivalent. The States have increased ownership and accountability for implementation. Capacity building and decentralization are taking place in the technical, financial as well as logistic aspects of the program. The States, via the STCS or its equivalent, are now directly responsible for monitoring and supervising the work of District TB Control Societies (DTCS) or its equivalent.

Structure of RNTCP at the state level is shown in Flow chart 49.2.

Flow chart 49.1: Organizational structure: Central level


Health Minister
Secratary (Health and FW)
Additional Secretary
Joint Secretary
Director General Health Services
Central TB division Deputy Director General (TB)
National institutes (TRC, NTI, LRS)
CMO (DPM)
CMO (DPM)
CMO (DPM)
CMO (DPM)
TB spicialist
Deputy Director administration
Procurement unit
HRD unit
Finance unit
Advocacy and IEC unit
Monitoring and Surveillance unit
Electronic connectivity cell
Section officer
Drugs and logistics cell
TB-HIV; EQA TB; PPM

Flow chart 49.2: Structure of RNTCP at the state level


State TB training and demonstration center
State TB cell
STO, deputy STO, MO, accountant, IEC officer, secretary, DEO
Nodal center for TB control in the district
District TB center
DTO, MO-DT, DEO, driver, support staff
One per 5 lakh population; 1 per 2.5 lakh in tribal, hilly and difficult areas
Tuberculosis unit
MO-TC, STS, STLS
One per 1 lakh population; 1 per 0.5 lakh in tribal, hilly and difficult areas
Microscopy center
MO, LT
DOT center

Functions of the State TB Cell

In major states of the country, a State TB Training and Demonstration Centre (STDC) supports the State TB cell. The STDC has three units—a training unit, supervision and monitoring unit and an IRL supporting an effective Quality Assurance system of the RNTCP Sputum smear microscopy network in the State.

Functions of the STDC

The **State TB Cells** have been provided with equipment, infrastructure and contractual staff to carry out its activities. The staff at the STC includes the State TB Officer, Deputy State TB Officer, Medical Officer STC, State IEC Officer, State Accountant, Secretarial Assistant, Pharmacist and Data Entry Operator.

State Drug Stores (SDS) for anti-TB drugs are essential for the effective management of drugs logistics. For the long-term sustainability of the program, decentralization of many aspects of drug management to the states has been done. One SDS (@ 1 per 50 million population) is established in all major states and in those states where management of drug logistics is difficult, e.g. hilly areas, difficult to access areas and areas prone to natural calamities.

District Level

The district is the key level for the management of primary health care services. The district level (or municipal corporation level) performs functions similar to those of the state level in its respective area. The Chief District Health Officer (CDHO)/Chief District Medical Officer (CDMO) or an equivalent functionary in the district is responsible for all medical and public health activities, including control of TB. The District Tuberculosis Centre (DTC) is the nodal point for TB control activities in the district. In RNTCP, the primary role of the DTC has shifted from a clinical one to a managerial one. The District TB Officer (DTO) at the DTC has the overall responsibility of management of RNTCP at the district level as per the program guidelines. The DTO is also responsible for involvement of other sectors in RNTCP and is assisted by an MO, Statistical Assistant and other paramedical staff. For each district, there should be a full-time DTO, who is trained in RNTCP at a central level institution.

Subdistrict Level (Tuberculosis Unit Level)

A major organizational change in RNTCP is the creation of a subdistrict level (Tuberculosis Unit). The Tuberculosis Unit (TU) will consist of a designated Medical Officer-Tuberculosis Control (MO-TC) who does tuberculosis work in addition to his/her other responsibilities, as well as two full-time supervisory staff for tuberculosis work—a Senior Treatment Supervisor (STS) and a Senior Tuberculosis Laboratory Supervisor (STLS). TUs are generally based in a Community Health Centre (CHC), Taluk Hospital (TH) or Block Primary Health Centre (BPHC). The team of STS and STLS at the Tuberculosis Unit Level (TU level) are under the administrative supervision of the DTO/MO-TC. The TU covers a population of approximately 5,00,000 (2,50,000 in tribal, desert, remote and hilly regions). The TU will have one Microscopy Centre for every 100,000 population (50,000 in tribal, desert, remote and hilly regions) referred to as the Designated Microscopy Center (DMC). DMCs are also provided in medical colleges, corporate hospitals, ESI, railways, Nongovernmental Organizations (NGOs), private hospitals, etc. depending upon requirements. The TU is responsible for the accurate maintenance of the Tuberculosis Register and timely submission of quarterly reports to the district level. The TU is the nodal point for TB control activities in the subdistrict.

MO-TC at the TU has the overall responsibility of management of RNTCP at the subdistrict level and is assisted by the STS and STLS. The MO-TC is trained in RNTCP at a state level institution, preferably State TB Training and Demonstration Centre (STDC).

MO-TC is expected to undertake supervisory visits in the TU for seven days in a month.

Health Institutions (PHIs)

For the purpose of RNTCP, a PHI is a health facility, which is manned by at least a medical officer (even if the post is currently vacant). At this level are the dispensaries, PHCs, CHCs, referral hospitals, major hospitals, specialty clinics/hospitals (including other health facilities)/TB hospitals/Medical colleges within the district. All health facilities in the private/NGO sector participating in RNTCP are also considered as PHIs under the program. Some of these PHIs will also be DMCs. All PHIs with/without DMCs should submit a monthly PHI level report to the respective TUs and the district.

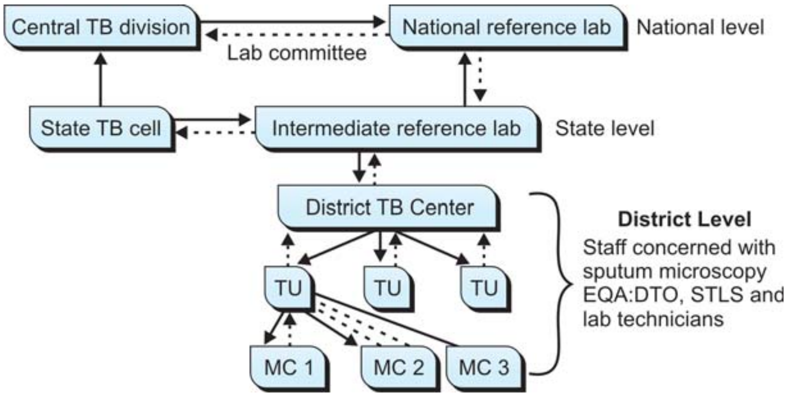
Case-finding and treatment of TB are integrated into the functions of the medical staff of government health services. The staff in specialized services, which support the program (DTC), has these functions in addition to supporting the DTO in the management of the program. In situations where more than one MO is posted in any of the peripheral health centers, one of them may be identified and entrusted with the responsibilities of the RNTCP.

TB Laboratory Services

The aims of the laboratory service are: (i) the diagnosis of cases, and (ii) monitoring of treatment.

The laboratory network for RNTCP in India consists of three designated National Reference Laboratories (NRLs) namely Tuberculosis Research Centre, Chennai; National Tuberculosis Institute, Bengaluru; and LRS Institute of Tuberculosis and Respiratory Diseases, Delhi (JALMA, Agra is the 4th NRL at present) about 24 IRLs at state level; and about 10,000 Microscopy Centers or peripheral laboratories. A nodal laboratory in each state will be designated as IRL. Usually the STDCs (State TB

Flow chart 49.3: Structure of RNTCP laboratory network



Training and Demonstration Centres) would be designated as IRL provided that they have a well functioning laboratory. Else, the state is to identify a Public Health Laboratory or Medical College Laboratory and designate that as the IRL after the laboratory is assessed by a visit from the NRL. The RNTCP microscopy centers in each district are the peripheral laboratories.

A Central Laboratory Committee has been constituted with the microbiologists of the three NRLs and CTD representatives as members. This committee works as a task force to guide laboratory-related activities of the program.

Structure of RNTCP Laboratory Network is shown in Flow chart 49.3.

The different levels of laboratories under RNTCP are as follows:

National Reference Laboratory: Each NRL will supervise sputum microscopy EQA of 8 to 11 states designated under them. The NRLs are internationally accredited laboratories as their EQA is being performed by a WHO reference laboratory for antituberculous drug susceptibility testing.

Intermediate Reference Laboratory: The states will designate one Intermediate Reference Laboratories in the STDC or medical college or in any Public Health Laboratory of the state. The IRL should be a facility deemed fit for accreditation by the respective NRL looking after the state. The designated IRL will conduct sputum microscopy EQA for the state and occasionally for a neighboring state or union territory based on an understanding between the two concerned STCSs or its equivalent/ CTD. The IRL will ensure proficiency of RNTCP staff for carrying out good quality diagnosis by providing technical training to district and sub-district technicians and STLS.

Designated Microscopy Center: Sputum microscopy diagnostic services under RNTCP are provided by Designated Microscopy Centers (DMC) established for every one lakh population (50,000 population in tribal and hilly areas). In addition the DMCs are also established at medical colleges, corporate hospitals, ESI, railways, NGOs, large private hospitals and other major hospitals.

The DMCs should satisfy the following criteria:

1. RNTCP-trained laboratory technician should be present.
2. Binocular microscope should be present in the laboratory.
3. Physical infrastructure in laboratory should meet RNTCP guidelines.
4. Daily new adult OPD of at least 60–100 and/or workload of at least three to five sputum smears per day for the laboratory technician in the laboratory.

DMCs in the public sector, at the onset of the program, were provided with funds to undertake minor civil works to build up their physical infrastructure and were provided with binocular microscopes.

In addition, before designating a DMC in other sectors, there should be a formal agreement by the hospital/laboratory to take part in the external quality assurance and to allow the concerned RNTCP staff for supervision as per RNTCP guidelines.

If the above criteria are met by any private laboratory, it can be considered for establishing as a DMC. However, the population norms for DMCs (one DMC per 100,000 population in the usual cases and 50,000 population in remote and difficult areas) should not prevent from designating a private hospital/laboratory as DMC if the decision is based on program needs and fulfillment of the above criteria.

Any laboratory/private health facility not fulfilling the above criteria may be considered for referral/ sputum collection center.

There is no provision from RNTCP for civil works, binocular microscope and LT for laboratories in private and NGO sectors. For such DMCs, the logistics, including laboratory consumables, registers and forms may be supplied from RNTCP as per guidelines. In exceptional cases provision of BMs may be considered for DMCs in other sectors by CTD.

Sputum Collection Centers

To improve access to diagnostic services in areas, such as the tribal, hilly, difficult to reach areas of the country sputum collection centers may be established. Collection and transport of sputum samples should be as per the RNTCP guidelines (refer section on "Diagnosis of Pulmonary Tuberculosis"). Each district shall identify such areas and plan for establishment of the sputum collection centers.

Private practitioners in urban and rural areas can also collect sputum samples and send to the nearest DMC as per PP scheme 1 (Refer guidelines on "Involvement of Private practitioners in RNTCP").

DIAGNOSIS OF PULMONARY TUBERCULOSIS

Tuberculosis affects the lungs in more than 85% of cases. This form of the disease is called pulmonary tuberculosis. Pulmonary tuberculosis is an infectious disease and spreads mainly by droplet infection. Sputum-positive pulmonary TB patients are the main source of infection. It is estimated that an untreated smear-positive pulmonary TB patient infects 10 to 15 persons annually. Therefore, it is very important to identify TB suspects and diagnose them early in order to effectively treat and make them noninfectious.

Identification of Tuberculosis Suspects

Most patients with TB visit health facilities promptly after symptoms occur. Hence, every adult patient with respiratory symptoms attending the health facility must be asked about symptoms suggestive of tuberculosis.

The most common symptom of pulmonary TB is a persistent cough for 3 weeks or more, usually with expectoration. It may be accompanied by one or more of the following symptoms, such as weight loss, chest pain, tiredness, shortness of breath, fever, particularly with rise of temperature in the evening, in some cases there will be blood in the sputum, loss of appetite and night sweats.

About 2 to 3% of new adult outpatients in a general health facility are expected to have cough for three weeks or more and on an average 10% of the suspects are expected to have sputum-positive pulmonary TB.

Case Finding Tools

The main tools for diagnosing pulmonary TB are sputum smear microscopy, chest X-ray, and culture of *M. tuberculosis* bacilli.

- *Sputum smear microscopy:* This is the primary tool for diagnosing TB as it is easy to perform at the peripheral laboratories, not expensive and specific with low inter and intra-reader variation. It is simple and requires minimum training. Can be used for diagnosis, monitoring and defining cure. Therefore, this is the key diagnostic tool used for case detection in RNTCP. If good diagnostic practices are followed, it is expected that at least 50% of the new pulmonary TB patients diagnosed will be smear-positive.
- *Chest X-ray:* X-ray as a diagnostic tool is sensitive, but less specific with large inter- and intra-reader variations. No shadow is typical of TB, 10 to 15% culture-positive cases remain undiagnosed and 40% patients diagnosed as having TB by X-ray alone may not have active TB disease. It is supportive to microscopy.
- *Culture:* Culture of *M. tuberculosis* bacilli is very sensitive and specific, but is expensive as it requires a specialized laboratory set-up and results are available only after several weeks. If available, culture of tubercle bacilli may be helpful, although in sputum-negative cases, a clinical decision to treat for TB based on X-ray findings and lack of response to broad-spectrum antibiotics would be more practical and also ensure prompt treatment. Culture and sensitivity testing is valuable for the diagnosis and management of drug-resistant tuberculosis, besides epidemiological surveillance and planning.
- *Tuberculin test:* Tuberculin test may be useful as an additional tool for diagnosing pediatric TB, in whom a positive test is more likely to reflect recent infection with TB and indicates a much higher risk of developing disease. However, the tuberculin test has no role in diagnosing adult pulmonary TB disease in India.

Case Finding Methods

- Examination of sputum of patients with symptoms suggestive of TB, who present on their own initiative at health facilities
- Promotion of awareness in the community, amongst the medical professionals and all medical staff

regarding respiratory symptoms, notably persistent cough for three weeks or more, and the need to obtain and examine there sputum specimens for the diagnosis of TB

- Examination of household contacts of smear-positive TB patients; irrespective of the duration of cough
- Examination of extrapulmonary TB cases with cough of any duration.

Diagnosis by Sputum Microscopy

A medical practitioner at a health facility screens patients and advises those who are suspected of having TB (cough for three weeks or more) to undergo sputum smear examination at the nearest RNTCP designated microscopy center. A laboratory form for sputum examination has to be filled and sent to the laboratory with the patient. The sputum specimen may be collected and transported to the laboratory if the patient is unable to travel to microscopy center.

Microscopic examination of sputum is, as a rule, the only way by which the diagnosis of pulmonary TB can be confirmed. Whenever TB is suspected, at least three specimens of sputum should be collected over 2 consecutive days and examined by microscopy. Only one laboratory form needs to be filled for all the three specimens of the patient.

Guidelines for Collecting Sputum for Smear Microscopy

- *First visit to the microscopy center:* When a TB suspect reports to the laboratory, a specimen is collected on the spot. She is given a sputum container with the laboratory serial number written on its side and is instructed to inhale deeply two to three times with his/her mouth open, cough out deeply from the chest, open the container, spit out the sputum into it and close the container tightly. This specimen is called a spot specimen. The patient is then given a similarly marked empty sputum container to collect a specimen early next morning and bring it to the laboratory. This specimen is called an early morning specimen.
- *Second visit to the microscopy center:* The early morning specimen brought by the patient is received and a further spot specimen is collected.

  Thus there will be three samples: SPOT-EARLY MORNING-SPOT. (Now two samples are required wef April, 2009)

  Obtaining a good sputum specimen is crucial for quality sputum microscopy. The following steps have to be observed to get good sputum specimen:

- *Tasks performed before sputum collection:* Before a health worker collects a sputum specimen, the reasons for sputum collection have to be explained to the patient. The laboratory technician/health worker must ensure that the patient's full address is entered in the laboratory form.
- *Tasks performed during sputum collection:* A specimen collected under the proper guidance of a health worker is likely to yield more conclusive results than one produced by a patient without any guidance. Sputum should preferably be collected in open air or in a vacant room with open windows. The health worker or the laboratory technician should stand behind the patient. The health worker should also ensure that no one stands in front of the patient. If a patient coughs out only saliva, she should be asked to try again to bring out sputum. Patient must be asked to rinse the mouth before bringing out the sputum samples.
- *Tasks performed after sputum collection:* Sputum specimens should be examined on the same day. In cases where sputum needs to be transported to a DMC, it must be examined within a week after collection. Storage of sputum samples should be in cool place/refrigerator. A smear is made, fixed and stained using the Ziehl-Neelsen staining technique.

If the first spot specimen is positive by microscopy and the patient does not return for the second sputum test, an immediate search must be made to find the patient to prevent the dissemination of infection in the community. In the interest of the patient, second and third specimens of sputum must be collected and examined. To facilitate this, it is important to note down the complete address of all symptomatic patients.

Smear Preparation, Staining and Reading

All specimens should be examined in the nearest designated microscopy center, as a rule, by the Ziehl-Neelsen method.

ZIEHL-NEELSEN STAINING PROCEDURE

1. A new unscratched slide is selected and the slide is labeled with the Laboratory Serial Number with a diamond marking pencil.
2. A smear is made from yellow purulent portion of the sputum using a broom stick. A good smear is spread evenly, 2 cm × 3 cm in size and is neither too thick nor too thin. The optimum thickness of the smear can be assessed by placing the smear on a

printed matter. The print should be readable through the smear. Smear preparation should be done near a flame. This is required, as six inches around the flame is considered as a sterile zone, which coagulates the aerosol raised during smear preparation.

3. The slide is allowed to air dry for 15 to 30 minutes.
4. The slide is fixed by passing it over a flame three to five times for three to four seconds each time.
5. One percent filtered carbol fuchsin is poured to cover the entire slide.
6. The slide is gently heated with carbol fuchsin on it, until vapors rise. Do not boil.
7. Carbol fuchsin is left on the slide for five minutes.
8. The slide is gently rinsed with tap water until all free carbol fuchsin stain is washed away. At this point, the smear on the slide looks red in color.
9. Twenty-five percent sulfuric acid is poured onto the slide and allowed to stand for two to four minutes.
10. The slide is gently rinsed with tap water and tilted to drain off the water.
11. A properly decolorized slide appears light pink in color. If the slide is still red, sulfuric acid is reapplied for one to three minutes and then rinsed gently with tap water.The back of the slide is wiped clean with a swab dipped in sulfuric acid.
12. 0.1% methylene blue is poured onto the slide and left for 30 seconds. Then the slide is rinsed gently with tap water and allowed to dry.
13. The slide is examined under the binocular microscope using ×40 lens to select the suitable area and then examined under ×100 lens using a drop of immersion oil.
14. The results are recorded in the laboratory form and the laboratory register.
15. The slides are inverted on a tissue paper till the immersion oil is completely absorbed. Xylene is not to be used for cleaning the slides, as it may give false results at repeat examination after storage.
16. All positive and negative slides are stored serially in the same slide-box until instructed by the supervisor.
17. All contaminated materials are disinfected as per guidelines before discarding (Refer to section on "Infection Control and Hospital Waste Management").

Sputum smears are examined and interpreted as indicated in Table 49.1.

Classification of Tuberculosis Cases

It is important to classify cases of TB in order to determine the correct combination of drugs and duration of treatment. Classification of pulmonary cases should be based on at least three sputum smear examinations. Sputum should also be examined for the cases of suspected extrapulmonary TB, if pulmonary symptoms are present.

Pulmonary Tuberculosis

a. *Smear-positive patient*: A patient with at least two initial sputum smear examinations (direct smear microscopy) positive for Acid-fast Bacilli (AFB);
   Or: A patient with one sputum examination positive for AFB and radiographic abnormalities consistent with active pulmonary TB as determined by the treating MO;
   Or: A patient with one sputum specimen positive for AFB and culture positive for *M. tuberculosis.*
b. *Smear-negative patient*: A patient having symptoms suggestive of TB with at least three sputum examinations negative for AFB, and radiographic abnormalities consistent with active pulmonary TB as determined by the treating MO, followed by a decision to treat the patient with a full course of anti-TB therapy;
   Or: A patient whose diagnosis is based on culture positive for *M. tuberculosis*, but sputum smear examinations negative for AFB.

TABLE 49.1: Ways to examine and interpret sputum smear

Examination finding	*Result as recorded*	*Grading*	*No. of fields examined*
> 10 AFB per oil immersion field	Positive	3+	20
1–10 AFB per oil immersion field	Positive	2+	50
10–99 AFB per 100 oil immersion fields	Positive	1+	100
1–9 AFB per 100 oil immersion fields	Positive	Scanty*	100
No AFB in 100 oil immersion fields	Negative	Negative	100

*Record exact number seen in 100 fields

Extrapulmonary Tuberculosis

Extrapulmonary Tuberculosis (EPTB) is tuberculosis of organs other than the lungs, such as the pleura (pleurisy), lymph nodes, intestines, genitourinary tract, skin, joints and bones, meninges of the brain, etc.

Diagnosis should be based on one culture-positive specimen from an extrapulmonary site, or histological or radiological, or strong clinical evidence consistent with active extrapulmonary TB followed by the treating MO's decision to treat with a full course of anti-TB therapy.

Pleurisy is classified as extrapulmonary TB: A patient diagnosed with both sputum smear-positive pulmonary TB and extrapulmonary TB should be classified as a case of pulmonary TB.

Diagnostic Algorithm of RNTCP

Patients with at least two positive smear results are diagnosed by the physician as a case of smear-positive TB. They are further classified as new or old cases based on their treatment history, and appropriate therapy is prescribed.

For patients with only one sputum-positive result on smear examination, chest X-ray is taken. If findings of the X-ray are consistent with pulmonary tuberculosis, patient is diagnosed by the physician as a case of sputum-positive pulmonary TB.

Patients in whom all three samples are negative on sputum smear examination are prescribed symptomatic treatment and broad-spectrum antibiotics (such as co-trimoxazole, doxycycline, amoxicillin) for 10 to 14 days. In such cases antibiotics such as fluoroquinolones (ciprofloxacin, ofloxacin, etc.), rifampicin or streptomycin, which are active against tuberculosis, are not to be used. Most patients are likely to improve with antibiotics if they are not suffering from TB. If the symptoms persist after a course of broad-spectrum antibiotics, repeat sputum smear examination (three samples) must be done for such patients.

If two or more smears are positive, the patient is diagnosed as having smear-positive pulmonary TB. If only one sputum sample is positive, chest X-ray is taken. If findings of the X-ray are consistent with pulmonary tuberculosis, patient is diagnosed by the physician as a case of sputum-positive pulmonary TB.

If the results for all the three sputum samples of repeat examination are found negative then a chest X-ray is taken. If findings of the X-ray are consistent with pulmonary tuberculosis, patient is diagnosed by the physician as a case of sputum-negative pulmonary TB.

Patients with EPTB who also have cough of any duration, should have three sputum samples examined. If the smear result is positive, the patient is classified as pulmonary TB and his/her treatment regimen will be that of a case of smear-positive pulmonary TB.

When the referring medical practitioner receives the results of sputum examination, and it is decided to put the patient on chemotherapy, patient must be counseled and motivated to adhere to treatment as recommended. The patient is told about TB, mode of transmission, precautions to be taken to prevent the spread, importance of directly observed treatment and its duration, and the need for prompt evaluation of children under six years or household contacts with cough of any duration. The patient should also be informed that his/her address would be verified by a competent person prior to the start of treatment.

Follow-up Smear Examination

During follow-up two sputum samples are to be tested each time. The schedule is as follows:

- For smear-positive TB patients, two sputum samples (Morning-Spot) have to be tested each time on three occasions—(i) At the end of the intensive phase (two months for new cases and three months for retreatment cases), (ii) Two months into the continuation phase (at the end of four months for new cases/five months for retreatment cases) and (iii) At the end of treatment. If the smear is positive at the end of the intensive phase, it should be tested again at the end of extended IP (three months in new cases and at four months in retreatment cases).
- For smear-negative patients, two sputum samples have to be tested on two occasions–at the end of IP and at the end of treatment.

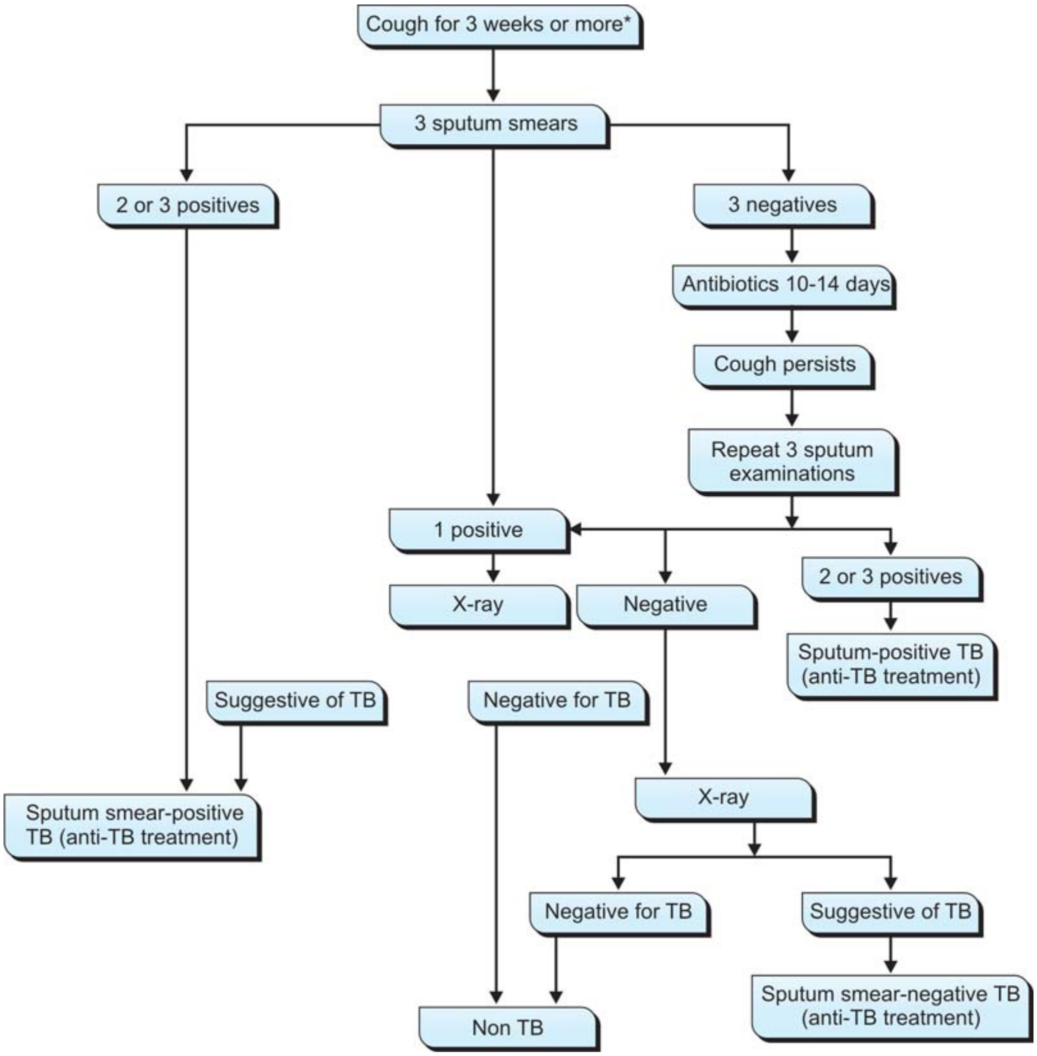
Diagnostic algorithm for pulmonary TB is shown in Flow chart 49.4.

Assurance

Effective Quality Assurance (QA) of the RNTCP sputum smear microscopy network is of crucial importance. QA is a total system consisting of internal Quality Control (QC), assessment of performance using External Quality Assessment (EQA) methods, and continuous Quality Improvement (QI) of laboratory services.

Quality Control (QC): Also called Internal Quality Assurance, includes all means by which the laboratory personnel performing TB smear microscopy, control the processes, including checking of instrument, new lots of staining solutions, smear preparation, grading, etc. It is a systematic internal monitoring of working practices, technical procedures, equipment, and materials, including quality of stains.

Flow chart 49.4: Diagnostic algorithm for pulmonary TB


Cough for 3 weeks or more*
3 sputum smears
2 or 3 positives
3 negatives
Antibiotics 10-14 days
Cough persists
Repeat 3 sputum examinations
1 positive
X-ray
Negative
2 or 3 positives
Sputum-positive TB (anti-TB treatment)
Suggestive of TB
Negative for TB
Sputum smear-positive TB (anti-TB treatment)
X-ray
Negative for TB
Suggestive of TB
Sputum smear-negative TB (anti-TB treatment)
Non TB

*Note: The duration is now 2 weeks wef 1st April 2009

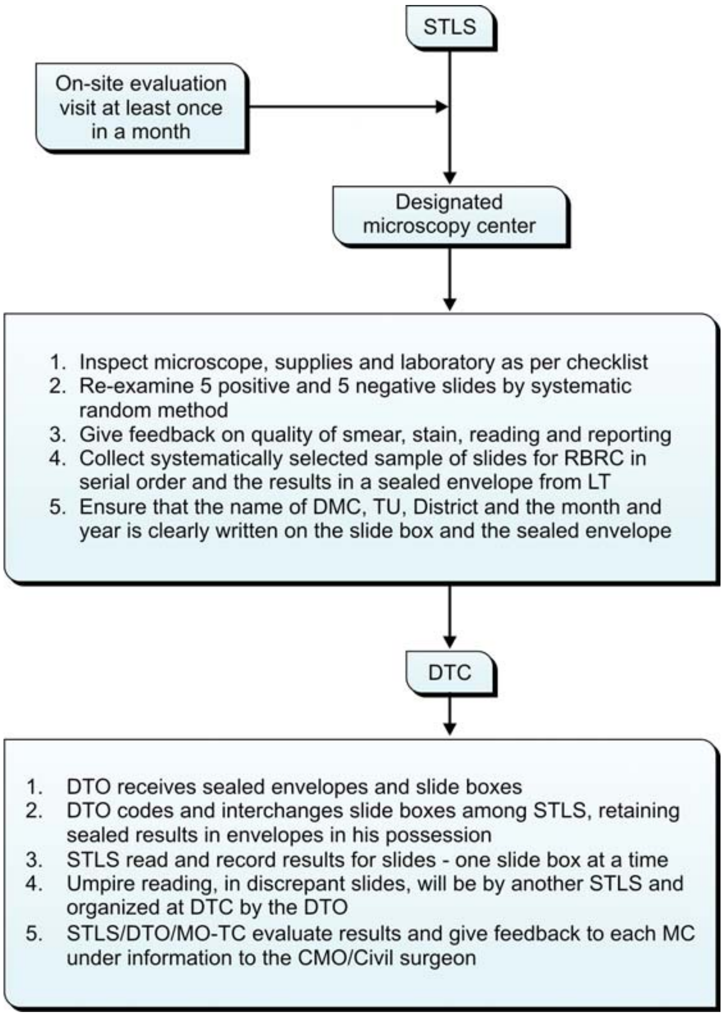
External quality assessment (EQA): A process to assess laboratory performance. EQA includes on-site evaluation of the laboratory to review QC and evaluation of entire process of smear microscopy, and random blinded rechecking of routine smears. EQA also allows participant laboratories to assess their capabilities by comparing their results with those obtained in other laboratories in the network through panel testing and rechecking of patient slides, using both unblinded and blinded procedures.

Quality improvement (QI): A process by which all components of smear microscopy diagnostic services are carefully analyzed with the aim of looking for ways to permanently remove obstacles to success. Appropriate data collection, data analysis, correct interpretation of the results and creative problem solving, are the key components of this process. It involves continued monitoring, identifying defects, followed by remedial action, including retraining when needed, to prevent recurrence of problems. QI mostly relies on effective on-site evaluation visits.

The network of DMCs is supported and supervised by regional/state laboratories (IRLs), and overseen by the NRLs.

Quality assurance network in sputum smear microscopy is shown in Flow chart 49.5.

Flow chart 49.5: Quality assurance network in sputum smear microscopy


STLS
On-site evaluation visit at least once in a month
Designated microscopy center
1. Inspect microscope, supplies and laboratory as per checklist
2. Re-examine 5 positive and 5 negative slides by systematic random method
3. Give feedback on quality of smear, stain, reading and reporting
4. Collect systematically selected sample of slides for RBRC in serial order and the results in a sealed envelope from LT
5. Ensure that the name of DMC, TU, District and the month and year is clearly written on the slide box and the sealed envelope
DTC
1. DTO receives sealed envelopes and slide boxes
2. DTO codes and interchanges slide boxes among STLS, retaining sealed results in envelopes in his possession
3. STLS read and record results for slides - one slide box at a time
4. Umpire reading, in discrepant slides, will be by another STLS and organized at DTC by the DTO
5. STLS/DTO/MO-TC evaluate results and give feedback to each MC under information to the CMO/Civil surgeon

External Quality Assessment

At the district level the activities of DTO, MO-TC and STLS for EQA of RNTCP laboratory network are:

- On-site evaluation of DMCs
- Blinded rechecking of DMC's slides at DTC, and
- Reporting the results of activities to LT and MO of the DMC and to STDC promptly.

The On-Site Evaluation (OSE) of DMC by the STLS includes a comprehensive assessment of laboratory safety, condition of the binocular microscope, adequacy of supplies, as well as the technical components of sputum smear microscopy, including preparation, staining and reading of smears. The frequency of on-site evaluation of any DMC is decided on the basis of its performance. On-site evaluation of every DMC is conducted at least once a month by the STLS of the respective TB Unit.

The DTO/MO-TC would also be supervising the DMC as per their tour program and hand over to MO of DMC the summary of observations and recommendations for corrective actions.

Random Blinded Rechecking (RBRC) at the district level involves the selection of a small sample of slides (sample size determined by the LQAS, i.e. lot quality assurance sampling methodology), which is representative of all slides of a DMC (both positive and negative). The original slide examination results by LTs are blinded and read by a STLS not belonging to the same TU to prevent bias.

The STDC/IRL conduct OSE, analyze district reports of RBRC during OSE and Panel testing of the districts.

Similarly NRL conduct OSE and Panel testing of the IRLs. (Details of QA activities of the NRL, IRL and district can be obtained from “Guidelines for Quality Assurance of smear microscopy for diagnosing tuberculosis”).

Checklists have been developed to assist supervisors during the field visit and to allow for the collection and analysis of standard data for subsequent remedial action.

TREATMENT

The objectives of tuberculosis treatment are:

- To decrease mortality and morbidity by ensuring cure, minimizing relapses and preventing the development of drug resistance
- To decrease infections and break the chain of transmission of infection
- To achieve the above whilst minimizing side effects due to drugs.

These objectives are achieved in RNTCP through intermittent (thrice weekly) treatment regimens given under direct observation for both pulmonary and extrapulmonary tuberculosis patients. Treatment regimens for tuberculosis have emerged as a result of controlled clinical trials in India and other parts of the world. It has been proven that thrice-a-week (intermittent) treatment is as effective as daily treatment and produces lesser side effects.

RNTCP provides standardized anti-TB treatment in three categories. Once the patient has been diagnosed as having TB, may be pulmonary or extrapulmonary, the MO is responsible for deciding the treatment regimen under one of the three categories depending on:

- Sputum smear results
- The history of previous anti-TB treatment
- Disease classification (pulmonary/extrapulmonary)
- Severity of illness.

Definition of Types of Cases

New

A TB patient who has never had treatment for tuberculosis or has taken antituberculosis drugs for less than one month.

Relapse

A TB patient who was declared cured or treatment completed by a physician, but who reports back to the health service and is now found to be sputum smear-positive.

Transferred in

A TB patient who has been received for treatment in a Tuberculosis Unit, after starting treatment in another unit where she has been registered.

Treatment after Default

A TB patient who received antituberculosis treatment for one month or more from any source and returns to treatment after having defaulted, i.e. not taken anti-TB drugs consecutively for two months or more, and is found to be sputum smear-positive.

Failure

Any TB patient who is smear-positive at five months or more after starting treatment. Failure also includes a patient who was treated with Category III regimen, but who becomes smear-positive during treatment.

Chronic

A TB patient who remains smear-positive after completing a retreatment regimen.

Others

TB patients who do not fit into the above mentioned types. Reasons for putting a patient in this type must be specified.

Seriousness of Illness

The severity of the illness depends on the bacillary load, the extent and the anatomical site of the disease. The involvement of an anatomical site helps in classifying if the disease is severe, depending on whether it is life-threatening or has high risk of developing subsequent severe handicap or both. The following forms of extrapulmonary TB and smear-negative pulmonary TB are classified as “seriously ill” (Table 49.2).

Treatment Regimens

Various categories of treatment regimens are shown in Table 49.3.

Drugs and their Dosage

The most important drugs used in the treatment of TB are isoniazid (H), rifampicin (R), pyrazinamide (Z), streptomycin (S) and ethambutol (E). The dosage strength is shown in Table 49.4.

TABLE 49.2: List of extrapulmonary and smear-negative pulmonary TBs that are classified as "seriously ill"

Extrapulmonary TB classified as 'seriously ill'	*Smear-negative pulmonary TB classified as 'seriously ill'*
• Meningitis	• Miliary TB
• Pericarditis	• Extensive parenchymal infiltration
• Peritonitis	• Coinfection with HIV
• Bilateral or extensive pleural effusion	• Cavitary disease
• Spinal TB with neurological involvement	• All forms of pediatric sputum smear-negative pulmonary TB except primary complex
• Intestinal	
• Genitourinary	
• Coinfection with HIV	
• All forms of pediatric extrapulmonary TB other than lymph node TB and unilateral pleural effusion are considered to be seriously ill	

TABLE 49.3: Various categories of treatment regimens[@]

Category of treatment	*Type of patient*	*Regimen**
Category I	New sputum smear-positive Seriously ill** new sputum smear-negative Seriously ill** new extrapulmonary	$2H_3R_3Z_3E_3$ + $4H_3R_3$
Category II	Sputum smear-positive relapse Sputum smear-positive failure Sputum smear-positive treatment after default Others***	$2H_3R_3Z_3E_3S_3$ + $1H_3R_3Z_3E_3$ + $5H_3R_3E_3$
Category III	New sputum smear-negative, not seriously ill	$2H_3R_3Z_3$ + $4H_3R_3$

**The number before the letters refers to the number of months of treatment. The subscript after the letters refers* to the number of doses per week. The dosage strengths are as follows: H: Isoniazid (600 mg); R: Rifampicin (450 mg); Z: Pyrazinamide (1500 mg); E: Ethambutol (1200 mg); S: Streptomycin (750 mg). Patients who weigh 60 kg or more receive additional rifampicin 150 mg. Patients who are more than 50 years old receive streptomycin 500 mg. Patients who weigh less than 30 kg, receive drugs as per body weight. Patients in Categories I and II who have a positive sputum smear at the end of the initial intensive phase receive an additional month of intensive phase treatment.

**Seriously ill also includes, any patient, pulmonary or extrapulmonary who is HIV positive and declares his serostatus to the categorizing/treating medical officer. For the purpose of categorization, HIV testing should not be done.

***In rare and exceptional cases, patients who are sputum smear-negative or who have extrapulmonary disease can have Relapse or Failure. This diagnosis in all such cases should always be made by an MO and should be supported by the culture or histological evidence of current, active TB. In these cases, the patient should be categorized as "Others" and given Category II treatment.

[@] As per Oct 2010 decision, the Cat III regimen has been deleted and merged with Cat I.

TABLE 49.4: The dosage strength of different drugs

Medication	*Dose (thrice a week)*	*Number of pills in Combipack*
Isoniazid	600 mg	2
Rifampicin	450 mg	1
Pyrazinamide	1500 mg	2
Ethambutol	1200 mg	2
Streptomycin	0.75 g	–

Drugs are supplied in Patient-Wise Boxes (PWB) containing the full course of treatment, and packaged in blister packs. The PWB have a color code indicating the category (Red for CAT I, Blue for CAT II and Green for CAT III). In each PWB, there are two pouches one for intensive phase (A) and one for continuation phase (B). For the intensive phase, each blister pack contains medicines for one dose. For the continuation phase, each blister pack contains one week's supply of medication. The drugs for extension of the intensive phase (prolongation pouches) are supplied separately.

For adults, drugs will be given in the recommended number of pills/capsules irrespective of body weight. However, for patients weighing more than 60 kilograms, an additional capsule of rifampicin 150 mg will be added to the treatment regimen. Patients who are more than 50 years old receive streptomycin 500 mg and patients who weigh less than 30 kg receive drugs as per body weight.

For children, the drugs will be given according to the body weight. Patient-wise boxes for children is being developed, however until these are available, the drugs are given to children as per body weight. The recommended dosages for children are given in section on Pediatric TB.

Regimen for Non-DOTS (ND) Treatment in RNTCP Areas

In RNTCP areas, all/most patients would be getting DOTS regimen. Unobserved rifampicin should not be given under any circumstance. However, RNTCP non-DOTS treatment (self-administered non-rifampicin containing regimen) may be needed in exceptionally few cases (e.g. adverse reaction to rifampicin and pyrazinamide). To facilitate registration of patients started on RNTCP Non-DOTS regimens, a tuberculosis treatment card should be filled. Up to a maximum of 5% of patients may get Non-DOTS treatment in an RNTCP area. Every effort should be made to minimize Non-DOTS, so that all patients are provided superior regimen under DOTS. The justification for initiating patient on non-DOTS treatment should be specified in the "Remarks" column of the treatment card and TB register. The prescribed Non-DOTS treatment regimen and dosages are presented below.

Non-DOTS Regimen 1 (ND1): 12-months conventional chemotherapy regimen, with streptomycin given in the first two months. This is given to patients who are: Cases of sputum smear-positive pulmonary TB and for seriously ill cases of smear-negative and extrapulmonary TB.

The treatment consists of 12-month conventional chemotherapy. The initial intensive phase lasts for two months and the continuation phase for 10 months. Isoniazid (300 mg) and ethambutol (800 mg) are self-administered by the patient daily for 12 months. Streptomycin 0.75 g per day (0.5 g for those over 50 years of age) is administered daily in the initial intensive phase for two months. Those who weigh less than 30 kg receive dosages calculated as per body weight.

Non-DOTS Regimen 2 (ND2): 12-month conventional chemotherapy regimen, without streptomycin for patients with smear-negative pulmonary TB who are not seriously ill; and for patients with extrapulmonary TB who are not seriously ill.

The treatment consists of 12-month conventional chemotherapy. Isoniazid (300 mg) and ethambutol (800 mg) are self-administered by the patient daily for 12 months.

Drug Administration

After the Medical Officer decides to treat the patient, the treatment card and patient identity card are prepared. The patient is put on treatment only after the verification of address by the Peripheral Health Worker (PHW) within a period of one week of diagnosis. The patient is also registered in the TB register during the supervisory visit of the STS within a period of one month from the start of treatment.

Prior to the starting of treatment, the MO of the Peripheral Health Institution (PHI) explains to the patient about the disease, dosage schedule, duration of treatment, the need for examination of contacts and frequency of follow-up sputum to monitor progress towards completion/cure. The MO also discusses with the patient to determine a DOT center, which is acceptable and easily accessible to the patient. Health education and motivation of the patient should be reinforced periodically during follow-up visits. The original treatment card is maintained at the PHI where the patient was started on treatment.

If the patient is to be treated by a DOT provider located outside the premises of PHI, a duplicate card will be prepared and given to the DOT provider to record all necessary information. The Medical Officer of the PHI will give the Patient-Wise Box (PWB) for the entire duration of treatment to the PHW. Issue of the PWB to the PHW will be duly recorded in the stock register maintained at the health facility. The PHW visits the house of the patient (definitely within a week) and has a detailed dialogue with the patient and other members of the family, emphasizing the treatment schedule, importance of regular uninterrupted drug intake, completion of the course of treatment, possible intolerance, etc. as well as the need for check-up of contacts. The treatment is initiated after this visit by PHW or community volunteer. For drug administration, a convenient location is decided mutually between the PHW and the patient.

Either of two cycles—Monday, Wednesday and Friday; or Tuesday, Thursday and Saturday—is fixed as days for drug administration. All doses in the intensive phase must be taken under observation of the DOT provider. The patient must be contacted within one day of missing a dose during the intensive phase. The dose missed on the specified day in the intensive phase can be administered on the following day. In the continuation phase, the first dose of the week should be taken under direct observation and the subsequent doses for the week are self-administered. On the next scheduled visit, the empty blister pack should be collected by the DOT provider before giving the next weekly dose. The patient must be contacted and retrieved for treatment within a week of missing a dose in continuation phase. All the empty blister packs (of IP and CP) should be retained in the PWB.

Treatment cards should be organized at DOT centers according to the day of scheduled observation and the phase of treatment (i.e. intensive phase and continuation phase). The cards should be organized in such a manner that the cards of patients who do not present for treatment will be apparent on the same day, and appropriate action for their retrieval can be taken.

As regards the administration of streptomycin injections at the peripheral level, the policy will be to entrust this responsibility to the Auxiliary Nurse Midwife (ANM) or equivalent at the subcenter level or to any registered medical practitioner who is acceptable and accessible to the patient. If the same is not possible, the patient has to come to the PHC/CHC or any other nearest health institution. The streptomycin injection should be given using disposable or sterilized syringes and needles.

The DOT provider records the drug administration, and refers the patient to the microscopy center for follow-up sputum examinations. He also enquires about any drug reaction and refers the patient to the MO if needed.

Side Effects

Serious side effects of anti-TB drugs are less with intermittent chemotherapy. Drugs should not be administered on empty stomach. DOT providers should identify common side-effects early and report to the medical officer.

Special Situations

Management of TB patients on DOT in special situations is described below.

Hospitalization

General policy of RNTCP is to treat patients on ambulatory basis. However, occasionally the general condition of the patient may be serious enough to require hospitalization. For example, in patients with pneumothorax or large accumulations of pleural fluid leads to breathlessness, massive hemoptysis, etc. These patients can be managed in general hospitals.

All indoor patients are to be treated with RNTCP regimens. The treatment is given using prolongation pouches, which will be supplied by DTO through the STS of the TU in which the indoor facility is situated. On discharge, patients may be given a maximum of three doses (one week drug supply) to cover the intervening period prior to their continuation of treatment at their respective DOT Center, which may/may not be in the same TU/district, hence ensuring no interruption in treatment. All indoor patients treated under RNTCP, should be registered under the local TU in which the indoor facility is located. If the patient resides outside the TU/district, on discharge she will be transferred out for continuing treatment.

Treatment of TB during Pregnancy and Postnatal Period

- Streptomycin should not be given; other drugs used in RNTCP are safe
- Breastfeeding should continue regardless of the mother's TB status
- Advise the mother to cover her mouth, if she is smear-positive, while breastfeeding the baby
- Chemoprophylaxis for the baby is recommended if mother is sputum smear-positive.

Treatment in Patients with Renal Failure

- Rifampicin, isoniazid and pyrazinamide can be safely given
- Streptomycin and ethambutol, if given, should be closely monitored with reduced dosage under the supervision of the treating physician.

Treatment in Women Taking Oral Contraceptive Pills

- Rifampicin decreases the efficiency of oral contraceptives; switch to another method of contraception.

Directly Observed Treatment (DOT)

Directly observed treatment is one of the key elements of the DOTS strategy. In DOT, an observer watches and supports the patient in taking their drugs. Direct observation ensures treatment for the entire course with the right drugs, in the right doses and at the right intervals.

DOT is necessary because at least one-third of patients on self-administered treatment fail to adhere to treatment and it is impossible to predict, which patients will take regular treatment.

The health worker or community volunteer who administers DOT is called the “DOT Provider”. DOT provider should be acceptable and accessible to the patient and is accountable to the health system. The “DOT center” is a place where DOT is given and is convenient to both patient and DOT provider. DOT can be provided by anyone other than the patient’s family members.

To ensure treatment success, patients must take all doses of treatment, in both intensive and continuation phases. During the intensive phase of treatment, each and every dose of medicine is to be taken under direct observation of the DOT provider.

After the patient takes the drugs under direct observation in the IP, the appropriate box in the treatment card is ticked (√) after the drugs are administered. If the patient misses a dose it is recorded “O” on the treatment card. If a patient does not take medication as scheduled in the IP, she should be traced and given the medication on the next day. The medication for the following day is then given as scheduled. If a patient misses any dose of medicine (does not come on two successive days in IP), these doses must be made up at the end of scheduled period and the duration of treatment will get prolonged.

During the continuation phase of treatment, all patients collect drugs from the DOT center (DOT provider) once a week on a designated day. One dose is administered under direct observation on the day of collection and the next two doses of the week are given to the patient for self-administration. An “X” is entered in the appropriate box to indicate the day the drugs were swallowed under direct observation. A line is drawn through the remaining days of the week (after the X) to indicate that the drugs for the remaining period of the week have been given (X......). The patients must present at the time of next week’s collection the empty strip/ blister pack of the drugs consumed. During the continuation phase, if the patient is late by a single day for drug collection, the dose may be given and other doses taken as scheduled. If the patient is late by two days or more days from the date on which he was scheduled to have the first directly observed dose of the weekly blister pack is given on the day he presents for collection the drug, the missed dose is marked as “O” on the treatment card. The drugs are given as when she returns for treatment and the missed doses must be made up at the end of scheduled period and the duration of treatment will get prolonged.

Patients who miss a dose must be contacted and put back on treatment through home visits. This should be done by the health staff or community health worker no later than the day after the patient was due to come for treatment in the intensive phase, and within a week of the missed dose in the continuation phase. It is important to take action immediately after knowing that the patient missed a dose. The reasons for the same interruption of treatment must be recorded in the treatment card.

Patient Flow for DOT

After receiving the sputum results, the MO of the Peripheral Health Institution (PHI) is responsible for the following measures:

- Establishing the diagnosis of tuberculosis
- Deciding the type of patient and category of treatment
- Explain to the patient about:
  The disease
  - The treatment (dosage schedule, duration, common side effects and methods to prevent them)
  - The need for examination of contacts (especially, if patient is smear-positive)
  - Frequency of monitoring of progress until cure
  - Importance of DOT
- Determines the DOT center and the DOT provider
- Initiates the tuberculosis treatment card (in duplicate when required) and the TB identity card
- Make the patient-wise box available at the DOT center along with the TB treatment card, TB identity card and sputum containers for morning samples of follow-up sputum examinations.

For the purpose of identifying a suitable DOT provider and an appropriate DOT center, a DOT directory should be maintained at PHI level. This directory should contain a locality-wise list of DOT centers/DOT providers in the area and should be updated regularly. The place identified for DOT (DOT Center) and name and designation of the DOT provider should be entered in treatment card in the space provided.

If the patient is to be given DOT by a PHW/ community DOT provider, the MO of the PHI where the patient is prescribed treatment, will send a duplicate copy of the treatment card along with the patients-wise box. The PHW visits the house of the patient as soon as possible (in no case later than one week) for confirmation of the address. This opportunity is used for a detailed dialogue with the patient and other members of the family, emphasizing on points similar to the ones mentioned above (for the MO-PHI) and screening of contacts. The initial home visit should be recorded in treatment card in the space provided. A convenient location for drug administration and a suitable DOT provider is decided mutually by the PHW and the patient.

The community DOT provider will be provided with the duplicate TB treatment card along with sputum containers (for morning samples of follow-up sputum examinations) and PWB. If untrained, on the spot training has to be done for the community DOT provider regarding directly observed treatment, adverse reactions, follow-up sputum examination and recording drug intake. The DOT provider should also be trained to give health education and motivation messages to the patient. The PHW is responsible for supervising and ensuring DOT and updating of the original card at the PHI on a fortnightly basis.

In case the patient misses any dose, PHW would have to take retrieval actions in case the community DOT provider fails to retrieve the patient. If the DOT provider is unsuccessful in retrieving such patients, it should be reported to the next level of supervisors (e.g. MPW, MO-PHI, STS, MO-TC, etc.). If the patient misses DOT on two occasions in the intensive phase, DOT provider should arrange a visit by the MO-PHI to the patient's home, so that the MO-PHI can review the reasons for the same, give intensive counseling to the patient and, if required, ensure that DOT is made more convenient for the patient.

The MO of the PHI (where treatment card was initiated) and the STS should also supervise DOT on a regular basis and support the PHW in patient retrieval. DTO and MO-TC should support them in their efforts through field-visits.

The DOT provider records the days the drugs are administered in the tuberculosis treatment card at the time of drug intake, and refer the patient to the DMC when follow-up sputum examinations are due. DOT provider also enquires about drug reactions and, if necessary, refers the patient to the MO.

Monitoring of Patients

Sputum smear microscopy is much more informative than radiology in monitoring the progress of chemotherapy. Hence, the patient should be referred for follow-up sputum examinations at the prescribed intervals. Other investigations like ESR, antibody detection, etc. are unreliable and have no role in diagnosing and/or evaluating the progress or results of treatment.

Follow-up Smear Examination

Follow-up of the patients is done as detailed below.

New smear-positive patients: Two smears are examined each time during follow-up. The first follow-up sputum examination is done at the end of two months of intensive phase. On the 22nd dose in intensive phase, the patient is given a sputum container and instructed to bring the early morning sample. The patient brings the sputum sample when he comes for the 23rd dose in the intensive phase when a spot sample is also collected. The results of both the smear examinations will be available at the next visit of the patient. If both smears are negative, the patient will be put on the continuation phase. If either of the smears is positive, the intensive phase will be extended by one more month, and sputum examination will be repeated at the end of the third month. Thereafter, the patient is put on the continuation phase regardless of his/her sputum status at the end of the extended intensive phase. Subsequent follow-up smear examinations are done after two months into continuation phase and if found positive the patient is declared as a treatment failure, re-registered and started on the retreatment regimen afresh. If the follow-up sputum is negative, the continuation phase is completed and smear examination repeated at the end of treatment. The sputum should generally be collected at the time of collection of the 16th blister so that the results are available at the time of supply of the last week's blister pack. Results of end of treatment sputum should be available not later than one week of completion of treatment.

Retreatment patients: The first sputum smear examination is done at three months after beginning of the intensive phase. On the 34th dose of the intensive phase the patient is given a sputum container and instructed to bring the early morning sample. The patient brings the sputum sample when he comes for 35th dose in the intensive phase when a spot sample is also collected. The results of both the smear examinations will be available at the next visit of the patient. If both smears are negative, the patient will be put on the continuation phase. If either of the samples is positive, the intensive phase of treatment will be extended by one more month, and another smear examination will be done at the end of the fourth month of treatment. Thereafter, the patient is put on the continuation phase regardless of his sputum status at the end of four months of the intensive phase. Subsequent follow-up sputum examinations are done after two months into continuation phase. Irrespective of the results of the follow-up smear examinations, the patient continues and completes the treatment when a final follow-up sputum smear is done. The sputum should generally be collected at the time of collection of the 20th blister so that the results are available at the time of supply of the last week's blister pack.

Smear-negative patients: Two smears are examined during the follow-up visit at the end of two months of the intensive phase and again at the end of treatment. If the patient becomes sputum smear-positive at the end of IP or at the end of treatment, his outcome is "failure" and is started on retreatment Cat II regimen after registration.

Treatment Outcome

The patient's treatment outcome is identified by reviewing her/his tuberculosis treatment card. The treatment outcome and the date the patient stopped treatment is written in the appropriate column in the tuberculosis treatment card. The date on which the patient stopped treatment is the date of the last dose of drugs taken.

The duplicate TB treatment card and the used/partially used PWB of the patient should be immediately returned by the PHW to the PHI. The MO of the PHI should record the treatment outcome in the treatment card and sign it. The treatment card of the patients whose outcome has been declared and partially used PWBs, if any, should be handed over to the STS during his routine monthly visits.

It is the responsibility of the STS to ensure that:

- The tuberculosis treatment cards reach the TB Unit from the treatment centers as soon as the treatment outcome is recorded and within a maximum of one month time.
- The treatment outcome is recorded in the TB Register within one month of the completion of the treatment in the case of cured and treatment completed cases. Similarly, the outcomes of patients declared defaulted or died should be recorded within one month of the event.
- Partially used PWBs, if any, is returned to the DTC for reconstitution.

Every patient started on treatment has to be given one and only one treatment outcome.

Patients whose outcome is identified as failure should be started on Cat II treatment afresh.

Determination of treatment outcomes are shown in Table 49.5.

MANAGEMENT OF PEDIATRIC TUBERCULOSIS UNDER RNTCP

Introduction

Childhood TB is a reflection of the prevalence of sputum smear-positive PTB and the extent of transmission of TB infection in the community. Children are likely to suffer from more serious forms of TB and are more likely to die if not treated properly. Reliable data on disease incidence and prevalence is, however, not available due to the difficulties in diagnosis of pediatric TB under field conditions.

TABLE 49.5: Determination of treatment outcomes

- If the patient Then the treatment outcome is identified as cured
- Was registered as pulmonary smear-positive, completed treatment and had negative smear cured results on two occasions, one of which is at end of treatment
- Was registered as pulmonary smear-positive, completed treatment with negative smears at the treatment completed end of the intensive phase but none at end of treatment
- Was registered as pulmonary smear-negative or extrapulmonary, and completed treatment
- Was known to have died from any cause whatsoever while on treatment died
- Was registered as pulmonary smear-positive CAT I, and was smear-positive at five months or later*
- Was registered as pulmonary smear-positive CAT II (retreatment), and was smear-positive at Failure five months or later of CAT II treatment
- Was registered as pulmonary smear-negative or extrapulmonary on CAT III, but was smear-positive any time during treatment*
- Has not taken drugs for more than two months consecutively any time after starting treatment Defaulted
- Was transferred to another TU/district and his/her treatment Transferred out outcome is not available

*Also, re-registered immediately as Category II and started on the retreatment regimen

Diagnosis

TB should be suspected among children presenting with fever and/or cough for more than three weeks, with or without weight loss or no weight gain; and history of contact with a suspected or diagnosed case of active TB disease within the last two years. Diagnosis should be based on a combination of clinical presentation, sputum examination wherever possible, Chest X-ray (PA view), Mantoux test (1 TU PPD RT23 with Tween 80, positive if in duration >10 mm after 48–72 hours) and history of contact. Diagnosis should be made by a medical officer and the existing RNTCP case definitions be used for all cases diagnosed. Purified protein derivative would be supplied by CTD to district headquarters.

Children showing neurological symptoms like irritability, refusal to feed, headache, vomiting or altered sensorium may be suspected to have TB meningitis.

Use of currently available scoring systems is not recommended for the diagnosis of TB among children. Where diagnostic difficulties are faced, the child should be referred to a pediatrician for further management.

Treatment of Pediatric TB

DOTS is the recommended strategy for treatment of TB and all pediatric TB patients should be registered under RNTCP. Intermittent short course chemotherapy given under direct observation should be used in children, as in adults.

RNTCP treatment categories and regimens for children are shown in Table 49.6.

In patients with TBM on Category I treatment, the four drugs used during the intensive phase should be HRZS (instead of HRZE) due to poor penetration of blood brain barrier by ethambutol. In TBM and spinal TB with neurological complications continuation phase of treatment should be given for six to seven months, thus extending the total duration of treatment to eight to nine months.

Steroids should be used initially in hospitalized cases of TBM and TB pericarditis and reduced gradually over six to eight weeks.

In all instances, before starting a child on Category II treatment, she should be examined by a Pediatrician or TB expert, wherever available.

As recommended by WHO, and in view of the growing evidence that the use of ethambutol in young children is safe, ethambutol is to be used as per RNTCP regimen for all age groups.

To assist in calculating required dosages and administration of anti-TB drugs for children, the medication would be made available in the form of patient-wise boxes, linked to weight bands. The recommended dosages for thrice weekly regimen in children are as follows: Isoniazid 10 to 15 mg/kg; Rifampicin 10 mg/kg; Pyrazinamide 30 to 35 mg/kg; Ethambutol 30 mg/kg and Streptomycin 15 mg/kg.

TABLE 49.6: RNTCP treatment categories and regimens for children

Treatment category	*Types of patients*	*Treatment regimen****	
		IP	*CP*
Category I	New sputum smear-positive PTB New sputum smear-negative PTB, seriously ill* New extra-PTB, seriously ill*	$2H_3R_3Z_3E_3$**	$4H_3R_3$
Category II	Sputum smear-positive relapse Sputum smear-positive treatment failure Sputum smear-positive treatment after default	$2H_3R_3Z_3E_3S_3$ $+ 1H_3R_3Z_3E_3$	$5H_3R_3E_3$
Category III	New sputum smear-negative, not seriously ill** New extra-PTB, not seriously ill**	$2H_3R_3Z_3$	$4H_3R_3$

*In children, seriously ill sputum smear-negative PTB includes all forms of sputum smear-negative PTB other than primary complex. Seriously ill EPTB includes TB Meningitis (TBM), disseminated TB, TB pericarditis, TB peritonitis and intestinal TB, bilateral extensive pleurisy, spinal TB with or without neurological complications, genitourinary TB, and bone and joint TB.

**Not seriously ill sputum smear-negative PTB includes primary complex. Not seriously ill EPTB includes lymph node TB and unilateral pleural effusion.

***Prefix indicates month and subscript indicates thrice weekly.

For monitoring treatment, follow-up sputum examinations are to be performed with the same frequency as in adults. Clinical or symptomatic improvement is to be assessed at the end of the intensive phase of treatment and at the end of treatment. Improvement should be judged by the absence of fever or cough, a decrease in the size of lymph node(s), weight gain, etc. Radiological improvement is to be assessed by chest X-ray examination in all smear-negative pulmonary TB cases at the end of treatment.

Chemoprophylaxis

Recent infection with tubercle bacilli is one of the risk factors for disease development. The younger the child, the higher is the risk of breakdown of infection into disease. Therefore, household contacts of smear-positive TB cases, especially those below 6 years of age, must be screened for the symptoms of tuberculosis. In the case of symptoms being present, the diagnostic algorithm for pediatric TB should be followed and the child should be given a full course of anti-TB treatment if s/he is diagnosed as a TB case. For asymptomatic children under 6 years, chemoprophylaxis with isoniazid (5 mg per kg body wt) should be administered daily for a period of six months. This is regardless of the BCG vaccination status.

Role of BCG Vaccination

Effective treatment of infectious patients under DOTS protects children against all forms of TB. The most effective way to prevent TB is to ensure that sputum smear-positive patients are cured. To protect contacts of smear-positive cases should be screened and managed as described above.

BCG vaccine is an attenuated strain of tubercle bacilli. After in depth reviews, it was concluded that though BCG may not protect against TB of lung, which occurs mostly in adults, it could provide substantial protection against the childhood forms of TB, such as tubercular meningitis, miliary TB. In India, it is recommended to give BCG vaccination to all children preferably at birth as part of National Immunization Schedule to give the benefit of protection against the childhood forms of TB (refer to National Immunization Schedule, Govt of India).

MANAGEMENT OF EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary Tuberculosis (EPTB) comprises about 10 to 15% of all new TB cases in our country. Among them, 75% have lymph node or pleural TB.

A person with extrapulmonary TB may have symptoms related to the organs affected, such as swelling of lymph nodes, occasionally with discharge of pus, pain and swelling of the joints; headache, fever, stiffness of the neck and mental confusion when the brain or meninges are involved. In addition, the following general symptoms like weight loss, fever, particularly with the rise of temperature in the evening and night sweats may be present.

Patients with suspected EPTB should be referred to a competent medical practitioner for expert opinion. Diagnosis of such patients may be made by using appropriate diagnostic procedures [such as Fine Needle Aspiration Cytology (FNAC)/biopsy/culture from the site of disease) as well as clinical methods. Patients with EPTB who also have cough of any duration, should have three sputum samples examined. If the smear result is positive, the patient is classified as pulmonary TB.

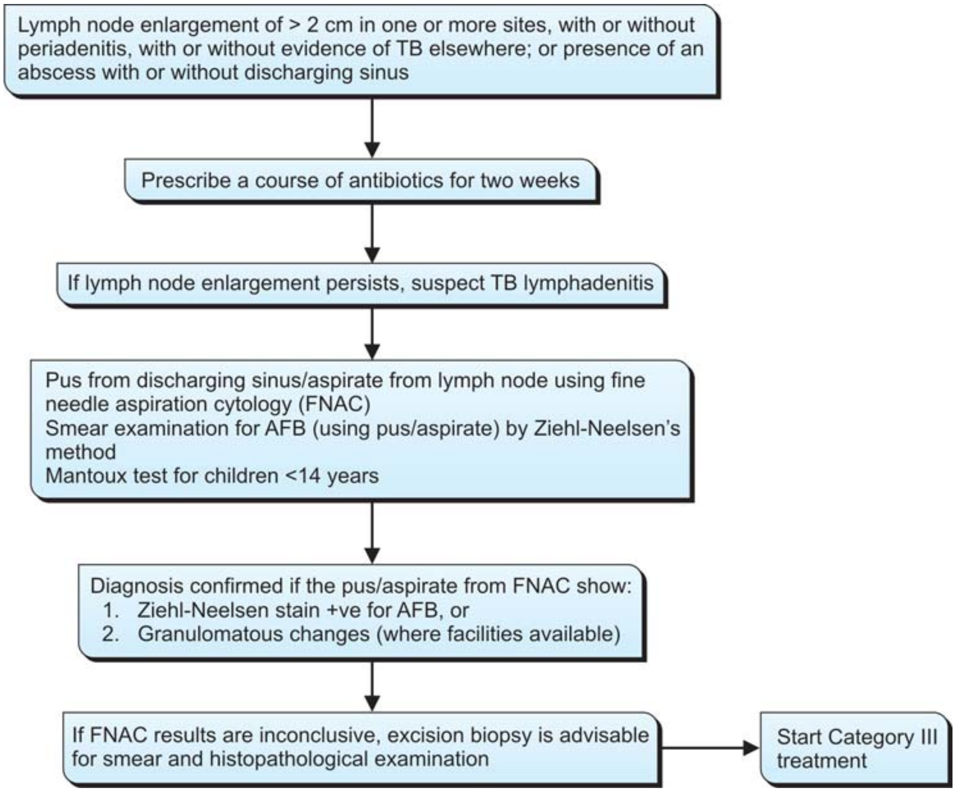
Intermittent short-course chemotherapy regimens of six to nine months are recommended internationally for all forms of extrapulmonary TB. In cases of TBM, initial hospitalization is recommended. In TBM, ethambutol should be replaced by streptomycin in the intensive phase and continuation phase of the treatment is for six to seven months. Adjunctive steroids may be useful in pericardial and meningeal TB.

Management of TB Lymphadenitis

Lymph node TB usually presents as slowly progressive, painless enlargement of the lymph nodes of neck, sometimes of axilla or groin. Cervical lymph node TB is the most common manifestation of extrapulmonary form of TB. Lymph node involvement of more than one group is common. Individual nodes are firm and discrete though matting of nodes may occur and may progress to abscess and sinus formation if left untreated. Tubercular abscess is also called “cold abscess” since inflammation is uncommon. In addition, constitutional symptoms like fever, malaise, weight loss, anorexia, etc. may be present, but not invariably. This form of TB is more common in children and adults who are less than 30 years of age.

Diagnosis based on clinical findings alone can lead to overdiagnosis in a high proportion of cases. Therefore, attempt should always be made to confirm diagnosis by undertaking FNAC. This procedure can be undertaken wherever facilities are available. Refer to the diagnostic algorithm on the next page for details. In addition, sometimes chest radiograph may reveal mediastinal widening suggestive of hilar adenitis.

Flow chart 49.6: Diagnostic algorithm for TB lymphadenitis


Lymph node enlargement of > 2 cm in one or more sites, with or without periadenitis, with or without evidence of TB elsewhere; or presence of an abscess with or without discharging sinus
Prescribe a course of antibiotics for two weeks
If lymph node enlargement persists, suspect TB lymphadenitis
Pus from discharging sinus/aspirate from lymph node using fine needle aspiration cytology (FNAC)
Smear examination for AFB (using pus/aspirate) by Ziehl-Neelsen's method
Mantoux test for children <14 years
Diagnosis confirmed if the pus/aspirate from FNAC show:
1. Ziehl-Neelsen stain +ve for AFB, or
2. Granulomatous changes (where facilities available)
If FNAC results are inconclusive, excision biopsy is advisable for smear and histopathological examination
Start Category III treatment

Intermittent six-month short-course chemotherapy regimen has been proven to be very effective in the treatment of superficial TB lymphadenitis.

Paradoxical reactions in the form of persistence or enlargement of existing nodes or appearance of new nodes may occur in about one-fourth of cases during treatment as well as after completing treatment, and sometimes even a few months later. These reactions do not indicate treatment failure and probably represent an immune response to the release of mycobacterial products caused by the rapid bactericidal activity of the drug regimens. Therefore, extension or modification of treatment is not warranted as they usually regress spontaneously. Residual lymphadenopathy, after treatment completion has also been reported in about one-third of patients. Studies have shown that retreatment is required only if residual lymph node biopsy is bacteriologically confirmed as positive by culture for *Mycobacterium tuberculosis*. As culture facilities are not available everywhere, FNAC may be resorted to. However, the granulomatous changes may persist for a long time even after adequate treatment. Hence, the decision to start retreatment cannot be based on histopathological proof alone. The relapse rates after SCC are reported to be quite low.

Diagnostic algorithm for TB lymphadenitis is shown in Flow chart 49.6.

Management of Pleural TB

Patients presenting with chest pain with or without difficulty in breathing for more than two weeks should be referred for chest radiograph. Constitutional symptoms like fever, anorexia, loss of appetite may be present, but not invariably. If chest X-ray is suggestive of pleural effusion, pleural aspiration should be performed for biochemical, cytological and smear examination by Ziehl-Neelsen stain for confirmation of diagnosis. Where available, pleural biopsy may be performed.

Patients with unilateral pleural effusion are treated with Category III regimen. Bilateral or extensive effusions are classified as seriously ill forms of extrapulmonary TB and treated with Category I regimen.

MANAGEMENT OF PATIENTS WITH HIV INFECTION AND TUBERCULOSIS

People coinfected with HIV and TB have a higher risk of developing TB disease. Irrespective of HIV status, RNTCP diagnostic algorithm should be followed for all TB suspects. Anti-TB treatment is the same for HIV-infected persons as it is for HIV- negative TB patients. Hence, they should be treated with RNTCP regimens. All new TB cases known to be HIV-positive are classified as seriously ill and treated with Category I regimen. The retreatment cases are to be treated with Category II regimen.

It is important to maintain confidentiality regarding HIV status of individuals, including TB suspects and patients, in order to prevent stigmatization and discrimination. TB patients should be encouraged to voluntarily share their HIV status with the treating physician for the purpose of taking clinical decisions like categorization for the treatment of TB, treatment of other opportunistic infections and provision of ART. The HIV-positive status should not be disclosed by the treating physician to any other staff involved in RNTCP. In addition, the HIV-positive status should not be mentioned in any RNTCP records.

TB patients who have other HIV-associated opportunistic infections, or report risk behavior for HIV, should be offered referral to the nearest Voluntary Counseling and Testing Center (VCTC) for voluntary counseling and HIV testing. Routine HIV testing of all TB suspects/patients is not the national policy.

DOTS in TB-HIV

Directly observed treatment with effective short-course treatment regimen is even more important for HIV-positive TB patients. Self-administration of treatment is associated with higher case fatality rates. Hence, a DOT strategy that ensures adherence to therapy should be used for all HIV-positive TB patients.

The relapse rate of TB in HIV-positive TB patients who complete directly observed treatment with short-course regimen is low, although slightly higher than in HIV-negative TB patients. However, this increase is more likely to be due to reinfections rather than true relapse of disease. Treatment interruptions, due to higher occurrence of adverse drug reactions or intercurrent opportunistic infections, could also lead to an increased risk of relapse of TB.

Antituberculosis Therapy and Antiretroviral Therapy (ART)

The antiretroviral drugs, which are used in HIV-positive patients, are effective in slowing down the progress of HIV disease and prolonging life. These drugs are grouped as Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs), nucleotide reverse transcriptase inhibitors, Protease Inhibitors (PIs) and fusion inhibitors. The current recommendations on ART are to use a triple drug combination. A combination of, Stavudine/Zidovudine plus lamivudine plus Efavirenz/Nevirapine is usually used. (For details refer to National AIDS Control Organization guidelines).

Protease inhibitors and nonnucleoside reverse transcriptase inhibitors may inhibit or induce cytochrome P450 isoenzymes and thus alter the serum concentration of rifamycins. Rifamycins induce cytochrome P450 and substantially decrease blood levels of these antiretroviral drugs. Dose adjustments for nevirapine coadministered with rifampicin has not been established. Hence, coadministration of Rifampicin with any of the protease inhibitors (ritonavir, indinavir, nelfinavir) or nonnucleoside reverse transcriptase inhibitors (nevirapine) should be avoided.

All TB patients coinfected with HIV should be treated with a rifampicin containing treatment regimen under DOTS. In TB patients coinfected with HIV, TB treatment should be completed prior to starting ART, unless there is a high risk of HIV disease progression and death during the period of TB treatment (i.e. a CD4 count < 200/mm^3 or the presence of disseminated TB). In a patient who has been on treatment with rifampicin, at least two weeks should have lapsed after the last dose of rifampicin before starting protease inhibitor or nonnucleoside reverse transcriptase inhibitors. This time gap is necessary for reduction of the enzyme-inducing activity of rifampicin prior to the commencement of anti-retroviral drugs.

In patients with very low CD4 counts requiring concomitant administration of ART and anti-TB treatment, the ARV regimen should be modified by replacing nevirapine with efavirenz. On the completion of TB treatment, such patients can be switched back to nevirapine.

Operationalization of VCTC-RNTCP Cross-Referral Linkages (VCTC now called ICTC)

Service linkages between VCTC and RNTCP diagnostic and treatment centers are the most important area of coordination between the HIV/Acquired Immuno-deficiency Syndrome (AIDS) and TB Control program. RNTCP visualizes VCTC as a PHI referring TB suspects irrespective of their serostatus. VCTC's will identify and refer suspected TB cases to the RNTCP Designated Microscopy Centers. Tuberculosis patients who have other HIV-associated opportunistic infections or report risk behavior for HIV, would be offered referral to VCTC for counseling and diagnosis of HIV infection.

Steps for Operationalization

- Ensure that the VCTC, DMC and DOT center are in the same campus so that referral linkages are easily established. In case they are not in the same campus, efforts should be made to establish effective referral linkages between them.
- Ensure that all the VCTC and RNTCP staff members are trained in TB/HIV.
- Provide VCTC with RNTCP laboratory forms for sputum examination to refer patients to DMCs.
- Provide VCTC with a list of DMCs and DOT centers in the district/state.
- Ensure IEC materials on TB are displayed and available at the VCTCs. IEC material on HIV provided by State AIDS Control Society (SACS) would be displayed at all RNTCP sites.
- Confidentiality of HIV status must be ensured at all levels by all staff. Remember that the HIV status of a patient should not be mentioned in the treatment card, TB Laboratory Register or any other document. Do not use any symbols/codes for the identification of HIV-positive persons.
- The VCTC counselors are to visit the DMCs, and the STSs are to visit the VCTCs to follow-up on referred cases.
- Monthly RNTCP Review meetings are to be attended by the VCTC staff. During this meeting information on cross referral and feedback on the utilization of the services, would be shared.
- State TB Officer, State VCTC Programme Officer, District TB Officer and District Nodal Officers (HIV/AIDS) to review TB/HIV coordination activities during their periodic field visits.

  For details, refer to guidelines on HIV/TB coordination.

Referral of Persons from VCTC to RNTCP

At VCTC

VCTC Counselors will identify persons with symptoms suggestive of TB disease amongst the clients. The counselor will ask each and every client for the history of cough for more than three weeks and other associated symptoms of TB. Patients, irrespective of their serostatus, having cough will be referred to a DMC for sputum examinations and in case of symptoms of extrapulmonary TB, the patient should be referred to a competent medical practitioner for expert opinion. The RNTCP sputum examination form will be filled in by the counselor. On the sputum examination form, the counselor should fill in all the required details including the name of VCTC, and take special care in obtaining and recording correct residential address of the patient. The counselor will not mention the HIV status of patient on the form or elsewhere, but shall encourage the patient to disclose his HIV status (if known) to the treating physician, in the interest of better case management. The sputum examination form is given to the patient with specific instructions on the location and timings of the DMC. The counselor should make a detailed note of the referral in the counseling register.

The counselor should impart information/counseling on TB to all VCTC clients and should document the same in the counseling register, irrespective of whether they have signs or symptoms of TB or not.

At Designated Microscopy Center (DMC)

Once the patient reaches the DMC, the same process would be followed as for any other TB suspect, i.e. the diagnostic algorithm of RNTCP would be followed. The laboratory technician would enter the details of the patient, including correct residential address and clearly mention the name of VCTC as the referring unit in TB laboratory register. After all the three sputum examinations are done, the results of the test are given to the patient. Patient would then go to the medical officer for further management.

In case of extrapulmonary TB, the VCTC would refer the patient to the medical officer for necessary investigations. After obtaining the test results, the medical officer would decide the further course of management.

If the patient has TB (pulmonary or extrapulmonary), treatment categorization is done as per the RNTCP treatment algorithm. Voluntary disclosure of the HIV status by the client should be encouraged. All new TB cases with known HIV-positive status, would receive RNTCP Category I regimen and retreatment TB cases will receive Category II regimen. Based on patient’s area of residence, these patients are referred for treatment to the nearest DOT center.

Referral of TB Patients to VCTC for HIV-Testing

TB patients who have signs/symptoms of other HIV-associated opportunistic infections, or report risk behavior for HIV would be offered referral by the medical officer to the VCTC. Thus, these diagnosed TB patients may be referred from DMC, DOT center, outpatient clinic, TB ward, TB clinic, etc. Sometimes the patient may simultaneously be investigated for TB and HIV. The doctor should first complete the investigations for TB and then refer for HIV investigations. While referring to the VCTC, the doctor should write a referral note to VCTC in which the TB status of the person is mentioned. The referral of the TB patients to the VCTC for eliciting the HIV status for the sake of categorization should never be done.

Once the referred TB patient reaches VCTC, the same procedure will be followed as that for any other client attending VCTC. At the VCTC, the patient/client will undergo pretest counseling. HIV testing is done after obtaining informed consent. The details of the patient/client will be entered into the PID register and counseling register. HIV testing is done and the test results are handed over by the laboratory technician to the counselor. The counselor reveals the HIV test result to the patient/client with post-test counseling. The HIV test results are not revealed to any other person other than the individual.

For details of operationalization of VCTC-RNTCP cross-referrals linkages separate modules for TB/HIV compiled by the Central TB Division may be referred.

RECORDING AND REPORTING

Maintenance of accurate records and registers of patients and program activities; and reporting data to the state/central unit every quarter, is essential for the proper monitoring and management of RNTCP. RNTCP records and reports are standardized and provide the required information for managing the program effectively.

The following standardized records and reports are used in the RNTCP:

Forms

- *Laboratory form for sputum examination:* Kept at all the PHIs. It is filled generally by the MO of the referring health facility. Only one form is filled for each patient. Patient will report to the DMC along with the laboratory form. In case PHI is a sputum collection center, sputum samples are sent to the DMC along with the laboratory form. It is essential to indicate in the laboratory form whether the sputum has been sent for diagnosis or follow-up. In the former case, the patient's detailed address should be given so that if the patient does not return to the health institution and the sputum is found to be smear-positive, the patient can be traced. The Tuberculosis No. of all patients whose sputum is being examined for follow-up must be written in the space provided.
- *Tuberculosis treatment card:* The card is filled at the PHI when patient is initiated on treatment. This card contains important information about a patient. It features name, age, sex and address of the patient; type of disease; history of past anti-TB treatment; regimen prescribed; duration of treatment; amount of drugs to be given; results of sputum smear examinations before and during treatment; drugs administered during the intensive and continuation phases of treatment; treatment outcome of the patient; retrieval actions for missing doses; preventive treatment for children; details of X-ray or other tests for diagnosis of EP TB; and remarks. It also has information on the DOT provider, person conducting the initial home visit and the signature of the MO.
  It is kept at the peripheral health institution where the patient receives treatment (either at the district hospital, CHC, PHC, health post, etc.). For the patients who do not come to these health institutions and have to be given treatment at the subcenter or village level by the multipurpose worker/anganwadi worker/ASHA/community DOT provider, a duplicate card is made and given to the above health functionary who is directly supervising drug administration of the patient. Information regarding administration of drugs during the treatment will be entered on this card and in case a duplicate is used for this purpose, the information is transferred onto the main card kept at the health institution by the most peripheral health functionary/community volunteer, on a fortnightly basis. The STS transfers the relevant data, particularly the results of bacteriological examinations, from the treatment card to the tuberculosis register kept at the Subdistrict (TU) level. Once the patient completes treatment or if s/he dies, defaults or is transferred, it should be ensured that all the information has been entered in the original card, which is retained at the Peripheral Health Institution.
- *Patient's TB identity card:* It is completed for each patient who has a tuberculosis treatment card. It is kept with the patient. Information from the tuberculosis treatment card is used to complete the identity card. The front part of the ID card has patient information, name and address of the TU/district and patient's treatment details, including disease classification, type of patient, sputum results, category and information on the date of starting treatment. The back portion of the ID card has the results of follow-up sputum examination, appoint-

ment dates for visits for drug administration and treatment outcome. This information will help to continue treatment, in case the patient is transferred or admitted to any other health facility anytime during the treatment period.

- *Referral form for treatment:* This form is available at all DMCs. Medical officer of the Designated Microscopy Centers, which refer patients for treatment to other peripheral health institutions needs to fills in the top half of the form that includes the patient characteristics. Once the patient arrives, the receiving unit fills in the bottom half of the form, and sends it back to the referring unit. Information regarding the referral of patient should also be noted in the referral for treatment register or in the remarks column of the TB laboratory register.
- *Transfer form:* It is kept at all the PHIs administering treatment for TB. This form is to be used when transferring registered patients on treatment from one reporting unit to another. If a patient is being “transferred out”, a tuberculosis transfer form and a copy of the tuberculosis treatment card will be sent from the “transferring unit”, i.e. referring health facility/TU to the “receiving unit”, i.e. health facility/ TU where the patient will receive further treatment. This form has four parts and should be filled up in triplicate. The first part of the form contains information about the patient, her/his disease, treatment details and address of the transferring unit. This information should be used to complete a new tuberculosis treatment card for the patient, who would be reregistered as a “transfer in” case in the receiving unit. When the patient has reported to the receiving unit, the bottom (fourth) part of the form is completed by the receiving unit and returned to the transferring unit. The third and second parts are to communicate patients’ sputum results at the end of intensive phase and treatment outcome respectively to the transferring unit.
- *Mycobacteriology culture/sensitivity test form:* Request for culture/sensitivity tests would be sent to the reference laboratory by the DTO along with the patient or patient’s sputum samples in case of failure to respond to directly observed Category II treatment regimen.

Registers

- *Tuberculosis laboratory register:* It is kept at all designated TB microscopy centers. The tuberculosis laboratory register is used to record the results of sputum smear examinations. The LT assigns a laboratory serial number for each patient who has been referred to the laboratory for sputum microscopy. The following information about the patient is recorded: Date of sputum smear examination; full name; sex, age, name of the health facility that requested the examination (e.g. primary health center, medical college, private practitioner, NGO, etc.); complete address; reason for examination (diagnosis and follow-up); and the results of sputum smear examinations. The last two columns of the register are for the LTs signature and any remarks the LT or supervisor wishes to make. The remarks column is also used by the STS, enters tuberculosis number (TB No.) and category of treatment from the TB register. The remarks column can also mention in brief the action taken for patients belonging to other TU/ districts, e.g. “Referred for treatment to…” The laboratory technician should summarize the information on sputum smear examinations done during that month. This information should be summarized in the format at the end of each month, printed in the laboratory register itself. The STLS should write their monthly supervisory abstract after the last entry of the month. Patients from the following month should be started from the next new page.
- *Tuberculosis register:* It is kept at the tuberculosis unit, which is at subdistrict level and contains information on all TB patients registered in the area. The tuberculosis register is used to record the following information about the patient: TB No.; Date of registration; name (in full), address, age/sex; name of PHI; date of starting treatment; regimen/category; disease classification; type of patient; details of sputum examinations; treatment outcome with date; remarks; and summary at the bottom of the page. The tuberculosis register is maintained by the STS at the TU level. All TB patients, who are put on DOTS and non-DOTS, must be registered in the tuberculosis register so that all the patients in the unit are monitored. The STS should register the patients as early as possible, and in no case more than a month after starting treatment. The TB register should be updated by the STS during the supervisory visits to the PHI. The initial and subsequent information required for registration and updating of the tuberculosis register is obtained from the tuberculosis treatment card. Information from the TB register is used to compile the quarterly reports.
- *PHI-level supervisory register:* This is maintained at each PHI. All supervisors (STO, CDHO, DTO, MO-

TC, STS, STLS, etc.) should summarize their observations in the supervision register. The "summary of observations and recommendations of visit" is filled in triplicate. A copy of the summary is detached for future record of the supervisor, a copy is sent to the next higher level officer, and the third copy is left in the register, which should be reviewed during all subsequent supervisory visits to ascertain whether corrective actions were taken by the concerned MO-PHI.

- *Referral for treatment register:* It should be maintained in all big hospitals and medical colleges where large numbers of cases are expected to be diagnosed and referred for treatment to other reporting unit. The referring unit should receive feedbacks on patients referred to other TUs in the same district within 14 days and for patients referred outside the district/state within one month.
- *Stock register:* It is maintained at state/district/TU drug store. It is used for recording the information on the stock of drugs and consumables received and issued by the health unit. The register also mentions the batch numbers and date of expiry of drugs and consumables. The reconstituted PWBs should be recorded in the DTC stock register as receipts. The format of the register can be referred to in the "Standard Operating Procedures Manual for State Drug Stores."
- *Reconstitution register:* It is maintained at all the DTCs for recording the receipt of drugs of patients who have defaulted, died, failed treatment or transferred out. Such drug boxes are reconstituted and the details thereof are also recorded in the register. The format of the register can be referred to in the "Standard Operating Procedures Manual for State Drug Stores".

Reports

The quarterly reporting system used in RNTCP enables analysis of cohorts of patients. A cohort in this context is a group of patients who were registered for treatment in a specified area over a specified period of time. Under RNTCP, specified areas are TB unit, district, state and country. The specified periods of time are four quarters of a year and one calendar year itself. A quarter is a three month period with the first quarter starting on 1st January of the year and one year is divided into four quarters (1st, 2nd, 3rd and 4th). This information helps national, state and district levels to assess the performance and monitor the implementation of the program. Every patient initiated on RNTCP treatment is registered in the TB register. The cohort-based quarterly reports are initiated from the TU level. Using the information in the tuberculosis register, the senior tuberculosis supervisor, under the supervision of the medical officer-tuberculosis control, prepares quarterly TU-level reports. The MO-TC submits the report to the district tuberculosis officer, who, in turn, compiles the reports received from all tuberculosis units in the district and sends the district-level reports to the state tuberculosis officer and the Central TB Division electronically. Computers with the Internet facilities have been provided at all District TB Centers in the country for electronic transmission of reports.

At the state, district and TU-levels, following reports are used:

Quarterly report on new and retreatment case of tuberculosis: It includes the number of tuberculosis cases diagnosed and registered under DOTS regimens CAT I, II and III during a quarter. Every patient started on treatment and registered (except those typed as "transfer in") must be included. The case-finding data provides details of the new sputum-positive (age and sex distribution), new sputum-negative, extrapulmonary and retreatment cases registered during the quarter. It also includes information on patients belonging to the pediatric age group.

Quarterly report on sputum conversion of new and retreatment cases registered four to six months earlier: This report gives the proportion of smear-positive cases of the cohort registered in the previous quarter who became smear-negative or are still positive at two and three months of treatment. Although sputum conversion rates are determined for all different types of smear-positive patients (new smear-positive, relapse, failure and treatment after default), the most important evaluation is that of new sputum smear-positive patients. The sputum conversion rate is not only an indicator of the efficacy of the treatment regimen, but also of the effectiveness of program implementation.

Quarterly report on results of treatment of tuberculosis cases registered 13 to 15 months earlier: This report shows the various treatment outcomes (cured, treatment completed, died, failure, defaulted and transferred out) of all cases registered during the corresponding quarter.

Quarterly report on program management and logistics (TU/District/State): It indicates the status of involvement of PHIs, staff position and training, supervisory activities, referral activities, microscopy, treatment initiation, quality of DOTS implementation, Laboratory Quality Control Network (EQA), TB-HIV cross-referrals, medications, consumables and equipment in place. The district level report has additional information on the involvement of medical colleges and other sectors, IEC and financial management in the district. In addition to the information stated above the state level report also collects information on district internal evaluations performed during the quarter, details of training held at STDC/state level; state level drug stock and the availability of drug susceptibility testing facility in the state.

At the PHI-level, the following report is generated:

Monthly PHI report on program management, logistics and microscopy filled at all PHIs by the MO on the last working day of the month and sent to the CMO/CDHO with a copy to the concerned TU, on or before fifth of the next month. This report contains information on drugs and consumables, staff position, referral activities, microscopy activities, treatment initiation and status of microscope. This report is to be complied after physical verification of the stock. It is the responsibility of the MO-TC and STS to ensure that all PHIs submit their monthly reports on time. The DTO should collect copies of this report from the office of CMO/CDHO for the close monitoring of microscopy activities and logistics in the district on a monthly basis. The copies at the TU level shall be used for monitoring as well as preparation of quarterly reports.

SUPERVISION, MONITORING AND EVALUATION

A “Supervision and Monitoring Strategy” with specific indicators to monitor and evaluate the program at different levels with the objective to further improve the performance of RNTCP, is in place. The detailed strategy can be referred to in the “Strategy Document on Supervision and Monitoring.”

Effective supervision at all levels (central, state, district, sub-district, designated microscopy and DOT centers) is crucial to the successful implementation of the program. RNTCP lays out clear responsibilities to the respective staff at each level in relation to supervisory activities.

Role of Central TB Division

- The role of the Central TB Division includes supervision of the state level implementation and of the State TB Training and Demonstration Centre (STDC), monitoring and evaluation of overall performance of RNTCP throughout the country and regular reporting on RNTCP performance. Regular supervisory visits are also made to the states implementing RNTCP and to districts of “concern”. The CTD provides overall oversight of RNTCP and its activities, and provides technical and policy guidance to the program.
- At the State level, the STO, with the support of the Deputy STO and MO of State TB Cell (STC), is responsible for the planning, supervision, monitoring and evaluation of all TB control activities in the respective state. The STC/STDC staff together is expected to make supervisory visits to all the implementing districts every quarter.
  The state level program review meetings should be held quarterly and chaired by the Secretary Health. The major points that require attention at the review meeting should be prepared by the STO prior to the meeting and provided to the secretary in advance of the review meeting. STO is responsible for the submission of the consolidated state level RNTCP quarterly reports, which are sent to the CTD as per program guidelines. The STO is also responsible for sending feedback to all districts on their quarterly reports within 30 days of the end of the quarter.
- At the district level, the DTO, with the support of Medical Officer (MO) of the District TB Centre (DTC), is responsible for ensuring the quality of diagnosis, treatment, logistics and reporting in their respective district. DTOs should be full time for RNTCP activities. The DTO, along with the MO, are expected to undertake supervisory visits (three to five days in a week, i.e. 20 days in a month) to all the tuberculosis units and any medical colleges in the district every month, and all the Designated Microscopy Centres, Community Health Centres (CHCs), Primary Health Centres (PHCs) and other hospitals in the district every quarter. One subcenter from each PHC, and a proportion of the tribal subcenters, and participating NGOs and private practitioners should also be visited every quarter. They should also visit at least three randomly selected NSP cases and their DOT providers on every field visit day.
- The DTO will complete a tour diary containing all relevant findings of his/her supervisory visits. The DTO, and DTC MO if in place, will also write all relevant findings in the “Summary of observations” sheet in the RNTCP supervisory register held at the relevant PHI/DMC. One copy of the summary of observations will be held by the DTO for his/her record and the second copy will be sent to the respective CMO.
- The DTOs will also review the monthly activity reports of all MO-TCs, STLSs and STSs within the respective district during the monthly district level meeting of said staff. The monthly PHI reports should be available at these meetings.

Representatives of the other health institutions should also be called for this review. The date of the review should be fixed in advance. Minutes of these meetings should be kept by the DTO.

- The DTO is responsible for the consolidated district level RNTCP quarterly reports, which are sent to the State TB Cell (STC) and the Central TB Division (CTD) as per the program guidelines.
- The Chief Medical Officer (CMO) is also expected to review the program on a regular basis. Guidance on program review will be provided to the CMOs, and also to district collectors.
- At the TU level, the MO-TC, STS and STLS, are responsible for undertaking supervisory visits to all the peripheral health facilities, NGOs and PPs. The MO-TC is responsible for supervising the work of TU and of the STS and STLS, in addition to his/her other responsibilities. The MO-TC should reserve seven days in a month for field visits and visit all DMCs every month, and visit most of the participating private as well as public PHIs every quarter.
- The STS is responsible for the quality of case detection and treatment activities being provided by all the health facilities, both in the public and private sector, NGOs, including PPs, medical colleges and community volunteers under the respective TU. He/she is expected to visit all CHCs and PHCs every month and subcenters, NGOs/PPs and community workers every quarter.
- The STLS is responsible for the quality of sputum smear microscopy services provided by the DMCs under the respective TU. She is expected to visit all the DMCs under the respective TU at least once a month. The STLS is also expected to do blinded rechecking of slides at the DTC as per the roster put up by the DTO.
- The supervisory team at the TU (MO-TC, STS and STLS) are primarily responsible for the supervisory activities in their area of coverage. Though they may go individually for supervisory activity, some visits should be made as a team for better coordination. The DTO will also supervise the field units as per program guidelines. During supervisory visits, one observes and reinforces stipulated practices in the various components of the RNTCP as well as identifies and corrects inadequate performance and recording discrepancies, if any, before these become a major problem. The focus of supervisory visits is on education, coordination, motivation, facilitation and guidance with the overall objective of implementing corrective action.
- A supervisory checklist and list of key indicators (refer “Strategy document on supervision and monitoring”) are to be used to identify the administrative and technical problems systematically. The indicators relevant to different levels of program management are grouped to indicate.
  - Political and administrative commitment
  - Human resource
  - Diagnostic practices
  - Drugs
  - DOT and follow-up services
  - Recording and reporting
  - TB/HIV coordination
  - Supervision
  - IEC, and
  - Financial management.

Prioritization of Health Units to be Supervised

The important guiding criteria for prioritizing health units, which are to be supervised are:

- Low proportion of patients receiving directly observed treatment as per guidelines
- High proportion of patients who were wrongly categorized
- Sputum conversion rate for new sputum smear-positive patients at three months is less than 85%
- Cure rate for new sputum smear-positive patients is less than 80%
- High proportion of sputum-negative and extrapulmonary cases
- Low case detection of new sputum smear-positive cases
- High default, death or failure rate.

By and large, the health units should be sent prior information of the supervisory visit. However, some surprise visits to the health units should also be undertaken.

Monitoring

The program is monitored on a quarterly basis from reports, which include the report on case finding, sputum conversion, treatment outcomes and program management. The program has also evolved an in-built monitoring system.

The quarterly reports are analyzed using the list of indicators at all levels, from the PHI, TU level, district, state to the center. Detailed feedback on the performance of the districts is sent to the districts by the state at the end of every quarter in order to support the districts to improve performance. CTD gives additional feedback and helps in building the capacity of the state to monitor and evaluate the program in their respective states.

Besides the routine monitoring of the quarterly performance reports, the program undertakes specific measures to monitor the program implementation in the districts. These initiatives include:

"Internal Evaluation" of the Programme

Intensive supervision and monitoring at all levels is critical to the success of RNTCP. The state level "Internal Evaluation" is a tool for comprehensive review of the district program, with the purpose of giving specific recommendations to improve the program performance. "Internal Evaluations" of two districts per state per quarter are expected to be carried out in large states. During "Internal Evaluation" there is an objective assessment of program services and activities. The objectives are:

- To validate the cure rates of the district for the last reported quarter
- To assess the program performance as well as financial as well as logistics management
- To give recommendations for improving the quality of recording and reporting
- To give recommendations for improving the performance (with a timeframe).

"Central Level Evaluation" of the Districts

In addition to the state level driven internal evaluations, a centrally driven evaluation with the active participation of the respective states to carefully review the systems and program implementation of poorly performing districts is undertaken. The purpose of the enhanced monitoring process is not only to improve the performances of the districts in question, but also to identify generic problems and find solutions, which might be equally relevant to or applicable in other districts as well. This evaluation will also cover districts where excellent performance is being reported. This is in part to check the validity and correctness of the data and reporting, but also to find out best practices, which could then also be implemented in other districts. These evaluations are not meant to be an exercise in criticism or praise, but as a strategic tool leading to the systematic and systemic improvement in the implementation and performance of RNTCP.

National Review of the Programme

Apart from the routine state level monthly review of RNTCP, a national review of the performance of the states is undertaken twice in a year. The national review helps to identify state level problems and suggest remedial measures or actions; deliberate on new initiatives and advocacy.

External Evaluation of the Programme

The program also plans for periodic external assessment of the program by international agencies and partners of the RNTCP, in order to enhance the quality of services provided under the program.

Assessment of Impact

The impact of the program on the TB epidemiology in the community will determine whether TB will be controlled in India. Impact related to TB control activities however, can only be seen after many years of activities. In addition, the outcomes seen can be the result not only of the program activities, but also due to other factors such as improved socioeconomic conditions, severity of the HIV epidemic, etc. The impact indicators should link directly with the Millennium Development Goal (MDG) targets and indicators (Table 49.7). Thus impact indicators, such as annual risk of TB infection and incidence rate, mortality rate due to TB, and levels of drug resistance, etc. are to be measured in the medium and long-term timeframe.

The RNTCP surveillance system collects routine information to measure treatment success and case detection. To evaluate the impact of RNTCP on the incidence of tuberculosis, ARTI survey will be repeated every three to five years. The first such ARTI study was completed in 2003. State-specific ARTI studies are also planned. Estimation of the prevalence and deaths due to tuberculosis in the country will be done directly through field surveys and indirectly by modeling exercises. Such estimations over a period of time will show the long-term impact of the program towards halting and reversing the incidence of TB by 2015.

TABLE 49.7: Millennium development goals

Relevant to TB control are:

Goal 6: To combat HIV/AIDS, malaria and other diseases

Target 8: To have halted by 2015 and begun to reverse the incidence of malaria and other major diseases, including tuberculosis.

Indicators for Target 8 to be used to evaluate the implementation and impact of TB control:

Indicator 23: Between 1990 and 2015, to halve the prevalence and death rates associated with tuberculosis; and

Indicator 24: By 2005, to detect 70% of new smear-positive TB cases arising annually, and to successfully treat 85% of these cases.

TRAINING

RNTCP is implemented through the state health systems. The states contribute significantly to RNTCP in terms of human resources and man-hours. The human resource development policy envisages having at all times adequate numbers of staff at different levels of the health system who have the skills, knowledge and attitude necessary to successfully implement and sustain TB control activities based on the DOTS strategy, including the implementation of new and revised strategies and tools. Development of standardized training material is the responsibility of Central TB Division. A wide range of standardized training material has been made available to the states by Central TB Division emphasizing the need for standardized training throughout the country. Continuous efforts are to be made to ensure good quality of training at all levels.

The states are expected to prepare the projections of training requirement and make an annual training plan, which would be sent to Central TB Division as a part of the States' Annual Action Plan. The training plan takes into account the existing staffing in the state, existing training status and ongoing turnover of staff. The training plan endeavors to have in place maximum numbers of trained staff and plans to minimize delay in training of newly placed staff.

The training is undertaken at different levels. National and central institutes like NTI, Bengaluru; TRC, Chennai; LRS Institute, Delhi; selected medical colleges as well other institutes of eminence undertake training for the state/corporation level officers implementing RNTCP. Trainers from State TB Training and Demonstration Centres, teachers and researchers of the medical colleges and other institutes from all over the country are also trained at the central institutes.

It is planned to have three tiers of training, which will address different needs of the staff providing RNTCP services:

1. *Initial RNTCP training:* This would include induction trainings for all new/replacement staff hitherto untrained in RNTCP. Standard modular training is imparted to all categories of staff responsible for program implementation. It would also include the initial training of NGO personnel, private practitioners, medical college faculty and students and health staff of other sectors.
2. *Retraining:* These trainings would be mainly for individuals who have already received initial RNTCP training, but during supervision activities have been identified to have needs, which require retraining on basic RNTCP activities. The retraining for the individual would be need based and hence staff may need retraining on the complete set of initial training modules, or only on sections related to specific activities.
3. *Updates on new activities and initiatives:* As RNTCP introduces new activities and initiatives, it is important that the field staff members are updated accordingly. These updates could be given during regular program review meetings, such as the monthly district level meeting of the DTO, MO-TCs, STSs and STLSs, or the quarterly state level review meetings.

Standardized training modules for different categories of staff have been developed. The entire training process should be closely monitored by the STO/CMO/DTO/MO-TC, even if she is not directly responsible for each step. The state/district must develop a schedule/calendar for training, select course facilitators, conduct the training, supervise and evaluate the quality. The training should run at least eight hours a day.

Retraining Schedules

During field visits, supervisors should identify staff requiring retraining and the specific areas for the same. Duration of the training will depend on the contents of the training. The maximum duration of training for different categories of staff is listed in Table 49.8.

SPECIAL INITIATIVES

Public-private Mix (PPM)

India has the largest private sector in the world that manages a considerable proportion of tuberculosis cases. The few available studies of the health-seeking behavior of TB symptomatic individuals and patients have shown that more than 50% of patients first approach the private health sector.

Tuberculosis is encountered at all levels and by all types of health services ranging from primary health care services to the highly specialized hospitals in the different health care sectors. Traditionally, control of tuberculosis was considered a responsibility of the public health sector. As a consequence, tuberculosis control programs were designed to be implemented through the available network of public health services. Over the years, the private sector has grown considerably in India. The private health sector in India varies considerably in its

The details of duration of training, size of each batch and veneus are as below:

Initial RNTCP Training

Category	*Duration (working days)*	*Batch size*	*Training material*	*Venue*
STO/STDC staff/District TB officer/ TB-HIV coordinator	14	20	RNTCP MO modules 1-9, STCS/DTCS guidelines, Financial Management manual, Procurement + SDS manual, Monitoring strategy	Central institute
MO-TC/Urban TB coordinator	12	20	RNTCP MO modules 1-9	STDC
MO	5	20	RNTCP MO modules 1-4	District
STS (2+6)	8	12	MPW module, then STS module	STDC
STLS (10+5)	15	6	LT module, then STLS module	STDC
LT	10	8	LT module	District
State drug store Staff/Pharmacist in RNTCP	2	25	MPW module/manual on Std. operating procedures for State drug store	District/TU
MPHS	3	25	MPW module, sections of STS module	District/TU
TB health visitor etc.	2	25	MPW module	TU/PHI
MPW/HA etc.	2	25	MPW module	TU/PHI
Anganwadi worker/midwives/community volunteers, etc.	2	25	DOT provider module	TU/PHI
Community-based DOT providers	1	25	DOT provider module	TU/PHI
Private/NGO/other sector medical practitioners (for PPM module)	6 hr	20	Training module for medical practitioners	DTC/IMA
TO/SA	6	12	STS module	STDC/District
IEC officer	6	Need based	IEC module + MPW module	Central level
Data entry operator	2+2	12	MPW module, then Epicenter training	MPW module and Epicenter at state level
Accountants for district	1	Need based	Manual on financial management and guidelines	State level
Accountant—state level	3	Need based	Financial management manual, DTCS/ STCS guidelines	Central TB division

Initial Training on EQA

Category	*Duration (days)*	*Batch Size*	*Training material*	*Venue*
EQA (Master trainers/ microbiologist)	5	10	EQA manual	Central institute
EQA IRL LTs	5	6	EQA manual	Central institute
EQA STDC Dir/ STO	2	5	EQA manual	Central institute
EQA DTO/MO-TC	2	25	Sections from EQA manual	State level
EQA STLS	2	6	Sections from EQA manual	District level
EQA LTs	1	25	Sections from EQA manual	District level

Initial Training on TB/HIV				
Category	*Duration (days)*	*Batch Size*	*Training material*	*Venue*
TB-HIV master trainers	5	10	TB HIV modules	Central
STO/DTO/MO-DT/MO-TC	2	10	Module for MOs on TB/HIV	State
MO	1	30	Module for MOs on TB/HIV	District
STS/STLS	2	10	Module for STS STLS on TB/HIV	District
DOT provider	1	30	Module for health workers on TB/HIV	TU/PHI

Initial RNTCP Training for Medical College Staff					
Category of	*Type of Duration (in days)*	*Place of training*	*Trainers training*	*Training material*	*staff to be trained*
Medical Staff					
STF chairperson	Concise modular	National institute	Central institute staff	RNTCP –Key facts and concepts	1*
Faculty incharge of RNTCP	MO-TC modular	State-level	STC/STDC staff	1-9 modules	12
TOT's	MO-TC modular	National/ State level	Central institute/ STC/STDC staff	1-9 modules	12
HODs and Senior staff	Concise modular	State level	STC/STDC staff	RNTCP—Key facts and concepts	1
Other faculty members (interested)	MO modules	Medical college	Faculty in-charge of RNTCP	1-4 modules	5
PG students/ Residents/interns/ UG's	Part of Curriculum + sensitization	Medical college	Faculty in-charge of RNTCP	Curriculum	2-3 hrs**
Paramedical Staff					
Nurses	MPW training	Medical college	Faculty incharge of RNTCP	MPW module	2
Pharmacists	MPW training	Medical college	Faculty in charge of RNTCP	MPW module	2
Other paramedical staff	MPW training	Medical college	Faculty in-charge of RNTCP	MPW module	2

*5 days or 12 days modular training for those interested

**Consists of theory classes. Practical training will be imparted during posting to the Chest or Medicine. Departments and the DOTS Cell.

size, composition, and level of organization, types of services delivered and socioeconomic groups served.

Public-private mix includes public-public as well as public-private collaborations. While involving the private sector and other sectors, it is important to have a well-functioning RNTCP in the public sector first. The involvement of other sectors is important to improve the case detection rates under DOTS and successfully treat additional numbers of TB patients. All RNTCP sites, including other sectors will be under regular supervision and monitoring by the programme using the same yardsticks for quality assurance.

TABLE 49.8: The maximum duration of training for different categories of staff

Category	*Maximum duration (days)*	*Venue*
STO/STDC	5	Central institute
DTO/MO-TC	3	STDC
STS	2	STDC
STLS	3	STDC
LT	2	District
MO/TO/SA/IEC officer	2	District
Pharmacist/Staff drug management (state/district/TU)	1	District/TU
MPHS	1	District/TU
TB health visitor, etc.	1	TU/PHI
MPW/HA, etc.	1	TU/PHI
Anganwadi worker/midwives/community volunteers, etc.	1	TU/PHI
Community-based DOT providers	1	TU/PHI
Accountant	1	State/district
EQA (Master Trs/Microbiologist)	2	Central institute
EQA-IRL LT	2	Central institute
EQA (STDC Dir/STO)	1	Central institute
EQA (DTO/MO-TC)	1	STDC
EQA (STLS)	1	District
TB-HIV(DTO/MO-TC)	1	STDC
TB-HIV (MO)	1	District
TB-HIV (STS/STLS)	1	District

Other Health Providers Involved in PPM

- Government health facilities outside state health departments
- Medical colleges
- Private providers
- Nongovernmental organization
- Corporate sector.

Government Health Facilities Outside State Health Departments

All health establishments under ESI, Railways, CGHS, Defense, Petroleum and Natural Gas, Chemical and Fertilizer, Coal, Steel, Mines, Power, Ports and Prisons come under this group. Most of these departments have been involved in the RNTCP at the central level. State/districts have to ensure that these facilities at the local level are also involved. Directives from the various ministries/departments that control these government health facilities have been made available to the DTOs so that they can facilitate the process.

Private Providers

Private providers are very accessible to patients and can play a key role in TB control. They can be private practitioners or private hospitals/nursing homes practicing modern medicine or other systems of medicine. The first contact of a large proportion of TB patients is a private practitioner. It has been acknowledged that involving private providers helps to improve both case detection and access to standard services under RNTCP. It is vital to have a regular and continuous interaction with the private health care providers to sustain their involvement. To achieve good treatment outcomes, private providers must follow standard RNTCP guidelines. A laboratory owned by a private provider could be considered to be designated as a microscopy center only after it has fulfilled all criteria laid down under RNTCP.

The details of schemes are available in the document “Involvement of Private Practitioners in the RNTCP” published by Central TB Division.

Corporate Sector

Corporate sector includes registered for-profit companies, whether under government or private ownership. They are involved in managing TB in the workplace, either by referring suspects to the RNTCP or, where appropriate, implementing their own workplace programs, especially as DOT centers or DMC-cum DOT centers.

Corporate sector may refer patients to the public sector DMC/DOT center, recognized private sector DMC/DOT center, or may run a DMC or DOT center on its own following the policies and guidelines of RNTCP. RNTCP provides drugs, laboratory consumables, printed material and training to the key staff. A laboratory owned by a corporate sector entity could be designated as a microscopy center only after it has fulfilled all criteria laid down under RNTCP.

Nongovernmental Organizations

For expanding the reach of RNTCP, the Government of India has prepared policies, guidelines and schemes to involve the NGOs. Commodity assistance and grant-in-aid are provided as per the scheme of involvement.

The details of schemes are available in the document "Involvement of NGOs in the RNTCP" published by Central TB Division.

Medical Colleges

Involvement of medical colleges in the RNTCP is a high priority. Continuing success of RNTCP requires involvement of all large providers of health care, including medical colleges. Under RNTCP medical colleges play important roles in service delivery, advocacy, training and operational research.

A National Task Force (NTF) and five Zonal Task Forces (ZTF) have been formed for their effective involvement in RNTCP. Within each zone, nominated medical colleges have been given the responsibility to function as nodal centers. All states, which have medical colleges have formed State Task Forces (STF). In each medical college, there should be a core committee to arrange for training and oversee the functioning of RNTCP in their respective institutions.

The NTF comprises of representatives from 7 nodal medical colleges, CTD, TRC, NTI, LRS and WHO. It has a chairman who is selected on rotational basis from amongst the 7 nodal medical colleges. DDG (TB) is the member-secretary of the NTF. The main task of NTF is to provide leadership and advocacy, coordination, undertake monitoring, lead operational research and support policy development on issues related to the effective involvement of medical colleges in RNTCP.

The ZTF has a representative from the nodal center as chairman, member secretary is the STO of the state where nodal center is located and the members include representatives of the State Task Forces within the zone (1 medical college per state) and STOs of the states within the zone.

The STF has a representative from a medical college in the state as chairman, member secretary is the STO of the state and the members include representatives of each of the medical colleges of the state, on rotation basis if required.

A Medical College Core is formed in each medical college, including least four members, with representatives from the department of medicine, chest medicine, microbiology and community medicine. Coordination of TB control activities is done by DTO.

Management of TB Cases Presenting to a Hospital as Outdoor Patients

RNTCP diagnostic algorithms are to be strictly adhered to by all attending physicians. Diagnosed TB patients should be referred to the local DOTS center in the respective hospital/medical college. Patients coming from the district in which the hospital is situated should be started on DOTS therapy only after the verification of their address. Wherever required RNTCP can provide medical colleges with additional human resource to implement and coordinate the activities with the TU/DTC. One medical officer, one STLS, one LT and one TB health visitor can be provided on contractual basis through the District TB Control Society. Drugs, consumables, etc. will be provided by the DTO.

If patient is required to be referred to another health facility for DOTS, the "referral for treatment" mechanism is to be followed (refer to section on recording and reporting). The respective STS is responsible for tracking of these referral cases. Program review meetings held in the district should be utilized to facilitate the tracking and feedback of referred cases. The receiving treatment facility should honor diagnoses made at the medical college/hospital and must provide feedback to the referring unit.

Management of TB Cases Presenting to a Hospital as Indoor Patients

All indoor patients are to be treated with RNTCP regimens using prolongation pouches, which will be supplied by DTO. The DOTS center of the respective medical college must be informed of the patient's admission at the earliest, to enable transfer of the patient to their respective DOTS center on discharge. On discharge, patients may be given a maximum of three doses (one week drug supply) to cover intervening period prior to their continuation of treatment at their respective DOTS center, hence ensuring no interruption in treatment.

All indoor patients treated under RNTCP, should be registered under the local TU where the medical college is located. The smear conversion and treatment outcome of all the transferred patients should be sent back to the TU of the medical college by the TU where the patient was transferred to.

MULTIDRUG-RESISTANT TUBERCULOSIS AND DOTS PLUS

Multidrug-Resistant TB is a specific form of drug-resistant TB due to bacilli resistant to at least isoniazid and rifampicin, with or without resistance to other anti-TB drugs. The diagnosis of MDR-TB is a laboratory-based diagnosis (from an RNTCP quality assured culture and drug susceptibility testing laboratory) and not a clinical diagnosis. Drug resistance arises due to the improper use of antituberculosis drugs during the treatment of tuberculosis patients. This improper use includes:

- Administration of inadequate treatment regimens by various health care providers
- Wrong treatment categorization due to failure to elicit the history of previous anti-TB treatment by attending physician
- Poor treatment management, when the treatment is not directly observed. Irregular and incomplete treatment due to the lack of effective counseling of patients

Regular chemotherapy under DOTS strategy can prevent the emergence of MDR-TB.

Extent of MDR-TB in India

The prevalence of MDR-TB among new smear-positive cases is relatively low in the country. Studies carried out in six districts during 1999–2002 as per the WHO guidelines on drug-resistance surveillance, showed that 0.5 to 3% of new cases and 12% of previously treated patients were found to harbor MDR-TB bacilli.

Drug Resistance Surveillance

In order to monitor the level of drug resistance in the country, Drug-resistance Surveillance (DRS) is being conducted among both new and previously treated cases in a phased manner in selected states. The national and state-level RNTCP culture and drug susceptibility testing laboratory network will undertake these DRS surveys. The RNTCP designated microscopy centers in each district are assigned the role of identification and enrolment of smear-positive cases for the DRS surveys. RNTCP accredited state level Intermediate reference laboratories perform the culture and Drug Susceptibility Tests (DSTs), with the three national reference laboratories (LRS, NTI and TRC) providing technical support. TRC, which is also a WHO Supranational Reference Laboratory, is responsible for overall quality assurance.

Prevention of MDR-TB

As the management of MDR-TB is very complex, its occurrence must be prevented by the effective implementation of the DOTS strategy.

Proper categorization for the treatment of patients by the attending medical officer, by eliciting any history of previous TB treatment, is very important. The diagnosed patients should be explained why it is essential to know about previous anti-TB treatment, and subsequently the need for them to take their drugs under direct observation. DOT providers should be supervised to ensure DOT provision is as per guidelines. DOTS has been documented to not only prevent the emergence of multidrug-resistance, but also to decrease its prevalence in the community.

Management of MDR-TB

Firstly, it must be remembered that the most important cause of treatment failure is the inability to administer complete and regular treatment to a patient, and not due to drug-resistant bacilli. However, TB cases that continue to be smear-positive at the end of four months or later of an RNTCP Category II treatment may be suspected of having MDR-TB. Only these patients should have a sputum sample collected and sent for culture and DST to an RNTCP quality assured culture and DST laboratory. The STDCs/IRLs are being strengthened to provide such facilities in each state. Diagnosed cases of MDR-TB should be referred to and treated only at a specialized center. Treatment of MDR-TB requires prolonged chemotherapy (24 months), which is also very expensive and toxic. Moreover, the chances of treatment success are moderate.

In 1998, WHO and several partners around the world conceived the DOTS-Plus strategy. DOTS-Plus works as a supplement to the standard DOTS strategy, and is a comprehensive management strategy to address both drug susceptible and MDR-TB, which includes sustained political commitment, diagnosis of MDR-TB through quality assured culture and DST, appropriate treatment strategies that utilize second line drugs under proper management conditions, uninterrupted supply of quality assured second line anti-TB drugs and a standardized

DOTS-Plus recording and reporting system. RNTCP plans to start treatment in 2006 of MDR-TB patients at selected DOTS-Plus sites in the country. By 2010, there will be a network of RNTCP DOTS-Plus sites throughout the country with the facilities to enroll on treatment at least 5,000 MDR-TB patients a year (refer to RNTCP DOTS-Plus guidelines).

INFECTION CONTROL AND HOSPITAL WASTE MANAGEMENT

The Government of India under its Environment Protection Act (1986), passed the Biomedical Waste (Management and Handling) Rules in 1998 and a subsequent amendment followed in 2000. The rules form the legal framework for the collection, segregation, transportation, treatment and disposal of biomedical waste throughout the country. The State Pollution Control Boards (SPCBs) in the states and the Pollution Control Committees (PCCs) in the union territories are monitoring the compliance to the rules in the respective states.

The RNTCP is integrated into the general health system of the states. Waste management is a component of overall facility management of the respective state health system institutions where RNTCP centers are located. Accordingly, the waste generated by RNTCP should not be viewed in isolation, but is to be integrated in the broad framework of the peripheral institutions' waste management practices. The peripheral health institutions would be responsible for the disposal of wastes and reporting to their respective PCBs.

Types of Wastes Generated by the RNTCP

- Human/biological waste (sputum)
- Sharp waste (needles, glass slides, etc.)
- Used blister packs, drug packaging material
- Plastic waste (waste generated from disposable syringes, cups and glasses)
- Laboratory and general waste such as liquid waste, broomsticks and paper waste
- Construction waste (waste generated from civil work activities).

Waste generated under RNTCP will be discarded with the overall waste of the health facility in which services under RNTCP are provided. The staff carrying out RNTCP activities like LTs and DOT providers in PHIs will adopt infection control techniques as detailed in these guidelines and will take action to integrate waste generated under RNTCP into the waste management activities of the concerned PHI. The activities by the PHIs will include organized waste collection, information dissemination, reporting and monitoring of disposal of the waste.

Disposal of Sputum Container with Specimen and Wooden Stick

Sputum containers procured under RNTCP should be made of non-PVC plastic material (polypropylene wherever available).

Step 1: After the smears are examined, remove the lids from all the sputum cups.

Step 2: Put the sputum cups, left over specimen, lids and wooden sticks in the foot operated plastic bucket/ bin with 5% phenol or phenolic compound diluted to 5%. The cups and lids should be fully immersed in the solution. Keep it overnight/ for at least 12 hours.

Step 3: Next day, after at least 12 hours of immersion, drain off the phenol solution into the drain.

Step 4: Take out the sputum cup/lid/wooden sticks and put into a reusable metal or autoclavable plastic container or red bag. The red bag should have a biohazard symbol and be of adequate strength in order to withstand the load of waste. It should be made of non-PVC plastic material.

Step 5: Put this container/bag into the autoclave with other autoclavable biomedical waste and autoclave at 12° C under 15 psi pressure for 15 to 20 minutes. The autoclave shall comply with the standards stipulated in the rules. Under certain circumstances, if autoclaving is not possible, boil such waste in a pressure cooker of approximately 7 liter capacity containing adequate amount of water to submerge the contents and boil for at least 20 minutes using any heating source, electrical or nonelectrical. However the district hospital/CHC/PHC, etc. shall ultimately be expected to make the necessary arrangements to impart autoclaving treatment on regular basis.

Step 6: After adequate cooling, the material can be safely transported to a common waste treatment facility for mutilation/shredding/disposal.

If a Common Waste Treatment Facility (CWTF) is not available in the area, the sputum cups/lids/wooden sticks after autoclaving, can be disposed in a deep burial pit.

LTs and support staff handling biological waste should wear gloves (universal infection control pre-cautions).

Refer to biomedical waste (management and handling) rules and guidelines.

Disposal of Used Syringes/Needles/Broken Vials

Step 1: Immediately after administering the injection, cauterize the needle on site using a suitable needle destroyer/cutter, followed by cutting of the plastic hub of the syringe without detaching the needle from the syringe.

Step 2: Put the cauterized needles, broken vials and ampules into a sturdy puncture proof white translucent plastic/cardboard container.

Step 3: Segregate and store cut plastic syringes in a reusable metal or autoclaveable plastic container/red bag. If a bag is used, its strength should be such that it can withstand the load of waste inside and be made of non-PVC plastic material.

Step 4: Label both the container with biohazard symbol as stipulated in the Schedule III of the Biomedical Waste (Management and Handling) Rules 1998.

Step 5: Put both the containers in the prescribed bag and transport in a dedicated vehicle to the common waste treatment facility for autoclaving, mutilation/shredding, and/or disposal.

Step 6: If a CWTF does not exist, put both sharp container (needles) and metal/plastic container/red bag (syringes) into an autoclave with other BMW, and autoclave at 12° C under 15 psi pressure for 15 to 20 minutes. Under certain circumstances if autoclaving is not possible, boil such waste in water for at least 20 minutes. However, the district hospital/CHC/PHC, etc. should ultimately be expected to make the necessary arrangements to autoclave the waste on regular basis.

Step 7: Dispose off the autoclaved waste as follows:

- Dispose off the needles and broken vials into a sharps pit; and
- Send the syringes for shredding/mutilation or as a landfill in a deep burial pit.

Disposal of Used Slides

Step 1: Place the slides into a puncture-proof container or red bag. The red bag should have a biohazard symbol and should be made of non-PVC plastic material. This bag/sharp container should then be put into an autoclave or pressure cooker for autoclaving/boiling.

Step 2: Dispose of the slides into a pit for sharps.

Under no circumstances should the slides be broken or recycled.

INFORMATION, EDUCATION AND COMMUNICATION

Information, Education and Communication (IEC) is an important component of the RNTCP. Information, education and communication activities under the RNTCP aim to promote a better understanding of TB, especially its diagnosis, treatment and cure; improve the quality of care provided to TB patients; reduce stigma and improve utilization of RNTCP services.

Information, education and communication under RNTCP has the strategic framework for communication that identifies the communication need (objectives), communication players/audience (target groups) and communication tools (channels, activities and materials).

Objectives of IEC under RNTCP

1. *Awareness raising* for behavior change to increase understanding about TB and the use of DOTS services among:
   - The public so that they make use of RNTCP services
   - Health care providers so that they adopt DOTS strategy.
2. *Advocacy* to create, facilitate, develop and forge political, administrative and community-level commitment to TB control in India.
3. *Patient-provider communication and counseling* to help ensure patient compliance with the treatment regimen, to enhance the reputation of a patient friendly service, and to encourage patients and their families to become advocates for the program.

Target Audience

The target audiences for IEC include:

- Patients and community
- Health care providers—both private and public
- Opinion leaders, that includes: Political leaders, state bureaucrats and administrators, PRIs, women groups (mahila mandals), youth clubs, self-help groups (SHGs), professional organizations, etc.

Communication Channels, Activities and Materials

The core messages for the target groups are standardized at central level to ensure that the accuracy of messages is not compromised or diverted from the program's objectives. The messages are tailor-made for each of the target audience. The center provides general outline, and states can develop adaptation using local innovations to reach all possible groups through the appropriate channels, material and activities.

A mix of media options is used to enhance the reach and impact of health communication messages. The use of interpersonal channels, mass media, and nonelectronic media and outdoor media is used to address the large gamut of target audience.

Interpersonal Channels

The value of interpersonal communication has been recognized: Satisfied cured patients are good advocates; interactive meetings are effective in addressing social issues and barriers.

Mass Media

Mass media plays an important role in raising general awareness of TB, efficacy and free availability of DOTS, and advocate support to the program among influential groups and individuals by raising the profile of the program and increasing its visibility amongst opinion leaders. Mass media is important to get information disseminated far and wide.

Nonelectronic and Outdoor Media

Interpersonal approaches are complemented by the options for reaching people in groups or on a collective scale. These include local popular folk media, street plays, use of local markets, mike publicity, puppet shows, activities in schools, wall paintings, hoardings, exhibitions at fairs, etc.

Roles and Responsibilities for IEC Activities at the Center, State and District

The Center takes leadership; states and districts plan and implement IEC activities. Districts draw support from local organizations, PRIs, NGOs, SHGs and there is a two-way flow of information/ideas from and to the center and the state.

Role of Center in IEC

The center has an Advocacy and IEC unit that is assisted by IEC Advisory Group, comprising of honorary members from the centers of excellence in the field of communication, research, media planning and teaching. The center provides:

- Overall leadership for the IEC component
- Procure services of IEC agency and coordinate activities
- Manage the mass media component at national level
- Provide oversight of the national level IEC strategy, assessing capacity for IEC at state level, and providing support where necessary.

Role of the State in IEC

The overall responsibility of planning and implementing IEC activities rest with the state tuberculosis officer. The IEC officer is the nodal person at the state level to assist STO for undertaking following activities:

- Planning of IEC activities for the state, including the district level activities
- Support to districts for planning and implementing IEC activities
- Monitoring and supervision of IEC activities
- Mobilizing support/resources for implementing IEC activities with the involvement of other state/district departments
- Developing material in local languages
- Organizing events for advocacy
- Capacity building of districts for implementing activities for awareness generation and social mobilization

The communication facilitator can be an individual, NGO or an agency to help and assist districts in planning and implementing IEC activities at the subdistrict level. One communicator facilitator is responsible for five to six districts. The responsibility for identifying and appointing communication facilitator is with the state. All districts must be covered by the communication facilitator.

Role of District in IEC

The district is a link between the state and the primary health institutions in the terms of training and dissemination of IEC activities. District is to develop IEC action plan (according to the needs, targets audiences and available communication channels) with the help of IEC officer of the state and is assisted by communication facilitator for the implementation of IEC activities. The district is responsible to:

- Develop plan for IEC activities with sufficient flexibility to allow for local initiatives and variations
- Use local appropriate medium for dissemination of information.
- Seek involvement of local organizations, leaders, *panchayats* and NGOs for IEC
- Organize certain minimum number of activities, such as community meetings, mike publicity, display of posters at each PHI, interaction meetings, wall paintings, puppet shows/street plays/*nautaukis*/*nukkad nataks*, etc.

Monitoring of IEC in RNTCP

Monitoring and supervision of IEC activities is an important aspect. States are responsible for overseeing district and subdistrict level IEC activities. Monitoring indicators for IEC activities have been included in the monitoring strategy for reporting on the activities conducted at the district level, as part of PMR report. Supervisory IEC checklist is used for overseeing that activities have been undertaken as planned.

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Treatment of Tuberculosis in Special Situations

Rajendra Prasad

INTRODUCTION

Treatment of tuberculosis poses a difficult clinical problem in special situations like pregnancy, renal insufficiency and liver diseases. There are various concerns regarding dosage, toxicity and the method of administration of drugs. Prior to discussing the specific issues, it is important to know the important pharmacokinetic characteristics of individual antitubercular drugs.

PHARMACOKINETICS OF ANTITUBERCULAR DRUGS

Some antituberculosis drugs are metabolized in liver; while others are excreted either unchanged or in metabolized form, by the renal route. Their secretion in milk and ability to cross placenta is important in the situations of lactation and pregnancy, where there is concern of safety and morbidity of the baby.

Isoniazid is rapidly absorbed from gut, metabolized in liver by acetylation and the inactive metabolites are excreted in urine within 24 hours. Its half-life varies from one group of population to other, depending upon hepatic acetylation. Half-life is less than one hour in rapid acetylators, and more than three hours in slow acetylators. It is secreted in milk, but the amount is not sufficient to provide antitubercular chemoprophylaxis to infant. It is safe in pregnancy, but the risk of hepatitis may be increased in the postpartum period.[1] Rifampicin is rapidly absorbed and widely distributed to tissues and bound to plasma protein. Its absorption is reduced if given with food (not of clinical significance), or if given along with Para-aminosalicylic Acid (PAS). It is extensively recycled by enterohepatic circulation, and the metabolites formed by deacetylation are excreted in feces. It is found to be safe in pregnancy, with some risk of postnatal hemorrhage.

Ethambutol is rapidly absorbed from the gut. It is predominantly excreted in urine in an unchanged form or an inactive hepatic metabolite (80%).[2] Only 20% is excreted in feces as unchanged drug.[3] Ethambutol is found to be safe in pregnancy and liver disease. Pyrazinamide is also rapidly absorbed from gut, metabolized in liver to metabolites, pyrazinoic acid and 5-hydroxypyrazinoic acid, which are excreted largely by the renal route.[4] Its safety in pregnancy is somewhat controversial.[4] Streptomycin is largely concentrated in the extracellular fluid. In pregnant women, it may interfere with development of fetal ear.[5] Plasma half-life is prolonged in the newborn, elderly patients and in patients with renal failure. It is excreted unchanged in urine. Pharmacokinetics of amikacin, kanamycin or capreomycin are similar to those of streptomycin, and found unsafe in pregnancy, where they may cause fetal nephrotoxicity or congenital deafness.[5] They are considered safe in liver disease.

Ethionamide and prothionamide are toxic to liver and teratogenic in pregnant animals. Their safety in liver disease and pregnancy is doubtful, and should not be used in pregnant women. They are considered relatively safe in mild renal disease. Cycloserine is about one-third metabolized, and the rest excreted in urine. It is not safe in patients with renal failure. In alcoholics, it may lead to seizures. It crosses the placenta in pregnancy, and its safety in this situation is not yet established. PAS is not safe in renal failure. About 80% of drug is excreted in urine, and it should be avoided in severe renal insufficiency, where it may aggravate the problem of metabolic acidosis.[6] Old preparation of PAS interacted with rifampicin absorption, but new preparation of granules has no interaction with it.[7] There are no studies on its safety, in pregnant women, but it has been safely used in pregnancy in the past. Fluoroquinolones are also not found safe, as they are found to inhibit the growing cartilages of bones in animal studies. About 80% of levofloxacin is cleared by kidney, its dose adjustment is recommended in the cases of renal insufficiency.[8] These drugs, except ciprofloxacin, which is metabolized in liver are generally safe in the cases of liver disease.

TREATMENT OF TUBERCULOSIS IN PREGNANCY AND LACTATION

Isoniazid is considered safe in pregnancy, except for some chance of postpartum hepatitis.[1] The American Thoracic Society (ATS) recommends supplementation with pyridoxine during pregnancy (25 mg/day).[4] Use of rifampicin and ethambutol is safe in pregnancy. Data regarding other rifamycins (rifabutin and rifapentine) is insufficient, and thus, they should be cautiously used. Safety regarding pyrazinamide cannot be assured, but when used for six months regimen, the benefits may outweigh the possible risk.[3]

Streptomycin may cause congenital deafness, as this drug interferes with the development of ear.[5] Other injectables, like amikacin, kanamycin and capreomycin having pharmacokinetics similar to streptomycin, may also cause fetal nephrotoxicity and ototoxicity.[5] One study reported that 17% of babies born to ladies who received streptomycin during pregnancy, developed hearing loss.[9] Ethionamide and prothionamide are contraindicated in pregnancy, as they are found teratogenic in animal studies. Cycloserine crosses placenta, and since, its safety in pregnancy is not established, it should be avoided, and used only if no other suitable alternatives are available.[5] PAS has been used safely in pregnancy in past. Since, no well designed study has been done to ascertain its safety in pregnancy, it should be used only in the absence of any other alternative. Fluoroquinolones being toxic and inhibitor of growing cartilage in animals, should be avoided in pregnancy.[9]

Treatment of tuberculosis in a pregnant woman is far less hazardous than leaving the disease untreated, both with regard to the baby and the mother. Tuberculosis in pregnancy may lead to the birth of an underweight infant or to congenital tuberculosis.[10] Risk of miscarriage is much higher in active tuberculosis than the risk from the drug treatment, so standard treatment should be given. Treatment regimen for drug sensitive tuberculosis should include at least the three first line drugs—rifampicin, isoniazid and ethambutol. Streptomycin should not be used. Opinion regarding the use of pyrazinamide is divided, but World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD) recommend its use.[3] ATS does not confidently advocate its use.[4] According to WHO, six months regimen based upon isoniazid, rifampicin and pyrazinamide should be used whenever possible, and ethambutol should be used only if a fourth drug is needed during the initial phase.[3] Contrary to this, ATS recommends that pyrazinamide should better be avoided in pregnancy, because of the lack of sufficient data for its safety.[4] If pyrazinamide is not used, duration of treatment should be prolonged to nine months. Although, isoniazid, rifampicin and ethambutol cross the placenta, they are not found to be teratogenic.[9]

Women taking first line antituberculosis drugs should not be asked for termination of pregnancy, while those on reserve drugs should be counseled for possible adverse effects. Breastfeeding should not be discouraged, as the amount of drugs secreted in milk is insufficient to cause any toxic or therapeutic effect. Supplemental pyridoxine is recommended for both the nursing mother and her infant, even if no isoniazid is being given to the infant. All antituberculosis drugs can be used during lactation, except fluoroquinolones.[9] Baby of a woman who has taken rifampicin during pregnancy should receive vitamin K at birth, to avoid the risk of postnatal hemorrhage.[3] Rifampicin may induce metabolism of vitamin K and hamper hepatic synthesis of vitamin K dependent coagulation factors.

Women taking oral hormonal contraceptives should be counseled for possible contraceptive failure and occurrence of pregnancy. This is especially so in women on rifampicin containing antitubercular treatment regimen, because of the induction of metabolism of contraceptive drug by rifampicin.[11,12] Such women should be advised to use non hormonal contraceptive measures during, and for one month after treatment with rifampicin containing regimen.[12,13]

TREATMENT OF TUBERCULOSIS IN RENAL INSUFFICIENCY

Treatment of tuberculosis in renal insufficiency poses a difficult clinical problem because various antituberculosis medications are cleared by kidney. On one hand, it raises the concern of drug-induced toxicity due to impaired excretion by the diseased kidney, while on the other hand, it raises the concern of under treatment of tuberculosis. In later situation, adequate peak serum concentration is usually low, and not of therapeutic use.[4] Another issue of concern is the achievement of the therapeutic level of antituberculosis drugs in patients with end stage renal disease, undergoing hemodialysis, which may alter/lower the serum drug levels.

The British Thoracic Society advocates dose reduction for drugs, which are excreted by the renal route, while the American Thoracic Society prefers increasing the dosing interval instead of decreasing the dose.[4,11] Administration of drugs,which are excreted by kidneys should be changed by increasing the dosing interval, if creatinine clearance falls below 30 ml/min. There is paucity of data to guide the dosing recommendation if creatinine clearance is above 30 ml/min, when standard doses should be prescribed.[4] Rifampicin and isoniazid are eliminated by liver, and they could be given in the usual dosages.[14] Population with slow hepatic acetylation of isoniazid, could be given supplemental pyridoxine to prevent peripheral neuropathy.

Alteration in dose of ethambutol, which is 80% excreted by kidney,[2] should be made if creatinine clearance falls below 70 ml/min,[4] to the lowest possible dose, but if it falls below 30 ml/min, it should be given intermittently as three times a week in dose of 15 to 20 mg/kg body wt.[4] Pyrazinamide is metabolized in liver, but its metabolites, pyrazinoic acid and 5-hydroxypyrazinoic acid are excreted by kidneys.[15,16] Thus, the drug should be given three times a week, in dose of 25 to 35 mg/kg body weight, to avoid toxicity, if creatinine clearance falls below 30 ml/min.[4] Apart from this, the risk of developing hyperuricemia with pyrazinamide is increased in the cases of renal insufficiency.

Since, streptomycin is predominantly excreted by the renal route, and removed by hemodialysis to a significant extent (about 40%), it should be administered three times a week in dose of 12 to 15 mg/kg body weight in patients of renal insufficiency with creatinine clearance below 30 ml/min, and those on hemodialysis.[4,17] Since, pharmacokinetics of other aminoglycosides are similar to those of streptomycin, they need similar modifications of dosages.[4] Renal clearance of fluoroquinolones varies from drug to drug. It is greater for levofloxacin than moxifloxacin.[18] Dose adjustment for fluoroquinolones is recommended if creatinine clearance is less than 30 ml/min (750 to 1,000 mg, three times a week).[4]

Ethionamide need no or little alteration of administration as it is not excreted by kidney.[19] If creatinine clearance is less than 30 ml/min, dose of ethionamide should be reduced to 250 to 500 mg/day.[4] Dose of cycloserine should be modified if creatinine clearance falls below 30 ml/min or patient is on hemodialysis. It should be changed to 500 mg thrice a week or 250 mg daily.[4] Evidence for safety of 250 mg daily dose of cycloserine is not yet established with regard to neuropathy; 500 mg three times a week, is preferred. Serum concentrations of drug should be monitored. PAS is not safe in renal disease and should only be given if no other alternative is available, as it may aggravate metabolic acidosis.[6] It should be given at a dose of 4 gm/dose, twice daily. Thioacetazone, also excreted in urine, should not be given to patients with renal disease.[20]

Hemodialysis may remove the drug before its therapeutic effect is established. If the drug is given sufficiently before hemodialysis, far less drug is likely to be removed. It therefore, gets time to be distributed throughout the body. Administration of drug after hemodialysis, will avoid the premature removal of drug. This may also facilitate the Directly Observed Treatment Short-course (DOTS) strategy indirectly.[4] Premature removal of second line drugs, by hemodialysis, may further aggravate the problem of drug resistance by exposing the tubercle bacillus to subtherapeutic drug concentrations. Rifampicin, isoniazid and ethambutol are removed to a much less by hemodialysis, but pyrazinamide is removed to a significant extent.[15] Thus, supplemental dosing is not needed with isoniazid, rifampicin and ethambutol, in patients of end stage renal disease, undergoing hemodialysis. Similar to streptomycin, about 40% of drugs like kanamycin, amikacin and capreomycin are removed from blood, if they are given just before hemodialysis.[17] Fluoroquinolone and ethionamide are not cleared by hemodialysis and thus, their dose need not be altered in this situation.[18, 19] Usually, hemodialysis does not pose significant problem, if drugs are given after the procedure.

Ideally, it is important to monitor serum concentrations of drugs in persons with renal failure who are taking aminoglycosides, cycloserine or ethambutol to provide effective therapeutic drug concentrations and also to minimize dose related toxicity. Patients with renal failure may have other comorbid conditions, like diabetes mellitus and gastroparesis, which may further complicate the pharmacokinetics of drugs.[21] Presently, there is no data to guide administration of antituberculosis drugs in patients undergoing peritoneal dialysis. For this subset of patients, recommendations as of hemodialysis, are applicable. The safest regimen that is being advised in patients diagnosed as the new cases of tuberculosis with renal insufficiency, is rifampicin, isoniazid and pyrazinamide for two months followed by rifampicin and isoniazid for next four months.[20]

TREATMENT OF TUBERCULOSIS IN LIVER DISEASE

Treatment of tuberculosis with deranged liver functions presents with two major clinical scenes. First is the issue of antitubercular drug-induced hepatotoxicity and second, use of antitubercular drugs in persons with pre-existing liver disease. Various antitubercular drugs are potentially hepatotoxic, and administration of these drugs may aggravate liver disease, in a patient with compromised liver function. Drugs like ethambutol, streptomycin, kanamycin, amikacin and capreomycin are safe in liver disease as they are neither significantly metabolized, nor toxic to liver. [4]

Drug-induced Hepatotoxicity

It is found that, the period of latency between the start of drug regimen and the occurrence of drug-induced hepatitis is usually four to nine days.[22] It must be known that, about 10 to 30% of patients receiving antituberculosis therapy may normally have the transient rise of bilirubin and liver enzymes [Serum Glutaryl Pyruvate Transaminase (SGPT) and Serum Glutaryl Oxalate Transaminase (SGOT)], to about one to three times the normal, during the first-two months of therapy. The levels generally come down on continuation of treatment. It is of interest to note that about 10% of patients, who develop mild transaminase elevation (i.e. 1 to 2% of all treated adults), may have severe hepatitis and liver failure until the drug is discontinued. This clinical condition has the case fatality of approximately 10%. Drug-induced hepatitis is diagnosed, when serum level of SGPT or SGOT rises more than 150 IU/lit on more than three occasions, or greater than 250 IU/lit on one occasion, along with values of serum bilirubin of more than 34.2 micromol/ lit (2 mg%).[22]

The incidence of isoniazid induced, clinical hepatitis is lesser than was previously thought. Hepatitis occurs in 0.6% patients, if isoniazid is given alone, but it is 1.6% if given with drugs, other than rifampicin.[23] With rifampicin, the incidence of hepatitis is 2.7%. Risk of drug-induced hepatitis, increases with age, and it is 2% in persons aged 50 to 64 years. Rate of fatal hepatitis is 0.023%. If it is given to patient with preexisting liver disease, it may accumulate in body and further increase the risk of drug-induced hepatitis.[4] Frequent monitoring of serum level of hepatic transaminases is indicated in this clinical setting.[3]

Patients with alcoholic liver disease, are at increased risk of peripheral neuropathy, and should be given pyridoxine prophylactically at a dose of 10 mg daily.[3] Rifampicin may cause normal transient hyperbilirubinemia in 0.6% patients. Incidence of hepatitis is 2.7% if it is given with isoniazid, and it is 1.1%, if given with a drug other than isoniazid.[23] Clearance of rifampicin, may be impaired, causing serum levels to rise, if it is given to a patient with pre-existing liver disease. Careful monitoring of liver functions is indicated in such patients.[3]

All the three first-line drugs isoniazid, rifampicin and pyrazinamide are associated with hepatotoxicity. Of the three, rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, ethionamide, protionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with the fluoroquinolones.[24]

Chemical structure of ethionamide is similar to that of isoniazid. It can cause liver toxicity in about 2% patients, and should be cautiously used in the presence of pre-existing liver disease. PAS may cause clinical hepatitis in 0.3% cases. Since, pharmacokinetics of PAS are not significantly altered in liver disease, it could be used in usual doses and usual regimen.[6] Cycloserine can be safely used in liver disease, except in the case of alcohol related hepatitis, where it increases the risk of seizures.[5] Thioacetazone is hepatotoxic, and it should be avoided. Fluoroquinolones except ciprofloxacin, are safe for use in liver disease.[13]

Advanced age, female sex, poor nutritional status, preexisting liver disease, chronic alcoholism, Hepatitis B carrier state and slow acetylator status are considered risk factors for antitubercular drug-induced hepatitis.[22,,24-26] Several studies have observed relation between serum markers for viral hepatitis and antituberculosis drug-induced hepatitis. It has been observed that viral hepatitis complicates treatment more frequently with regimen containing both rifampicin and isoniazid, than with regimen having only one or none of them.[22, 25]

It is often difficult to find the culprit drug, in a multidrug regimen, causing drug-induced hepatitis. The rise in serum transaminase activity within 15 days of starting regimen is usually attributed to rifampicin, but if it occurs after one month, it is usually attributed to pyrazinamide.[25] Whether the toxicity occurs due to their additive effect, synergistic effect, hypersensitivity phenomenon or direct effect is not known. The Joint Tuberculosis Committee of the British Thoracic Society recommends that liver functions should be monitored weekly during the first-two weeks, and then at two weekly interval, in patients who have pre-existing liver disease.[27] Recommendation for the frequency of monitoring liver functions, in patients with no known risk factors is not clear.

If a patient on antituberculosis therapy develops mild and transient elevation of serum bilirubin or liver enzymes, treatment need not be stopped. They usually come down during the course of treatment. If patient develops hepatitis related symptoms with the significant elevation of bilirubin and liver enzymes, treatment should be stopped and viral hepatitis should be ruled out by serology.[27] Drugs should be gradually reintroduced one by one starting from less hepatotoxic drug first, after liver functions come down to normal, with close monitoring for deterioration.

Antituberculosis Treatment with Pre-existing Liver Disease

In case of stable liver disease, all antituberculosis drugs can be used, with close observation for liver functions. In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment. If the serum SGPT level is more than three times normal before the initiation of treatment, lesser hepatotoxic regimens should be considered. The alternate regimens are devised on the premise that the more unstable or severe the liver disease is, the fewer the hepatotoxic drugs employed. Possible regimens include those that employ two hepatotoxic drugs (rather than three in the standard regimen): (a) Nine months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented); or (b) Two months of isoniazid, rifampicin, streptomycin and ethambutol, followed by six months of isoniazid and rifampicin; or (c) Six to nine months of rifampicin, pyrazinamide and ethambutol is administered.[28]

When the liver disease is too serious to permit use of more than one hepatotoxic drug, a regimen comprising two months of isoniazid, ethambutol and streptomycin, followed by ten months of isoniazid and ethambutol is preferred.[28] In the extreme case of fulminant hepatic failure where antitubercular treatment is indispensable, a regimen devoid of any hepatotoxic drug is prescribed; such as 18–24 months of streptomycin, ethambutol and a fluoroquinolone.[28]

In conclusion, different options are used for the treatment of tuberculosis with deranged liver functions; mild derangements in liver enzymes require merely a close watch on the liver function without modifying the regimen while the progressively declining hepatic reserves prohibit the use of any potential hepatotoxic drug requiring a substantial revision of the antitubercular regimen. Expert consultation is hence desirable in treating patients with advanced liver disease.[28]

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Tuberculosis and Human Immunodeficiency Virus Infection

SK Jindal

INTRODUCTION

The Acquired Immunodeficiency Syndrome (AIDS) recognized first in 1980–81 in patients diagnosed with Kaposi's sarcoma and Pneumocystis Carinii Pneumonia (PCP), was attributed to the Human Immunodeficiency Virus (HIV) infection. In a short span of a little over a quarter of a century, the disease has made an enormously devastating impact on the global health care infrastructure. In particular, it has worsened the scene of Tuberculosis (TB) all over the world by adversely influencing its epidemiology, clinical outcomes and treatment-strategies, forcing major changes in the control programs.

Both TB and HIV infections are deadlier together, TB causing one quarter of AIDS-related deaths and HIV infecting at least 15% of patients with TB worldwide.[1] The HIV and TB coinfection has come to be known as a deadly duet, a difficult and frequently fatal combination. TB is the most common opportunistic infection in HIV infected persons in several countries, including in India.[2]

EPIDEMIOLOGY

There are estimated 33.2 million persons infected with HIV, of whom about one-third are also infected with *Mycobacterium tuberculosis* (*M. tb*).[3] The TB incidence in HIV infected persons is about 100 fold more than in the general population. According to the WHO/UNAIDS estimates, up to half of the patients with HIV or AIDS develop TB. The estimated number of new cases of TB in HIV infected individuals rose by almost 100% from nearly 0.7 million in 2006 to 1.4 million in 2008, TB also accounted for 26% of AIDS related deaths.[2-4]

Most of the increase in HIV related TB, as well as the deaths from TB in patients of AIDS occurred in the developing countries. HIV infection was an important factor for the resurgence of TB in the United States and Europe around the turn of the millennium. However, the effective steps undertaken by these countries have successfully contained the dual epidemic. A recent assessment of population based TB rates among HIV infected persons in the New York City (from 2001 to 2005) was made from the city's TB and HIV/AIDS surveillance registries; TB in HIV infected persons was 16 times the TB rate of a "non-HIV" population.[5] However, the decline was primarily limited to the US born and not the foreign born HIV infected population.[5] A majority of foreign born persons are likely to come from the developing countries, clearly demonstrating the disparities in the prevalence of HIV-TB coinfection.

Although the HIV-TB scene in several countries is dismal, this may not be so, in the India. This is partly attributed to the successful implementation of the Revised National Tuberculosis Control Programme (RNTCP) and the strategy of Directly Observed Therapy Short-course (DOTS). There is an effective HIV-TB coordination undertaken under RNTCP. Moreover, the estimated number of people living with HIV/AIDS (PLWHA) in India has been revised to 2.5 million people from the earlier reported figure of 5.7 million.[6,7] The revised figures are also likely to reflect the reduced HIV-TB burden.

The HIV epidemic has greatly upset the TB control programs of several countries. Tuberculosis has proven to be difficult to control in high HIV prevalence zones.[8]

Considering the observation that almost 80% of persons with TB have HIV infection in some African countries, it has been strongly felt that an integrated preventive strategy is essential for both TB and HIV infection.[8-10] Enhanced implementation of TB-HIV collaborative activities and a focused research agenda are critical to the success of control programs, especially in the resource-limited countries.[10,11]

PATHOGENESIS

The lifetime risk of active TB in HIV infected individuals is as high as 30 to 50% compared to 5 to 10% risk of active disease in tuberculin positive, non-HIV infected individuals.[12] In India, it is estimated that 50 to 60% of HIV infected persons will develop TB during their lifetime.[13] HIV induced immunosuppression is the most important risk factor for an increased occurrence of TB. While HIV infection is responsible for the resurgence of TB in the West, it is an important cause of an increased morbidity and mortality in the high TB burden developing countries.

There are several immunological defects in HIV infection, which predispose to TB and encourage HIV-TB coinfection (Table 51.1). HIV infection is primarily responsible for impaired Cell-Mediated Immunity (CMI) by causing a decline in the number and function of CD4+ subset of T-cells.[14] There is a diminished recruitment and activation of CD4 cells. The other components of CMI, such as the macrophages and peripheral blood monocytes are also affected and their function impaired. There is resultant reduced production and activation of mediators, such as the cytokines and lymphokines. HIV infection also results in an increased secretion of TH-2 (IL4 and IL10) cytokines that are antagonist to (IL-2, IL12 and IFNγ) cytokines, which mediate the immunity to tubercle bacilli. In addition, there is a failure of macrophage differentiation to epithelioid cells and formation of Langham cells. This global impairment of cellular arm of immunity seriously reduces the immune defenses against several intracellular and other pathogens, especially the mycobacteria.

TABLE 51.1: Immune alterations/defects in HIV infection, which predispose to TB

1. CD4+ T cell: Decline in number
    - depletion
    - Functional impairment
    - Diminished recruitment and activation
2. Impairment of macrophages and peripheral blood monocytes.
3. Increased secretion of TH-2 cytokines (IL-4 and IL-10) by the mono nuclear cells.
4. Failure of macrophage differentiation (to epithelioid cells)
5. Lack of formation of Langhans giant cells
6. Enhanced HIV replication by:
    - Increased production of TNF- α by *M. tb*
    - MTB and its cell wall components
    - Beta chemokine monocyte chemotactic protein
    - Down regulation of chemokines

Factors additional to or other than CD4 T-cell decline and impairment may also partly account for increased predisposition to TB.[15] *Mycobacterium tuberculosis* infection may induce nuclear factor binding to the NF-KB sequences in the HIV replication. The increased HIV replication by *M. tb* sets a vicious cycle in both promoting growth of each other and therefore, the continuing damage to the host cells. Tuberculosis can occur in patients with HIV infection at all levels, but the type, severity and manifestations depend on the CD4 T-lymphocyte counts. The greater the degree of immunosuppression and the lower the CD4 counts, more likely the atypical presentation.

As the immunosuppression progresses, there occurs increased likelihood of infection by atypical and opportunistic mycobacteria and decreased tuberculin reactivity. Granuloma formation is impaired while the lesions show high content of intracellular organisms. The absence of inflammatory cellular response in the presence of a large number of organisms and "naked necrosis" is sometimes referred to as "nonreactive" form of TB.

CLINICAL EFFECTS OF HIV ON TUBERCULOSIS (TABLE 51.2)

Increased Susceptibility

HIV infected persons acquire TB infection more frequently when exposed to *M. tb*.[16] This phenomenon of increased susceptibility is now supported by the reports of explosive outbreaks of TB among HIV infected persons exposed to a patient with infectious tuberculosis, 11 of 30 (37%) residents who were exposed to a patient with infectious TB living in a residential care facility for HIV infected persons in San Francisco, developed TB within 120 days.[17] It was also shown with the help of Restriction Fragment Length Polymorphism (RFLP) analysis that all 11 of those patients had TB caused by the same strain of *M. tb* supporting the single source of origin of infection.

Infectivity

On an individual basis, HIV infected patients with TB are less likely infectious than those without HIV infection.

TABLE 51.2: Clinical effects of HIV infection on TB

- i. Increased susceptibility to TB
- ii. Increase infectivity?
- iii. Reactivation of latent TB
- iv. Clinical manifestations:
  - – "Typical"- pulmonary
  - – "Atypical" pulmonary/Pleural TB
  - – Extrapulmonary – Lymphadenopathy, meningitis, brain abscess, pericarditis, peritonitis, liver abscess (and others).
- v. Drug resistant TB
  - – Multidrug resistance
  - – Extensive drug resistance
  - Poor treatment response
  - Higher mortality rates
- vi. Tuberculin skin sensitivity
  - – Diminished or absent

There are several possible reasons, for example, TB in HIV infected patients is generally noninfectious extrapulmonary or paucibacillary pulmonary with fewer bacilli in the sputum.[18] This however, is not always true. There are other studies, which report the opposite findings.[19] However, in HIV infected communities with HIV-TB coinfection, the number of persons with communicable TB keeps on multiplying with increased transmission to other people regardless of their HIV status.[20]

Reactivation of Latent Infection

Human immunodeficiency virus increases the rate of TB reactivation in a previously infected patient (latent TB). The annual risk of developing TB in a PLWHA, coinfected with *M. tb* is 5% to 15%.[21,22] Both reactivation of previous infection and exogenous reinfection are reported to occur in these patients.[23] Possibly, reactivation is the more likely mechanism in low prevalence Western countries with a lower level of exposure to patients with active disease, although the occurrence of new infection has been also shown with the help of RFLP analysis.[20,24,25] New infections from different strains are however, common in the high TB-burden countries.[26]

A recent study from Malawi explored differences in "clustering" (i.e. sharing of identical *M. tb* strains) in patients clustered by prior *M. tb* infection and HIV status. In HIV positive TB cases, clustering was similar in patients with previous *M. tb* infection and without prior infection.[26] It was thus concluded that the HIV infection also increased the risk of reinfection following exposure in patients with latent TB.[26]

Clinical Manifestations

The clinical features of TB in HIV infected patients depend upon the severity of immunosuppression.[27-30] (Table 51.2). The presentation in early HIV disease is almost similar to that observed in otherwise healthy individuals, in whom pulmonary disease with focal infiltration and cavities is more common, while extrapulmonary manifestation and other atypical features are common when the CD4+ counts are less than 200/mm^3.[4,31,32]

"Typical" pulmonary disease presenting with fever and other constitutional symptoms, cough, expectoration and hemoptysis is not uncommon. Several of these patients are diagnosed to have HIV coinfection on only serological tests. On the other hand, several series have emphasized the presence of frequently disseminated disease with extrapulmonary organ involvement.[27,28,33-35] Lymphadenopathy, including mediastinal, hilar and peripheral is commonly described. Relatively uncommon sites for TB, such as the gastrointestinal, genitourinary, cardiac and central nervous system are more often involved in the presence of HIV infection. Disseminated disease is a common presentation in childhood TB.[35] Night sweats, fatigue, diarrhea and hepatosplenomegaly are other common features in these patients.[36]

Both pleural and parenchymal pulmonary involvements are common in HIV-TB coinfection.[37] Pleural fluid in the presence of HIV infection may more often show the presence of Acid-Fast Bacilli (AFB), on both smear and culture examinations.[38] These mycobacteria may also show the presence of drug resistance, similar to that seen in parenchymal TB.[38,39]

Occurrence of TB in an HIV infected patient in the previous two years is also used for HIV/AIDS staging. It is categorized as clinical stage 3 disease in case of pulmonary and stage 4 in case of extrapulmonary TB.[40] Systemic manifestations include the presence of associated/complicating illnesses attributed to HIV immunosuppression. Recurrent pneumonias, diarrhea, herpes zoster infection and mucosal (oral/genital/gastrointestinal) ulcerations are common. Weight loss of more than 10 kg or more than 20% of original weight loss is an important AIDS defining criterion.

Drug Resistance

Emergence of Multidrug Resistance (MDR) and Extensive Drug Resistance (XDR) TB strains is a serious challenge all over the world[41] (see Chapter 48). There occur around 490,000 cases of MDR-TB with more than 110,000 deaths and 40,000 XDR-TB cases every year as per the WHO estimates.[42] It is further assessed that only 7% of MDR-TB were identified and reported to WHO, of whom only one-fifth were noted according to WHO standards.[41] Although there is no real evidence to suggest an increased predisposition, there exists a theoretical association in view of the increased susceptibility and higher risk of treatment failure in HIV infected patients to develop MDR-TB.[43] There is little doubt that the prevalence of both MDR-TB and XDR-TB have substantially increased, following the HIV epidemic.[44] The threat of an "untreatable TB," i.e. XDR-TB has particularly posed a global concern.[44]

The clinical and radiological manifestations of MDR-TB in HIV infected individuals are generally similar to those of MDR-TB in non-HIV infected patients, but pose greater problems of symptom and severity control due to poor treatment with pulmonary cavitary and/or disseminated disease. High mortality rates are reported in MDR-TB patients with than in those without HIV infection.[45] Transmission rate of MDR-TB in HIV infection is also high. Ninety-eight percent mortality was reported in 53 patients of XDR-TB, of whom 44 were HIV infected with a median survival of only 16 days after the diagnosis was established.[46]

DIAGNOSIS

Diagnosis of TB in HIV infected patients is established on the same lines and methods as in non-HIV infected patients (see Chapter 40). However, diagnosis in the presence of HIV infection is somewhat difficult in view of the difficulties of AFB demonstration in cases of extrapulmonary and noncavitary pulmonary TB. There is lesser likelihood of sputum smear and culture positivity in the presence of HIV infection, this observation is not corroborated in some of the studies.[47,29] The lesser sensitivity and specificity of sputum microscopy is attributed to the presence of fewer bacilli in the sputum because of the diminished chances of cavitation from a disregulated cellular response and due to increased incidence of infection with nontuberculous mycobacteria.[48,49] Culture of *M. tb* from sputum and/or other pathological specimens and secretions is diagnostic of TB. The practical utility of mycobacterial culture is however limited, especially in control programs.

Radiological diagnosis of TB is nonspecific. This is especially so, in the presence of HIV coinfection when the chest X-ray findings are generally atypical.[50] Moreover, the chest radiology is frequently negative in extrapulmonary manifestations of TB. More importantly, one relies on cytological and/or histopathological examination for the demonstration of caseation, granuloma formation (which are ill formed and rare) and AFB. Investigational procedures, such as fine needle aspiration biopsy, pleural fluid aspiration, lumbar puncture, forceps biopsy, bronchoscopic or trans-bronchial biopsy and other methods are used to obtain the appropriate specimen for these examinations.

Interpretation of the Tuberculin Skin Test (TST) in the presence of HIV infection for the diagnosis of TB is somewhat difficult, especially in the high TB prevalence countries. A positive TST is considered as suggestive of TB-infection or latent TB in any individual, more so, in the presence of HIV infection in whom the test sensitivity is further reduced. In countries, such as India, where there is presence of TB infection diagnosed by a positive TST in up to 40 to 50% of normal healthy population, the positive test cannot be considered as an indication for the treatment.

In the presence of immunosuppression due to HIV infection, the positivity of TST can be considered as more valuable. The probability of positive TST in these patients is significantly low,[51] therefore, a positive test may "strongly" suggest TB. It is for this reason that the cutoff values for positivity for TST are lower for HIV infected patients.[52,53] However, a lower "cutoff" may not necessarily differentiate between "infection" and "disease". In a retrospective medical record database review (1988 to 2007), the administration of TSTs to newly diagnosed HIV patients was inconsistent and different according to the country of birth, among other factors, resulting in "missed opportunities for TB prevention." [54]

The Interferon-Gamma Release Assays (IGRA) tests are now employed for the detection of latent TB with the help of QuantiFERON-TB Gold test and T-Spot tests.[55] These tests like TST are unable to differentiate between TB infection and active TB disease. We do not have figures on positive IGRA in otherwise healthy people, but the interpretation is somewhat similar to that of TST.[56] The updated guidelines for using IGRA in the United States suggest their use as aids in diagnosing TB infection in different populations.[57] A lot of work is still required before a recommendation of their use to guide treatment in India can be made, including in the presence of HIV infection.

MANAGEMENT

The greatest challenge in managing HIV-TB coinfection lies in the simultaneous treatment of both the infections and frequently of other concomitant opportunistic

TABLE 51.3: Important issues in the treatment of TB-HIV coinfection

1. Antitubercular therapy
   - i. Choice of drugs
   - ii. Choice of regimen
   - iii. Optimum duration of therapy
   - iv. Directly observed therapy short course (DOTS)
   - v. Treatment for MDR-TB and XDR-TB
   - vi. Prevention of recurrence of TB
2. Anti-HIV (Retroviral) therapy
   - i. Polypharmacotherapy
   - ii. Overlapping side effects of drugs

infections. The basic principles of treatment are similar as for TB treatment in non-HIV patients. There are however, several important issues related to the treatment (Table 51.3). One needs to consider the HIV related problems, such as the compliance with the therapy, presence of drug resistance, the level of immunosuppression and presence of complicating or other coinfections. The outcomes of treatment in the presence of HIV infection are similar, if the basic principles are adequately taken care of.[58-60]

Antitubercular Therapy (Also see chapters 42 and 43)

The four primary drugs, rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) constitute the main stay of treatment in drug-susceptible TB, administered as the standard two phase regimen: Initial intensive phase of two months of all the four drugs, followed by the maintenance phase of H and R for four months (2HRZE, 4HR). The treatment-strategy adopted in India in the RNTCP provides fairly comprehensive guidelines for the management. Under the strategy, the treatment to HIV positive patients referred from the Integrated Counseling and Testing Centres (ICTC), is provided at the tuberculosis control facilities, such as the DOTS centers as a coordinated activity.

Treatment of HIV-TB with DOTS has been shown to prolong the life,[61] prevent drug resistance and quickly render a TB patient noninfectious. It is the most effective method of promoting adherence to TB treatment, particularly in the presence of HIV coinfection.[62,63]

The issues related to intermittent versus daily regime and the optimum duration of therapy have remained somewhat debatable. Most of the studies of standard six month regimen (2 HRZE, 2 HR) have shown similar rates of treatment failure and relapse among HIV infected and non-HIV infected patients.[58,64,65] The current recommendation is to use standard six month regimen for all cases and to extend to nine months for patients with delayed clinical (continued symptoms) or microbiological response (sputum culture positivity) at two months.[66,67] The RNTCP guidelines provide similar recommendations.

Management of MDR-TB and XDR-TB in the HIV infected patients poses the biggest challenge. The choice of drugs and the duration of therapy for MDR-TB are variably recommended. Generally, the treatment duration is guided by AFB smear and culture reports. Most regimens contain four to six drugs, administered for at least 18 months after culture conversion, but extended to 24 months in patients with extensive pulmonary damage (Chapter 48).[68-70] The DOTS-Plus regimen for MDR-TB under the RNTCP comprises of six drugs (kanamycin, ofloxacin, ethionamide, Z, E and cycloserine) during the six to nine months of the intensive phase followed by four drugs (ofloxacin, ethionamide, cycloserine and E) for the 18 months of the continuation phase.[71]

A number of new drugs are there in various phases of development to reduce the number of drugs, as well as shorten the duration of therapy.[72,73] No drug as yet has proven to achieve the goals. Immunotherapy, including the new vaccines and vitamin D have also been used as adjunctive treatments.[74]

Antiretroviral Therapy (ART)

Concurrent treatment of both TB and HIV infections has significantly improved the outcome of patients.[74-76] HIV treatment with Highly Active Antiretroviral Therapy (HAART) comprises a combination of at least three Antiretroviral (ARV) drugs. There are four major groups of antiviral drugs, which are currently available that include:

- Protease inhibitors
- Reverse transcriptase inhibitors
- Viral integrase enzyme inhibitors
- Viral entry inhibitors (Table 51.4).

Antiretroviral treatment does not completely cure the disease, but effectively suppresses the viral replication. Antiretroviral therapy is costly and requires to continue life long. The ARV drugs also have a high-toxicity profile. There are several important issues in the administration of ART, especially when used along with antitubercular treatment (Table 51.3). The decision for HAART is best made in consultation with an HIV expert. The National AIDS Control Program (NACO) and WHO Guidelines are generally followed in resource limited countries.[77]

TABLE 51.4: Antiretroviral drugs

- I. Reverse Transcriptase Inhibitors
  - a. Nucleoside reverse transcriptase inhibitors
    1. Lamivudine
    2. Stavudine
    3. Zidovudine
    4. Didanosine
    5. Zalcitabine
    6. Emtricitabine
    7. Abacavir
    8. Tenofovir
  - b. Non-nucleoside reverse transcriptase inhibitors
    1. Nevirapine
    2. Efavirenz
    3. Delavirdine
    4. Etravirine
- II. Protease inhibitors
  1. Amprenavir
  2. Atazanavir
  3. Indinavir
  4. Nelfinavir
  5. Tipranavir
  6. Darunavir
  7. Saquinavir
  8. Lopinavir
  9. Ritonavir
- III. Integrase enzyme and viral entry inhibitors
  1. Raltegravir
  2. Enfuvirtide
  3. Maraviroc

The short-term risk of HIV disease progression in HIV related tuberculosis is related to the degree of immunosuppression (measured by CD4 cell count or CD4 cell percentage).[75,76] Patients with advanced immunosuppression (CD4 + T cell counts <100/μL) are likely to develop treatment failure, relapses and development of MDR-TB.

Use of Antiretroviral along with Antitubercular Therapy (ATT)

Combination of ART along with ATT has the potential of overlapping adverse effects of both therapies. Moreover, the presence of other opportunistic infections add further to the complication list. The HIV related complications (e.g. thrombocytopenia) cause additional problems. Drug-drug interaction is an important problem, especially seen with use of rifamycins, which increase the synthesis of a number of hepatic enzyme system. Rifampicin use results in a marked decrease in the concentrations of ARV agents, such as the protease inhibitors, which are metabolized by CYP3A. Rifabutin, with which the CYP3A expression is much less marked, is generally considered as an alternate drug. The dosages of these drugs, when used in combinations are therefore altered to maintain effective concentrations.[67,78-80] Thiacetazone should not be used in HIV-TB coinfection.

When to Start ART?

In view of the drug-drug interaction stated earlier, the ART was earlier withheld during the ATT administration. It is now believed that an early institution of ART helps in an early control of immunosuppression and improves mortality in patients with CD4 + T cell count of less than 200 cells/mm^3. In such patients, ART is started as soon as ATT is tolerated within the first two weeks to two months.[76] If the CD4 + T cell count is between 200 to 350 cells/mm^3, ART can start after the first two months of ATT. ART in patients with CD4+ counts of more than 350/mm^3 can be deferred until antitubercular therapy is completed.

In India, the integrated activities of the national programs, such as RNTCP and NACO, allow the treatment of HIV-TB coinfection. The ARV treatment is provided through the ART centers and ATT through the DOTS centers. The fewer number of ART centers however, is a limiting factor. The choice of regimens for ATT under RNTCP is made on the basis of standard categorization for different forms of tuberculosis irrespective of the HIV status. Regimens for MDR-TB are also being put in place at selected centers.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Improvement in immunity following ARV therapy results in an increase in inflammatory response to mycobacteria in tuberculosis lesions. The worsening of clinical symptoms following institution of both ATT and ARV is termed as the IRIS.[81-83] This paradoxical reaction is often noticed particularly with lymph node and pleural tuberculosis.

The common features of IRIS comprise of fever and increase in lymphadenopathy, effusion and pulmonary infiltrates.[84,85] Occasionally, there is worsening of meningeal, central nervous system, hepatopulmonary, soft tissue or other forms of tuberculosis when it can even be life threatening.[85] The tuberculin skin reaction may frequently becomes positive.

Immune reconstitution inflammatory syndrome develops generally, in the presence of low baseline CD4+ cell count, a higher viral load and a shorter interval between the start of ATT and HAART. The presence of disseminated disease or a "better" response to treatment, i.e. a greater increase in the CD4+ cell count and a greater reduction in the viral load are other likely risk factors of IRIS.[86] Besides the "paradoxical" type of IRIS in which there is clinical worsening following ATT, an "unmasking" type of IRIS is also recognized in which the undiagnosed TB becomes apparent after the institution of HAART.[87] The pathogenesis of this unmasking is not clear, but it poses problems in the management.

Most cases of IRIS are self-limiting. Treatment with anti-inflammatory drugs, (usually nonsteroidal) is generally adequate. ATT and ART should not be stopped, but for very severe reactions.[88] Corticosteroids are rarely required for severe and persistent IRIS. On an average, IRIS lasts for a period of six to eight weeks, but for the presence of lymph node enlargement, which may persist for longer periods.

BCG Vaccination

BCG vaccination in an HIV positive child is a cause of concern in view of the reports of local complications and disseminated BCG disease. The risk is not substantiated by the results of prospective studies in HIV infected and non-HIV infected infants. As per current recommendations, routine BCG vaccination in infants in the high HIV prevalence areas is not withheld, but not given to known HIV infected individuals.[89]

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Nontuberculous Mycobacterial Infections

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INTRODUCTION

There are a large number of mycobacteria other than *Mycobacterium tuberculosis,* which are now being increasingly recognized as a cause of human disease. Commonly referred to as Nontuberculous Mycobacteria (NTM), they are also known as atypical mycobacteria, anonymous mycobacteria, or Mycobacteria Other Than Tubercle bacilli (MOTT). They are weak pathogens and they are distinct from *Mycobacterium tuberculosis* in their characteristics. NTM are ubiquitously distributed in the environment and hence also known as environmental mycobacteria. Often these bacteria inhabit the respiratory passages in the form of commensal organisms. Pulmonary infection from NTM though rare, can cause disease similar to tuberculosis. They more commonly infect the skin, soft tissue, lymph nodes, implant devices, wounds, bones and joints. Occasionally, the infection is disseminated systemically in patients who are immunosuppressed or who have Acquired Immunodeficiency Syndrome (AIDS).

Classification

Runyon's classified atypical mycobacteria into four groups based primarily on colony morphology, pigmentation and growth characteristics.[1]

Group I consists of photochromogens. *Mycobacterium kansasii* is an important pulmonary pathogen belonging to this group. It grows slowly over two to four weeks and becomes yellow on exposure to light. *Mycobacterium scrofulaceum* belongs to Group II and is a scotochromogen. It grows slowly over two to four weeks and produces yellow colonies even in dark. It turns orange on exposure to light. *M. scrofulaceum* affects cervical lymph nodes. It occurs exclusively in children.

Nonchromogens belong to Group III. They grow slowly and produce white colonies that do not change color on exposure to light. *Mycobacterium avium* and *Mycobacterium intracellulare* (Mycobacterium avium complex or *Mycobacterium avium* and *M intracellulare,* MAI) belong to this group, and are responsible for pulmonary lesions, or cervical lymphadenopathy, and occasionally may also cause a virulent disseminated disease. The organisms, which belong to Group IV grow within three to five days on culture, and are hence referred to as "rapid growers." They do not change color on exposure to light. *Mycobacterium fortuitum, Mycobacterium chelonei* and *Mycobacterium smegmatus* are examples of this group. They often produce subcutaneous abscesses.

More recently, the mycobacterial species are classified on the basis of genetic differences, such as the sequence differences in the 16S ribosomal RNA. The NTM species are divided into rapid and slow growers. They also vary in their nutritional requirements and grow on either the simple media or on the media supplemented with nutrients.

Human Disease

Though the nontuberculous mycobacteria are widely distributed in the environment, the clinical infection is rare.[2] They may be falsely recovered from clinical specimens due to laboratory contamination or contamination of medical instruments. More than

TABLE 52.1: Some of the important nontuberculous mycobacterial species linked with disease in humans

Mycobacterium avium
M. intracellulare
M. kansasii
M. paratuberculosis
M. scrofulaceum
M. simiae
M. habana
M. interjectum
M. genavense
M. xenopi
M. marinum
M. malmoense
M. fortuitum
M. ulcerans
M. chelonei
M. smegmatis
M. xenopi
M. hemophilum

90 species of NTM have been recognized. Of them nearly one-third have been linked with disease in humans (Table 52.1).[3,4]

Chronic pulmonary infection due to *M. avium* complex and *M. kansasii* generally occurs in elderly persons. Cervical lymphadenopathy occurs in children due to *M. scrofulaceum*, while skin and soft tissue infections may develop from *M. fortuitum*, *M. chelonei, M. xenopi* and *M. ulcerans*. Exposure of humans to NTM may occur while bathing, swimming and drinking, and the organism can also gain entry through cuts and abrasions. However, the risk of infection is generally less. Disseminated lesions are found in immunocompromised patients due to infection from *M. avium* complex. Sometimes, *M. chelonei* may cause very indolent pulmonary infection.

Epidemiology

Nontuberculous mycobacteria are commonly isolated from soil, water and house dust except *M. kansasii* whose natural reservoir remains undetermined.[5] *Mycobacterium Avium Intracellular Complex* (MAIC) is commonly recovered from residential bath rooms and showers.[6,7] Colonization of human body especially of upper airways, skin and gastrointestinal tract by NTM is common without any evidence of disease. The pulmonary infection appears to result from the inhalation of infectious droplets that have been aerosolized from the environmental sources. Ingestion of organism especially *M. avium* complex by patients with AIDS infects the gastrointestinal tract and gets disseminated. Direct inoculation may result in the infection of skin, soft tissues and joints. Human-to-human transmission is very unusual.[5] Familial clustering, however, is reported that suggests the role of genetic factors contributing towards host susceptibility.[8]

The infection from NTM has been reported from the different parts of the world especially United States, Europe and Japan. In the United States, a rising prevalence of sensitization of one in six persons was reported in 1999-2000, up from one in nine persons in 1971-1972.[9] The infection from NTM has been reported infrequently in India. However, the frequent occurrence of low-grade tuberculin reaction suggests a varying risk of human disease. NTM may be responsible for a significant proportion of mycobacterial infections in HIV seropositive patients. Due to the higher endemicity of tuberculosis in India, the presence of NTM should be ruled out especially in immunocompromised HIV seropositive patients.[10]

In India from Agra, 119 isolates of environmental mycobacteria were grown from 291 (116 soil and 175 water) samples, gene amplification restriction analysis confirmed the identity of 85.7% isolates and the remaining 17 isolates by 16S rRNA sequencing.[11] The isolates included pathogenic species such as *M. fortuitum, M. chelonei, M. avium* and *M. kansasii.*

In a study at Puducherry, South India, among 22 isolates of mycobacteria isolated from 635 samples of suspected tuberculosis, 17 were of *M. tuberculosis*, 3 of *M. kansasii* and one each of *M. fortuitum* and *M. gordonae.*[12] The study has highlighted the importance of NTM as potential pathogens from both pulmonary and extrapulmonary sites.

In another study from Guwahati, north-eastern India, in 25 pus/discharge specimens from non-healing postoperative wound infections that did not respond to antibiotics, 20 revealed growth of NTM sp.[13] All of them were identified as *M. fortuitum-chelonei* complex. The sputum specimens from 6,829 patients diagnosed as "relapsed cases" of pulmonary tuberculosis and chronic nonspecific respiratory disease were cultured for the growth of Acid-Fast Bacilli (AFB) at Manipal, coastal Karnataka, India. In this sample, growth in 13.7% cases was due to atypical mycobacteria.[14]

Clinical Features

Infection in a healthy person from NTM (commonly *M. kansasii* and *M. avium* complex) presents a picture of chronic pulmonary disease resembling tuberculosis. The lung infiltrates are more diffuse and nodular in appearance. Cavitary disease is common. Mediastinal lymph node involvement and pleural effusion are uncommon. The lymph nodes, skin, soft tissues, bones and joints are other important sites of NTM infection.[4]

NTM infection maxy present in one of three different forms: A tuberculosis-like pattern; nodular bronchiectasis and hypersensitivity pneumonitis.[15] The classical TB-like presentation commonly occurs in older male smokers frequently with underlying chronic obstructive pulmonary disease. It is more indolent than typical tuberculosis and presents with cough and expectoration. Though there can be fever, night sweats, weight loss, and hemoptysis occasionally, these constitutional symptoms are less severe. The progress of the disease is slow. These patients may have preexistent pulmonary diseases such as Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis, silicosis and even prior pulmonary tuberculosis. In such situations, the features of infection due to NTM may pose difficulty to distinguish from those of the underlying disease. The disease is commoner in persons with diabetes and those having a history of smoking.

A "non-classical" form of illness has also been described. It is noted in elderly nonsmoker women. Though the condition has an insidious onset with chronic cough, it is not associated with any pre-existing lung disease seen in "classical" form. The constitutional symptoms are rare.[6] Hypersensitivity pneumonitis may present a typical episodic picture on exposure to bacteria such as to *Mycobacterium avium* complex. MAC infection can present with any of the three different forms: Classical, non-classical or disseminated.[15]

The disseminated infection may occur in patients with immunosuppression due to hematological malignancy or use of immunosuppressive agents.[16] Its incidence has shown an increase in patients with advanced stages of AIDS especially when the infection is due to *M. avium* complex.[4,12] The condition presents with persistent fever, weight loss, anorexia and weakness. The pulmonary symptoms are infrequent and exhibit cough or dyspnea. There can be vomiting, diarrhea and abdominal pain. There is generalized lymphadenopathy, hepatomegaly, splenomegaly and nodular skin lesions. The condition is noted in children and young adults.

Diagnosis

Diagnosis of NTM pulmonary disease is made on the basis of the presence of a variety of clinical, radiological and microbiological criteria, several of which may only suggest the diagnosis. The exact disease etiology then needs to be confirmed (Table 52.2).

TABLE 52.2: Guidelines for making the diagnosis of NTM-pulmonary disease

i. Clinical features of an indolent, respiratory disease – cough, expectoration, fever and other constitutional symptoms.
ii. Positive smear for AFB and/or heavy growth of NTM on culture in respiratory specimens.
iii. Histopathological features of mycobacterial/granulomatous disease or culture of NTM from biopsy specimens.
iv. Radiological features of nodular infiltrates with or without cavitation and/or bronchiectatic lesions.
v. Underlying host conditions: Immunosuppression, AIDS, alcoholism, COPD, cystic fibrosis, diabetes, malignancies, etc.
vi. Absence of other causes of pulmonary lesions, such as tuberculosis, aspergillosis, etc.
vii. Persistence of AFB after antituberculosis treatment for two weeks or more.

Radiology

The radiographic appearance in the "classic" form of disease resembles chronic indolent tuberculosis. The most common radiological pattern is the presence of fibronodular infiltrates involving the upper lobes especially apical and posterior segments.[13,17] Unlike tuberculosis, the cavities are thin-walled with little surrounding infiltrate. The "non-classical" form of disease is characterized by multiple bilateral opacities, similar to those in bronchiectasis. The infiltrates are seen predominantly in middle lobe and lingula and are not associated with apical shadow resembling post-primary tuberculosis.[10]

The pleural involvement, especially effusion, is rare. CT of the chest defines the radiologic features precisely. Small nodular opacities are seen in the regions of maximal disease and also in areas away from the predominant site of the disease. Changes related to bronchiectasis are present adjacent to the apical cavities in the "classical" form. In non-classical form of disease, bronchiectasis is bilateral and widespread.

Disseminated form of disease may not show any radiological abnormality or exhibit bilateral infiltrates. It may be associated with hilar or mediastinal adenoapathy and/or pleural effusion.[14] The radiological abnormalities are more likely to be produced by coexistent conditions in AIDS patients.

Bacteriology

Since NTM may colonize the respiratory tract of patients with preexisting lung disease, their isolation from sputum, bronchial washings or lung biopsy may not establish the infection. In a study from Korea, only about a fourth of 794 patients from whom NTM was isolated from respiratory specimens were found to have clinically significant NTM lung infections.[18] Repeated sputum cultures demonstrating heavy growth of NTM are necessary to pinpoint NTM as the etiologic agent, in a patient with compatible clinical picture and radiograph. However, there is no need for repeated isolation of *M. kansasii* as it rarely occurs in the form of a saprophyte. In disseminated form, blood culture demonstrates causative agent. The NTM are traditionally classified as rapid and slow growers on the basis of their growth. Other bacteriological investigations, which are employed for identification include the biochemical tests such as serotyping and protein electrophoresis. The newer molecular methods, such as the gene probes and gene amplification (polymerase chain reaction) are now available for the detection of NTM, such as *M. avium, M. intracellulare* and some rapid growers. More advanced techniques, such as DNA fingerprinting are sometimes used for the characterization of NTM.

Histopathological dissection of granulomas with or without AFB staining in biopsy specimens from lymph nodes, liver, bone marrow or lungs may also help in the diagnosis. Immunodiagnostic techniques, such as the "Regions of Difference (RD) antigens," encoded proteins have been used for the diagnosis of both latent and active tuberculosis. Some of these RD antigens are located in the genome of *M. tuberculosis, M. africanum and M. bovis,* but absent in many of NTM and Bacillus-Calmetter-Guérin (BCG) substrains.[19] However, their role in the diagnosis or exclusion of NTM infection yet remains to be esta-blished.[19]

Treatment

The disease produced by NTM makes a slow progress, though it may remain stable for long periods. The disseminated form of disease has a rapid fatal course. NTM except *M. kansasii* may exhibit a high degree of in vitro resistance to many of the standard antituberculosis drugs.

Treatment in NTM infection is indicated only if the organism is causing the disease and is not simply a colonizer. Multiple antimicrobials are required for prolonged periods.[20,21] The infection from *M. kansasii* is treated with a combination of isoniazid, rifampicin and ethambutol (15 mg/kg) for 18 months.[22] Pyrazinamide largely remains ineffective.

The treatment of infection due to *M. avium* complex is difficult. Multidrug therapy is indicated in patients exhibiting a progressive course or those who are severely ill. Treatment consists of a macrolide, rifampicin and ethambutol given three times weekly for noncavitary disease and daily with or without an aminoglycoside for cavitary disease.[23] The choice of drugs depends upon the isolated NTM and the severity of manifestations (Table 52.3). The success rate is low particularly in the AIDS patient as the organisms are usually resistant to most of the commonly available antituberculosis drugs, including isoniazid.

TABLE 52.3: Suggested drugs for the treatment of infections with common NTM-isolates

NTM	*Suggested drugs*
1. *M. avium intracellulare*	H,R,E Aminoglycosides (Streptomycin, Amikacin) Quinolones (Ciprofloxacin/Ofloxacin) Clofazimine Macrolides (Clarithromycin/Azithromycin)
2. *M. fortuitum/ M. chelonei*	Amikacin/Streptomycin Macrolides Doxycycline Cefoxitin Imipenem
3. *M. kansaii*	H,R,E
4. *M. ulcerans*	Surgery (with or without drugs as for *M. fortuitum*)
5. *M. scrofulaceum*	Surgical excision H,E, cycloserine Macrolide

(H = Isoniazid, R = Rifampicin, E = Ethambutol)

Disseminated lesions due to *M. avium* complex in AIDS patients may be treated with rifampicin, ethambutol, clofazimine and ciprofloxacin. Those exhibiting stable disease are observed and underlying pulmonary disease is treated with bronchodilators, antibiotics (if sputum is purulent) and smoking cessation. Mycobacterial disease may get eradicated without specific therapy. When specific treatment is initiated, it consists of isoniazid, rifampicin and ethambutol (25 mg/kg for the first 2 months followed by 15 mg/kg) with an initial supplementation of streptomycin for three to six months.[22,23] Treatment has to be given for 18 to 24 months. For the patients exhibiting an extensive disease and those who fail to show sputum conversion on the four drug regimen, additional drugs, such as cycloserine and ethionamide are to be added to the therapeutic regimen. Surgical resection of the lesion may be undertaken in those having a localized disease. Some newer agents that may be active against NTM are rifabutin, clarithromycin, azithromycin and ofloxacin.[24-27] *M. chelonei* is generally resistant to the antituberculosis drugs and other conventional antibiotics. It shows susceptibility only to amikacin, cefoxitin and imipenem.

Nonpulmonary Manifestations

Nonpulmonary features of NTM infection are more common than that of tuberculosis. Infection of the extrapulmonary sites may occur through skin-contact, penetrating injuries, ingestion of contaminated water or aerosol inhalation. Hematogenous spread may be responsible for disseminated disease.

Lymphadenitis

Several NTM species have been identified to cause cervical lymphadenitis in healthy individuals, especially in children. MAC group is the most common species in both the immunocompetent and the immunosuppressed patients.[28-30] Presence of cervical lymphadenopathy in an adult with HIV infection or with organ transplantation on immunosuppressive therapy should always arouse the strong suspicion of MAC infection. The other causative organisms may include *M. scrofulaceum* and *M. malmoense*. Constitutional symptoms are generally absent. Poor response to standard antituberculosis therapy or repeated appearance of lymph nodes inspite of therapy arouses the suspicion of NTM-lymphadenopathy. The lymph nodes may also undergo central caseation, or lead to development of sinuses or abscess formation. Surgery should be considered for treatment in addition to the antimicrobial therapy.

Skin and Subcutaneous Abscesses

Skin gets commonly infected following penetrating injury, inoculation or surgery with contaminated instruments. Clusters of cases of incisional and subcutaneous abscesses are reported following laparoscopic surgery especially when performed in camps. A series of 145 laparoscopy post site infections were found in 35 patients following laparoscopy at a single hospital, where the water was used for washing chemically disinfected instruments.[30] The organism *M. chelonei* in this report had survived and grown within the biofilm at the bottom of the disinfectant trays.

Inoculation of superficial skin and subcutaneous infections as above are commonly caused by the rapidly growing mycobacteria, such as *M. fortuitum, M. chelonei, M. ulcerans, M. marinum* and *M. abscessus. M. fortuitum* and *M. chelonei* are sometimes responsible for deeper lesions, as well as disseminated infections, for example following the cardiac surgery. The rapid growers may occasionally cause superficial, intestinal ulceration, although the mere isolation from feces or colonoscopic specimens does not conclude a causal relationship with the gastrointestinal disease.

Treatment of infections with rapid growers consists of combined antibiotic therapy from amongst aminoglycosides, macrolides, doxycycline and fluoroquinolones. A prolonged course of 12–24 months treatment is generally required.

Disseminated NTM Infection

Disseminated disease with NTM generally occurs in patients with HIV infection. Several other groups of diseases and clinical conditions are now described where NTM are recognized as responsible pathogens. Renal transplant recipients and patients with underlying treatment for rheumatic disease, cystic fibrosis, lymphomas, leukemia and disseminated malignancies are particularly liable.[31-33] An increasing trend in non-HIV infected patients was reported from Thailand. Only 12% of 129 patients had an underlying disease.[34] The patient in this series reported with lymph node, skin, soft tissue and lung involvement, sometimes with coinfection from other opportunistic organisms.

Disseminated disease may present rarely with localized lesions in the central nervous system, kidney, liver, joints, bones and multiple lymph nodes. Constitutional symptoms are common with multiple organ involvements. Involvement of multiple sites may sometimes mimic metastases on PET/CT scans.[35]

Nontuberculous Mycobacteria Infections in Children

Nontuberculous mycobacteria infection is frequently recognized in children. In a nationwide active surveillance network amongst Australian children, the NTM was isolated in 68 cases with MAC being the most frequent organism.[36] In children, the NTM infection is typically associated with lymphadenopathy, while pulmonary involvement is rare in otherwise healthy children.[36]

Isolated pulmonary NTM disease is recognized more commonly in patients with cystic fibrosis.[33,37,38] Occasionally, pulmonary NTM-infection in otherwise healthy children, presenting with refractory stridor or wheezing with endobronchial lesions or hilar lymphadenopathy without any recognized underlying immune deficiency or CFTR mutations has also been described.[37]

Miscellaneous Clinical Manifestations

Besides the pulmonary manifestations, lymphadenitis, skin and soft tissue infections, several other organs may also show isolated or disseminated NTM involvement. MAC disease, which commonly occurs in patients with HIV infection, may involve the eyes (corneal ulcers), heart (endocarditis), central nervous system (meningitis) and bones (osteomyelitis). Similar involvement may rarely occur with *M. fortuitum*, a chelonae group of mycobacteria. Meningitis and hepatitis are known to occur with *M. scrofulaceum* and *M. gordonae*. *M. smegmatis*, the first mycobacteria identified after *M. tuberculosis* is found to be associated with pneumonia, sternotomy wound infections and soft tissue infections.[39] *M. bovis* was commonly considered responsible for lymphadenitis and gastrointestinal manifestations due to the ingestion of milk from infected cows before the pasteurization era. A report of 73 cases, seen during a 12-year period was described from San Diego.[40] More recently, the cases are reported to occur in patients with HIV infection and those working in the cattle farms or slaughter houses.

In summary, an increased trend of NTM infections is recognized, especially in patients with HIV infection or with the other causes of immunosuppression. Pulmonary manifestations and lymphadenitis are most common, while disseminated forms, skin and soft tissue involvement may also occur. Diagnosis is established on the basis of clinical features, radiological and microbiological investigations. Treatment is somewhat difficult requiring multiple drugs for prolonged periods.

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Section

8

RESPIRATORY INFECTIONS

SK Jindal

53

Community-acquired Pneumonia

Charles Feldman, Ronald Anderson

INTRODUCTION

Community-Acquired Pneumonia (CAP) is described as a lung infection, acquired in the community, most commonly bacterial in nature, associated with the inflammation of the lung parenchyma, distal to the terminal bronchiole, with clinical and radiological evidence of consolidation of part or parts of one or both lungs. It is an extremely common infection that causes considerable morbidity and mortality, even in the modern world, especially among the very young, the elderly and patients with underlying comorbid disease.[1] The overall mortality of CAP varies from less than 1% in outpatients to approximately 14% in cases admitted to hospital and to 50% or more in patients requiring intensive care unit admission.[1-3] CAP puts an enormous burden on medical and economic resources, particularly if patients are hospitalized, since this is associated not only with direct hospital costs, but also with intensified laboratory investigation and broader empirical anti-microbial chemotherapy.[1,4] Studies from the United States,[1] Europe[4] and the United Kingdom[5,6] attest to the considerable burden of disease that is associated with this infection in the developed world. Furthermore, most countries in Africa and Asia have two to ten times more pneumonia in children than in the United States. In the Asian region, the two most populous countries, namely China and India, contribute significantly to these numbers.[7] In developing countries like India, infectious diseases, including pneumonia are a leading cause of mortality, particularly among the lower social classes.[8] One review of the burden of pneumonia indicated that in children, pneumonia was estimated to be the cause of approximately 2 million deaths per year (20% of all childhood deaths), with 70% of these deaths occurring in Africa and Asia.[7]

EPIDEMIOLOGY

A number of studies have investigated in detail the global and regional burden of diseases in the world.[9-11] As early as 1990, the Global Burden of Disease Study using Disability-Adjusted Life-Years (DALYs) compared disease and death in different regions of the world.[9] Lower respiratory infections were the most common specific cause of global DALYs and the highest disease burdens were in sub-Saharan Africa (21.4%) and India (20.9%). In 2001, slightly more than 56 million people died.[10] Five of the ten leading causes of death in low- and middle-income countries were infectious diseases, including lower respiratory tract infections, which were the most common infectious cause, being even more common than Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS), diarrheal diseases, tuberculosis and malaria.

Similarly, in 2002, it was reported that slightly over 57 million people died in the world with lower respiratory tract infections, being the third leading cause of death (3.94 million deaths–6.9% of total deaths).[11] Lower respiratory tract infections were the second leading cause of burden of disease in low- and middle-income countries as measured by DALYs [92.2 DALYs (millions) – 6.7% of total DALYs.][11] In sub-Saharan Africa, lower respiratory tract infections were the second leading cause of disease burden (second only to HIV/AIDS) [37.2 DALYs (millions)–10.0% of all DALYs.][11]

One factor that has contributed significantly to the impact of CAP, particularly in patients in sub-Saharan Africa, has been the associated epidemic of human immunodeficiency virus (HIV) infection.[12] Worldwide, more than 40% of new HIV infections have occurred in adults aged 15–24 years, with 95% of these infections and associated deaths having occurred in developing countries. Sub-Saharan Africa is home to almost 64% of persons living with HIV and this burden is seen particularly among women.[12] However, a number of studies attest to the fact that the HIV epidemic is growing very rapidly in Asia, particularly in countries such as India and especially among the youth, such that an epidemic may be faced on the same scale as that in sub-Saharan Africa.[13-16] Pulmonary infections, including tuberculosis, opportunistic infections, but also CAP occur much more commonly in HIV-infected persons than in non-immunocompromised individuals and CAP is second among the pulmonary complications.[17,18]

MICROBIAL ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA

While CAP may be caused by a wide range of pathogens, in reality the majority of cases are caused by a relatively small number of predominantly bacterial pathogens, even among HIV-infected patients.[1] By far, the most common pathogen is *Streptococcus pneumoniae,* which accounts for some 20 to 80% of cases and remains the commonest pathogen even among cases requiring intensive care unit admission.[1,3] In HIV-infected patients, as in non-immunocompromised cases, *S. pneumoniae* remains the most common pathogen in CAP.[17] Interestingly, on the basis of initial studies, it was commonly believed that *Pneumocystis carinii* (now called *Pneumocystis jirovecii*) was an uncommon cause of infection and/or death in patients in the developing world with HIV infection; however this was probably as a consequence of the lack of recognition, and subsequent studies indicated its common occurrence in countries such as South Africa and India.[19-21]

Table 53.1 shows the prevalence of the common etiological agents of CAP.[3] A number of studies have been conducted in India with the aim of identifying the common bacterial pathogens associated with CAP. One study in Shimla (in India) using sputum, blood and pleural fluid culture, and serology for *Mycoplasma pneumoniae* identified 70 patients with CAP of whom 53 (75.5%) had an identifiable cause and 12 patients were noted to have mixed infections.[22] No cause was identified in 17 patients despite extensive investigation, including the bronchoscopic aspiration of respiratory tract secretions. The most frequent pathogens were *S. pneumoniae* (19; 35.8%), *Klebsiella pneumoniae* (12; 22%), *Staphylococcus aureus* (9; 17%), *M. pneumoniae* (8; 15%), *Escherichia coli* (6; 11%), beta-hemolytic streptococci (4; 7.5%) and other gram-negative bacilli (5; 9%). Another study from Chennai, which noted that the prevalence of infection with *M. pneumoniae* was comparatively higher in HIV-infected persons when compared with HIV-noninfected adults, also documented *S. pneumoniae* as the most common cause of lower respiratory tract disease.[23] A study from New Delhi documented the serological evidence of *Legionella pneumophila* infection in 9 of 60 patients (15%) admitted to the All India Institute of Medical Sciences with CAP and the authors suggested that infection with *Legionella spp*., may be a more frequent cause of CAP than previously recognized and recommended that empirical antibiotic therapy should

TABLE 53.1: Pathogens associated with community-acquired pneumonia**

	Relative frequency (%)
• *Streptococcus pneumoniae*	35%–80%
• *Haemophilus influenzae*	5%–6%
• Atypical pathogens	
— *Legionella spp.**	2%–15%
— *Mycoplasma pneumoniae*	2%–14%
— *Chlamydia spp.* †	4%–15%
• *Staphylococcus aureus*‡	3%–14%
• Enteric Gram-negative bacilli§	6%–12%
• *Pseudomonas aeruginosa*¶	4%–9%
• *Coxiella burnetii*	2%–4%
• *Moraxella catarrhalis*	<1%
• Influenza A virus	10%–15%
• Other viruses»	5%–10%
• *Mycobacterium tuberculosis*¥	<1%–5%
• Unknown	15%–40%

*Vary in importance between countries; more than 95% are *L. pneumophila* serogroup 1; outbreaks are common.

†More than 99% due to *Chlamydophila pneumoniae* in adults.

‡Increasing in areas with high prevalence of community-acquired methicillin-resistant *S. aureus*.

§Main species associated with CAP are *Escherichia coli* and *Klebsiella pneumoniae.*

¶Risk factors include chronic steroid therapy, structural lung disease, previous hospitalization.

»Including respiratory syncytial virus, adenovirus, parainfluenza virus, metapneumovirus, varicella-zoster virus, measles and hanta virus.

¥Relative frequency varies considerably in different parts of the world.

** Reprinted from Garau J, Calbo E. Community-acquired pneumonia. Lancet 2008; 371: 455-8, and adapted with permission.

include a combination of agents that cover both "atypical" and conventional bacterial pathogens.[24]

A number of studies have been undertaken in India in order to document the pneumococcal serotypes causing invasive disease and/or respiratory tract infections.[25-27] These studies have frequently documented serotypes 1, 6, 19, 7 and 5 to be the most common, with serotype 23 emerging in the later years. Among these isolates that were serotyped, resistance to co-trimoxazole, tetracycline and chloramphenicol was found to be common, whereas resistance to penicillin was infrequent and if present, was of intermediate resistance.[26-28] The prevalence of macrolide resistance in India has also been documented to be very low, as opposed to a number of other countries in Asia.[29] However, a number of investigators throughout India and Asia are continuing to report the increase and spread of penicillin resistant and even multidrug resistant, invasive and colonizing, *S. pneumoniae* isolates.[30-35] Clearly, these investigators recommend that when choices of empirical antimicrobial therapy are made, they need to take into account local susceptibility patterns of the common infecting microorganisms.

RISK FACTORS FOR COMMUNITY-ACQUIRED PNEUMONIA

Risk factors for CAP are many and varied and include among many other factors, extremes of age (very young and the elderly), underlying comorbid conditions [in particular cardiovascular disease, chronic obstructive pulmonary disease (COPD) and HIV infection], lifestyle factors [including excessive alcohol consumption, cigarette smoking, and variations in body mass index (malnutrition or obesity)], various medical treatments, and socioeconomic factors (Table 53.2).[36-43] The exact mechanisms by which these conditions actually predispose to pneumonia is unclear, but in general terms they may predispose to an increase in bacterial colonization of the airway, and/or allow direct access of the bacteria to the lower respiratory tract, and/or be associated with impairment of normal host defences and/or clearing mechanisms. In the case of the elderly, it appears that it may not be simple chronological age that is the important risk factor, but rather the underlying comorbid conditions that commonly exist in the aged. HIV infection itself is a risk factor for CAP, even in the era of Highly Active Antiretroviral Therapy (HAART), but the exact mechanisms are uncertain and are the subject of ongoing investigations. Many of the usual risk factors for pneumonia that exist in non-immunocompromised patients also act as risk factors in HIV-infected persons.[44,45]

TABLE 53.2: Risk factors for community-acquired pneumonia*

- Extremes of age (very young and the elderly)
- Low socioeconomic status
- Lifestyle factors (cigarette smoking, excessive alcohol use, malnutrition or conversely high BMI)
- Underlying comorbid conditions (chronic cardiovascular, respiratory and renal disorders)
- HIV infection
- Other immunodeficiencies
- Medications

*Reprinted from Feldman C, Anderson R. New insights into pneumococcal disease. Respirology 2009; 14(2):167-79, and adapted with permission.

Many of the studies documented above, as well as several others, have clearly indicated the substantial role that cigarette smoking plays as a major risk factor for CAP, in both HIV-infected and uninfected individuals.[37,46-52] The exact mechanisms by which cigarette smoking predisposes to pneumonia are uncertain, but are almost certainly multifactorial and cigarette smoking has multiple effects on host defences. Nasopharyngeal colonization by microorganisms, such as the *Pneumococcus* is an essential first step in the pathogenesis of pneumococcal infections (see below). Cigarette smoking and exposure to tobacco smoke has clearly been shown to increase pneumococcal carriage rates in both adults and children[53] and therefore, represents a major risk factor for pneumonia. The importance of cigarette smoking as a risk factor for nasopharyngeal colonization has been shown in south Indian infants, who experience high rates of pneumococcal carriage in the first six months of age, at least partly explaining their increased risk of pneumonia.[54] In that study, the odds of pneumococcal carriage were significantly increased in infants living in households in which 20 or more cigarettes were smoked each day. Interestingly those same investigators documented that vitamin A supplementation at birth, delayed the onset of pneumococcal colonization.[55]

Cigarette smoking may also enhance the risk of CAP because of its association with COPD. The population prevalence of COPD is very high in India, the risk being related to the smoking of *bidis* and cigarettes, as well as environmental tobacco smoke exposure in non-smokers.[56] In a study in Shimla (in India), in addition to extremes of age, smoking and underlying COPD were significantly associated with the development of CAP.[22]

PATHOGENESIS OF CAP WITH PARTICULAR REFERENCE TO THE PNEUMOCOCCUS

Virulence Factors and Pathogenesis

The section will focus on *S. pneumoniae*, the most common bacterial cause of CAP. Pneumococcal colonization of the airways is mostly asymptomatic, but is nevertheless the first step in the pathogenesis of invasive disease. This may be precipitated by infection with respiratory viruses, resulting in the increased expression of receptors for bacterial adhesins on airway epithelium.[57]

Biofilm Formation

Prior to reviewing virulence factors, a brief consideration of the role of biofilm in microbial colonization/persistence is important, as this is a strategy utilized by the *Pneumococcus* to evade host defences.[58] Biofilm also restricts the penetration of antibiotics, favoring antibiotic resistance. Importantly, the *Pneumococcus*, by the mechanisms described below, adheres to and invades airway epithelium. Biofilm-encased bacterial aggregates attached to the epithelial surface, or sequestered intracellularly, therefore provide an effective mechanism for bacterial persistence.[58] Concealed in biofilm, in which it communicates by quorum sensing mechanisms, the *Pneumococcus* can reemerge at times, when host defences are transiently or irreversibly compromised, as may occur during infection with influenza virus/respiratory syncitial virus or HIV-1, respectively.

Virulence Factors

The polysaccharide capsule is generally recognized as being the major virulence factor of the *Pneumococcus*, promoting resistance to both entrapment by mucopolysaccharides present in mucus and opsonophagocytosis. Other non-protein virulence factors include hydrogen peroxide and phosphorylcholine. Hydrogen peroxide promotes structural damage to respiratory epithelium, interfering with the protective activities of the mucociliary escalator,[59] favoring attachment of the *Pneumococcus* to epithelial cells via the interaction of phosphorylcholine with the platelet-activating Factor (PAF) receptor.[60,61]

The *Pneumococcus* also possesses an array of protein virulence factors, which contribute to evasion and/or suppression of host defences. Some of these are recognized as potential vaccine candidates and include the choline binding proteins (Cbps), neuraminidase, hyaluronidase, zinc metalloproteinase, divalent metal-binding proteins, the pneumococcal lipoprotein surface adhesin A (PsaA) and the cholesterol-binding, pore forming toxin, pneumolysin, generally recognized to be the most potent of the pneumococcal protein virulence factors. During colonization of the nasopharynx, virulence factors that neutralize both innate and adaptive host defences enable bacterial adhesins to promote attachment of the *Pneumococcus* to airway epithelium. In addition to the polysaccharide capsule, the pneumococcus utilizes numerous strategies to subvert innate and adaptive host defences. These include: i) interference with the protective actions of the mucociliary escalator, primarily by pneumolysin, acting in concert with hydrogen peroxide and hyaluronidase;[59,62] ii) interference by PspA and PspC (also known as CbpA) with activation of the alternative complement pathway; iii) pneumolysin-mediated depletion of complement via activation of the classical pathway; and iv) cleavage of secretory IgA by the zinc metalloproteinase, favoring adhesion of the *Pneumococcus*.[60,61,63]

Notwithstanding the pro-adhesive interactions between pneumococcal phosphorylcholine and the PAF receptor on airway epithelium, PspA and PspC also promote attachment via binding to the epithelial polymeric Ig receptor that normally transports secretory IgA, while E-cadherin, the cell-cell junction protein of respiratory epithelium is a receptor for PsaA.[60,64] In addition, some serotypes possess pilus-like structures that promote epithelial adhesion via interaction with uncharacterized receptors. A novel pneumococcal protein adhesin has been described recently. This is the 120 kDa plasminogen- and fibronectin-binding protein B (PfbB), which significantly increases the ability of the pneumococcus to adhere to epithelial cells.[65] Unmasking of these various pneumococcal adhesins necessitates a reduction in capsule size, with the accompanying risk of increased vulnerability to phagocytosis. This is apparently minimized by production of biofilm, a process in which bacterial neuraminidase[66] and possibly H_2O_2 participate. These aforementioned virulence mechanisms facilitate the translocation of the pneumococcus to the lower airways, while transcytosis of the pathogen across the epithelial barrier via the polymeric Ig receptor enables access to the bloodstream and invasion of the central nervous system.

Antipneumococcal Host Defences

Although nasopharyngeal colonization by the pneumococcus is the first stage in invasive disease, it may also protect against severe infection by activating host defences.[67] Innate and adaptive immune responses triggered by the aforementioned virulence factors, as well as cell wall components such as lipoteichoic acid (LTA) and proteoglycans, if efficiently mobilized, can control and eradicate pneumococcal colonization.

Innate Host Defences

Interactions of LTA and pneumolysin with toll-like receptors (TLRs) -2 and -4, respectively, result in the mobilization of circulating neutrophils to the airways. These TLRs are the prototype pattern recognition molecules, which function as the sentinels of the innate immune system. Interaction of LTA and pneumolysin with TLRs on airway epithelium and other cells of the innate immune system in the airways, triggers a signalling cascade, which leads to the production of the cytokines, interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF), as well as the chemokine IL-8, all of which cooperate to promote transendothelial migration and the chemotaxis of neutrophils. In addition, Nucleotide Oligomerization (NOD)-like receptors also contribute to innate anti-pneumococcal host defences. These are a specialized group of intracellular pattern recognition molecules, which like TLRs recognize highly conserved structures on bacterial pathogens. In the case of the pneumococcus, bacterial proteoglycans are recognized by epithelial NOD proteins, specifically NOD-2, resulting in the production of pro-inflammatory cytokines/chemokines and influx of neutrophils. This TLR/NOD-2-mediated inflammatory response contributes to the early control of colonization and also favors adaptive mucosal immunity by promoting the degradation of bacteria required for efficient delivery of pneumococcal antigens to nasal-associated lymphoid tissue.[68-71]

Adaptive Host Defences

IgG and secretory IgA antibodies directed against the polysaccharide capsule of the pneumococcus are generally considered to be the primary determinants of immune-mediated type specific protection. Antibodies to pneumococcal proteins, particularly CbpA, PsaA and pneumolysin also confer protection, which although less efficient, are not serotype restricted.[72] Based on experimental animal and clinicoepidemiological studies, it is now evident that antibody-independent, $CD4^+$ T cell-mediated adaptive immune responses to pneumococcal protein antigens also contribute to the natural development of immunity to pneumococcal infection.[60,73,74] T lymphocytes of the TH1 and TH17 subsets appear to be critically involved in these cell-mediated immune responses.[73,75,76] Protection mediated via TH1 cells may involve interferon-γ-mediated enhancement of the antimicrobial activity of macrophages, especially mannose receptor-mediated phagocytosis.[77] In the case of TH17 cells, production of the cytokine IL-17A leads to the recruitment of neutrophils and increased pneumococcal killing by these cells.[73] Following initial partial control of colonization by innate neutrophil-mediated mechanisms, recent evidence favors a primary role for Th17 cells in the recruitment of monocytes/macrophages to mucosal surfaces, resulting in the clearance of primary bacterial colonization.[73,78]

In summary, entry of the *Pneumococcus* into the nasopharynx has several possible outcomes: i) eradication by innate/adaptive host defences; ii) a carrier state in which the bacteria and host coexist in relative harmony; iii) a state of persistence in which bacteria are encased in biofilm, either extracellularly or intracellularly following adherence to, and invasion of epithelial cells, enabling evasion of host defenses (this could also be considered as being a chronic infection); and iv) acute infection. In the case of carrier and persistence states, the bacterial pathogen, seemingly subdued, may strike when host defences are transiently compromised, as may occur during infection with influenza or other respiratory viruses.

DIAGNOSTIC TESTING

A vast number of studies have been undertaken over many years to assess the value of the various microbiological techniques that are available for the diagnosis of likely microbial etiology in patients with CAP. Among more commonly used investigations currently available are sputum examination by Gram's stain and culture and pneumococcal antigen detection, blood for culture and serological testing, and urine for legionella and pneumococcal antigen detection. Much less frequently used are invasive techniques such as fiber-optic bronchoscopy. While some studies have indicated that there is good diagnostic yield from many of these tests, including simple sputum examination,[79,80] others have suggested that routine initial sputum examination is of little value, particularly in non-severely ill cases,[81] such that this investigation is frequently not used even in hospitalized cases.[82] One technique that has significantly improved the rapid sputum diagnosis of pneumococcal pneumonia is Real-Time Quantitative Polymerase Chain Reaction (RQ-PCR), which appears to be particularly useful in patients who have already received antibiotics.[83] While isolation of microorganisms from blood culture is considered a "gold standard" for the diagnosis of likely etiology of CAP, a number of studies have indicated that there is a low yield from blood cultures and that even a positive result does not frequently result in a change in antibiotic management, or subsequent cost saving, particularly in non-severely ill cases.[84-87] One study documented that the yield of blood cultures increased as the severity of infection increased, as measured by the Pneumonia Severity Index (PSI), as did the likelihood of blood cultures changing antibiotic therapy. Rapid urine antigen tests for the detection of *S. pneumoniae* and *Legionella pneumophila* serogroup 1 infection are very useful for indicating these pathogens as likely cause of CAP in adults.[88] These tests have good sensitivity and specificity, but are expensive and in many guidelines, both in developed and developing countries, are not routinely recommended, but are reserved for special cases, such as severely ill patients requiring Intensive Care Unit (ICU) admission.[89,90] Other serological testing for so-called atypical pathogens is not routinely recommended.[89] In HIV infected patients, additional microbiological testing for *Pneumocystis jirovecii* and *Mycobacterium tuberculosis* may need to be undertaken.[89]

There is considerable debate about the routine need for a chest radiograph in all patients with CAP, particularly in cases not apparently severe enough to require hospital admission. Some have suggested that it remains an "essential initial test" in the diagnosis of CAP that is recommended in most guidelines, certainly for hospitalized cases.[89-91] There are studies, however, indicating that the admission chest radiograph lacks sensitivity and that it may not demonstrate abnormalities initially in some 21% of patients.[92] The chest radiograph is unhelpful in suggesting likely microbial etiology and is performed in order to confirm the presence of pneumonia, to delineate the extent of the pulmonary involvement, as an indicator of the severity of infection, to delineate the presence of underlying disorders and to determine the presence of any complications.[89,90,93] The assessment of oxygenation is recommended in both outpatients and inpatients and can be undertaken by pulse oximetry, particularly in outpatients or by arterial blood gas analysis.[94] Routine hematological and biochemical testing do not help to determine likely etiology, but will assist in the assessment of comorbid illness, and influence decisions regarding need for hospitalization, severity of infections and choice and dosage of initial, empiric antimicrobial therapy.[89] Table 53.3 indicates the diagnostic testing that is commonly recommended in patients with CAP. These investigations are particularly recommended in high-risk cases, in those patients with underlying comorbid illnesses and in those with more severe infections.[89]

TABLE 53.3: Diagnostic testing recommended for more severely ill, hospitalized patients with community-acquired pneumonia

- Chest radiograph
- Sputum Gram stain and culture
- Blood cultures
- Blood gases (or assessment of oxygenation by pulse oximetry)
- Routine hematology and biochemistry
- Rapid urine antigen testing for *S. pneumoniae* and *Legionella* spp. serogroup 1
- Thoracentesis for pleural effusions

PROGNOSIS

The outcome of CAP is influenced by a number of factors, including host factors, bacterial factors and antibiotic factors.[95] In a study of overall factors influencing the outcome of adult patients with CAP in New Delhi, India, factors such as old age, history of smoking, presence of COPD, high blood urea, low serum albumin and development of septic shock were associated with a higher risk of complications and a poorer prognosis.[96] In addition, older patients with a poor prognosis had a greater duration of symptoms and a poor neutrophil response to the infection.

Host Factors Including the Severity of Infection

Among the host factors, older age, the presence of underlying comorbid illness and various genetic characteristics of the host, all are potentially associated with the increased risk of pneumonia, as well as a worse outcome.[95] Severity of illness on its own may impact negatively on pneumonia outcome, even in the absence of any of these other risk factors.[3,95,97] Severity of illness assessment is therefore important not only because it gives an indication as to the likely outcome of the patient with CAP, but because it dictates the appropriate site of care of these patients, the extent of the microbiological work-up needed and the choice of initial empirical antimicrobial chemotherapy.[3,95,97] A number of severity-of-illness indices and various scoring systems have been developed to assist in severity assessment, among which the PSI and the CURB-65 score (derived from the British Thoracic Society rules) are the most commonly used.[97] The PSI score comprises of 20 variables that include details of demographic characteristics, comorbidity, clinical features and results of laboratory and radiographic data.[98] The CURB-65 includes variables, indicative of severity including mental confusion (abbreviated mental test score ≤ 8), raised urea (>7 mmol/l), rapid respiratory rate (≥ 30 breaths/min), low blood pressure (systolic <90 mm Hg, diastolic ≤ 60 mm Hg) and age

TABLE 53.4: Parameters used to determine the CURB-65 severity of illness score[¶]

C = Confusion
U = Raised urea (>7 mmol/l)
R = Rapid respiratory rate (≥30 breaths/minute)
B = Low blood pressure (systolic <90 mm Hg, diastolic ≤60 mm Hg)
65 = Age ≥65 years

[¶] A point is assigned for each parameter, when present. Patients with a score of 0 or 1 have a mild pneumonia associated with a low mortality, those with a score of 2 have a moderate pneumonia with an intermediate mortality and those with a score of 3 or more have severe pneumonia associated with a high mortality.

≥65 years).[99] The PSI was developed primarily to identify low-risk patients who could safely be managed at home, whereas the CURB-65 score was developed to identify patients with severe CAP at high risk of mortality.[100,101] A modification of the latter score, the CRB-65 score has also been developed and studied with the advantage that it does not require the measurement of blood urea levels. It has been found to have similar accuracy to the CURB-65 score. A number of guidelines on the management of pneumonia, particularly from the developing world, have primarily recommended the use of the CURB-65 or CRB-65 as the severity scoring index of choice because of its simplicity, immediate applicability and ease of use, combined with an accuracy that is similar to that of more complicated systems such as the PSI.[89,90,102] The parameters that make up the CURB-65 score are indicated in Table 53.4.

Several other severity scores and indices have been developed and/or studied, particularly for use in predicting the outcome and need for ICU admission among severely ill cases[101,103,104], as well as in the subset of patients with pneumococcal CAP.[105,106] It is important to remember that these scoring systems have a number of limitations, including lack of inclusion of certain social factors and other clinical conditions that may impact on outcome. Thus, while each scoring system has its own individual strengths and weaknesses, none of them is able to replace sound clinical judgment of the attending physician.[101]

Bacterial Factors

Among the bacterial factors that may impact on the outcome of pneumonia, are the nature of the infecting microorganism, its associated virulence factors and its susceptibility to commonly prescribed antibiotics.[95] Significant consideration also needs to be given to the potential impact of antibiotic resistance, particularly pneumococcal resistance to beta-lactam agents on the outcome of pneumonia.[1,95,107-110] While much has been published on this subject, it does appear, overall, that the current levels of beta-lactam resistance among pneumococcal isolates are such that if appropriate beta-lactam agents are used in appropriate dosages, resistance should not impact negatively on the outcome of respiratory tract infections.[107,108,110] This is further supported by the fact that in January 2008, the Clinical and Laboratory Standards Institute (CLSI) revised its pneumococcal susceptibility breakpoints for penicillin for non-meningeal infections being treated with parenteral antibiotics, supported by a careful consideration of microbiological, pharmacokinetic/pharmacodynamic and clinical data.[111] Breakpoints are now much higher with isolates with a MIC of equal to or less than 2 µg/ml being considered susceptible, those with a MIC of 4 mg/ml being considered intermediately succeptible and those with a MIC equal to or greater than 8 mg/ml being considered resistant.

The situation is less clear-cut in the case of macrolide antibiotics, which have received much less attention, but it does appear that when these agents are used on their own, particularly in the presence of high-level macrolide resistance, failure of therapy, including breakthrough bacteremias might well occur.[95,112] With regard to pneumococcal fluoroquinolone resistance, while it is well recognized that phenotypic resistance with the presence of multiple mutations in the quinolone resistance-determining regions (QRDR) of parC and gyrA is known to be of clinical significance, what is not commonly appreciated is that first-step mutations in these regions, not producing MIC-defining phenotypic resistance, can easily mutate to the further levels of fluoroquinolone nonsusceptibility and lead to clinical failure.[112-114] However, the prevalence of such first-step mutants among populations of susceptible pneumococcal isolates is not reported and is therefore unknown in most parts of the world.

Of considerable concern internationally is the fact that there are very few new antibiotics in the developmental pipeline that would be available to combat infections due to highly resistant microorganisms, should these become more widespread.[115,116] While other adjunctive strategies are being studied for use, together with antibiotics, to improve the outcome of severely ill patients with CAP, it still remains true that the mainstay of therapy of such infections will always be effective antibiotic therapy.[97,117-119]

Antibiotic Factors

Among the antibiotic factors, choice of agent, dosage and duration of therapy and time to the initiation of antibiotics from the time of presentation of patients to hospital, all potentially play a role in the outcome of pneumonia.[3] Importantly, new strategies recommended for antibiotic management, for example, the use of combination antibiotic therapy in more severely ill hospitalized cases with pneumonia, including the subset of patients with bacteremic pneumococcal infections, have been said to have a positive impact on pneumonia outcomes.[43,95,120,121] The most commonly used combination therapy, which has been shown to be beneficial, is the addition of a macrolide to standard beta-lactam therapy; although benefit has also been shown with other combinations.[95,120] A number of questions still remain with regard to combination therapy, including an understanding of the reason(s) that some studies appear to indicate no beneficial effect of combination therapy on the pneumonia case-fatality rate.[122] Alternatively, should combination truly be shown to be beneficial, clarification is needed regarding which combination(s) are best,[123] as well as the exact mechanism(s) by which combination therapy may prove to be beneficial.[95,120] One of the reasons suggested for the benefit of combination therapy is that it may be associated with the addition to the beta-lactam agent of an antibiotic effective against so-called atypical pathogens (i.e. a macrolide, azalide, ketolide, tetracycline, or fluoroquinolone). Interestingly, a recent study investigated the outcome of bacteremic pneumonia in relationship to initial antibiotic therapy and although the investigation confirmed that the use of an agent active against atypical pathogens was independently associated with decreased 30-day mortality, further analysis suggested that this benefit was limited to the use of macrolides and not fluoroquinolones or tetracyclines.[124] Furthermore, an additional study documented that macrolide use was associated with a decreased mortality in patients with severe sepsis due to pneumonia, including the subset of patients infected with macrolide-resistant pathogens.[125] The role of macrolides in therapy is discussed further below (adjunctive therapy).

Guidelines for the Management of Pneumonia

As a part of the global strategy, a number of national and international guidelines have been developed describing the optimal management of patients with CAP, with the intention of improving the care and outcome of these patients.[89,104,126,127] However, consensus on the optimal management of lower respiratory tract infections, particularly with regard to antibiotic therapy, has not been attained in the various guideline documents.[126] Part of the reason for the differences in the guideline recommendations may relate to local factors, such as different patient populations, causative microorganisms, antimicrobial resistance patterns and availability of resources, together with differences in the interpretation of existing data by the guideline committee members.[127] Certainly, until more recently, there has been a relative lack of a robust evidence base for several aspects of the guideline recommendations.[127] Many of the newer guidelines are being informed by the various studies of CAP and in particular, very large multicenter, international, collaborative studies of CAP being conducted currently, which are able to recruit large number of cases throughout the world.[128]

Yet another issue is whether there is general adherence to the guideline recommendations and or whether adherence has any impact on the outcome of patients with CAP.[117,129,130] Some studies have suggested that compliance with guidelines may be associated with better outcome and lower costs of management in patients with CAP.[117,126,131,132] One recent study from Italy, conducted in three phases, documented an advantage for compliant versus noncompliant therapy, both in terms of failure rate (OR 0.74: 95% CI 0.60-0.90; p = 0.004) and mortality (OR 0.77: 95% CI 0.56-1.04; p = 0.082).[130] This was despite relatively low compliance with the national guideline recommendations, which did not increase substantially even after the guideline implementation phase of the study (from 33 to 44% compliance). These findings prompted the authors to suggest that there was need for a more aggressive and proactive approach to ensure guideline compliance. A single study from South Africa has documented very poor adherence to the local CAP Guideline, with the number of patients receiving compliant therapy being too low to confirm a clinical benefit from guideline adherence.[129]

TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA

Antibiotic Treatment

The mainstay of therapy for CAP is the use of antibiotics. Empirical antibiotic therapy should particularly take into consideration severity of illness, likely etiological agent, resistance patterns among commonly identified pathogens, especially *S. pneumoniae* and underlying comorbidities.[1] An additional consideration in the developing world is the cost of the individual drugs.[133] Antibiotic therapy should be commenced as soon as possible after diagnosis. With regard to outpatient therapy, a recent Cochrane review concluded that currently available evidence from randomized controlled trials was insufficient to make any evidence based recommendations for antibiotic choice in the ambulatory setting.[134] A number of guidelines, both in developed and developing worlds, recommends the use of oral therapy with amoxicillin for outpatients.[89,102] Macrolide monotherapy has been suggested as an alternative, particularly for patients allergic to penicillin, but this recommendation would need to take into consideration local susceptibility patterns to macrolides. Other oral agents, such as amoxicillin/clavulanate, second-generation cephalosporins and fluoroquinolones can be used, but are more expensive and are generally reserved for elderly patients, for those cases that are more severely ill and those that have underlying comorbid conditions, or that have failed initial therapy.

For more severely ill, hospitalized cases, most guidelines recommend the use of a beta-lactam/macrolide combination or monotherapy with a respiratory fluoroquinolone.[89,102]

For cases requiring ICU admission, additional agents are recommended; for example, the addition of an aminoglycoside to a beta-lactam/macrolide combination to provide additional cover for suspected gram-negative infection.[89,104] If a fluoroquinolone is used for an ICU patient, it is commonly recommended that it should be combined with another agent such as beta-lactam.[89,104]

Caution must be exercised with the routine use of fluoroquinolone monotherapy for patients presenting with CAP in regions where tuberculosis is endemic, since such cases may actually be infected with *M. tuberculosis* (Table 53.1), for which fluoroquinolones have excellent in vitro activity. Studies have indicated that in this situation, fluoroquinolone use may be associated with delay in the diagnosis of tuberculosis with the masking of this infection.[135,136] Consequent to this is the potential for patient morbidity and even mortality, as well as ongoing secondary transmission. Furthermore, there are additional concerns that fluoroquinolone monotherapy used in this situation may result in fluoroquinolone-resistant tuberculosis, although studies have suggested that this really only occurs in patients who have been exposed to multiple previous courses of fluoroquinolones.[137,138]

Supportive and Adjunctive Therapies

General support for patients with CAP includes attention to nutrition and hydration, analgesia and supplemental oxygen. A number of adjunctive therapies have been studied, particularly in severely ill patients, including those in the intensive care unit setting, in an attempt to further decrease the ongoing high mortality among these patients.[139] The two agents that appear to be most promising are the macrolide group of antibiotics and corticosteroids. The role of macrolides in the therapy of pneumonia has been fully described above (antibiotic factors). The reason they are included as possible adjunctive therapy is that many believe that the benefit of adding a macrolide to standard beta-lactam therapy may not be related to their antimicrobial activity, but rather to the considerable anti-inflammatory, immunomodulatory activities that the macrolide group of antibiotics possess translating not only into beneficial effects in the human host, but also attenuation of the virulence factors of bacteria, such as the pneumococcus, even at low, sub-minimum inhibitory concentrations that do not kill the microorganisms.[121,140-143]

With regard to corticosteroids, while two more recent systematic reviews[144,145] came to somewhat differing views as whether to recommend the routine use of corticosteroids in patients with CAP, there are clearly a number of studies documenting benefit of their use in hospitalized patients and/or cases with severe CAP[139,146-148] with some documenting a decrease in mortality and others a more rapid resolution of symptoms and a reduced duration of intravenous antibiotic therapy. There is also good scientific evidence to understand possible mechanisms by which corticosteroids may have benefit, considering their significant effects on inflammatory responses.[139] Corticosteroid use is most commonly recommended in patients with severe CAP in association with septic shock.

Thus, while some suggest that final recommendations regarding routine macrolide and/or corticosteroids use should await comprehensive randomized control trials, most clinicians would consider using them in severely ill cases with CAP.[119,120]

PREVENTION OF INFECTION—VACCINATION

An important aspect to consider in the overall control of CAP, and in particular pneumococcal pneumonia, is the prevention of infection using vaccination. Currently two pneumococcal vaccines are commercially available, namely the Polyvalent Polysaccharide Vaccine (PPV), used predominantly in adults and the Pneumococcal Conjugate Vaccine (PCV), used predominantly in children.[149,150] While there remains considerable debate as to the efficacy of the PPV, meta-analysis certainly supports the evidence for its use in the prevention of invasive pneumococcal disease in adults.[150] Evidence is considered by some to be somewhat less compelling with respect to efficacy in adults with chronic illness and in its routine use to prevent all causes of pneumonia or reduce overall pneumonia mortality.[150] However, others have suggested that the evidence points to a lower, but not insignificant protective effect, even in nonbacteremic pneumonia, such that this should not preclude the more widespread use of the vaccine.[151] Furthermore, recent studies also point to a significant beneficial effect in preventing pneumococcal pneumonia and decreasing disease severity, even in the vaccinated elderly.[151] A lower overall rate of pneumonia and improved outcome have also been seen in HIV-infected adults who have received PPV previously.[152,153]

Even more compelling is the evidence for the use of the PCV in the safe prevention of pneumococcal infection in children in both low income and industrialized countries, including HIV-infected individuals, meeting international criteria of cost-effectiveness even for lower income countries.[149,154] For this reason, the vaccine is recommended by the World Health Organization for inclusion in national vaccination programs in countries such as South Africa and elsewhere. Interestingly, in some of the studies, the PCV has been effective in lowering the rate of invasive pneumococcal disease not only in vaccinated children, particularly those below the age of 2 years, but also in non-vaccinated children and even in adults and the elderly in the community.[155] As such the vaccine appears to have both direct immune benefits in those vaccinated, as well as indirect "herd immunity" effects.

Influenza vaccination is also recommended in many CAP guidelines, even in the developing world.[89,90] While influenza vaccine may be administered to any individual wishing to reduce the risk of being infected with influenza, systematic annual vaccination is routinely recommended for individuals at high-risk of being infected with influenza and/or experiencing complications, such as pneumonia, from this infection.[90] It is also recommended that individuals that can transmit influenza to high-risk cases, such as health-care workers, should be immunized yearly.[94]

CONCLUSION

It has been stated that the mortality of CAP remains substantial in both the developed and developing worlds, despite all recent advances in medicine, including the availability of potent antimicrobial therapy and even the establishment of intensive care unit facilities. A number of questions and challenges still remain with regard to a full understanding of the nature of CAP and its optimal management that require continuing research.[100]

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54

Pulmonary Fungal Infections

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INTRODUCTION

Fungi rarely cause respiratory tract infection in the healthy population, except for the dimorphic fungi. In contrast, fungal infections of the respiratory tract are important causes of morbidity and mortality in immunocompromised patients; the range of people at risk of these infections has been expanding over the last two decades with the increased use of immunosuppressive agents in the treatment of malignancies and autoimmune disorders, the growing number of transplant recipients and due to the aging of the population.[1,2] Fortunately, in some of those patient groups, a downwards trend of the fungal infections related mortality has been observed in the last decade with the improvement in medical care.[3,4] However, parallel to this positive development, the spectrum of patients at risk for respiratory fungal infections is also expanding.[2,5] Pulmonary mycoses can either be the primary presentation of the disease or be a manifestation of disseminated fungal infections.

EPIDEMIOLOGY

The susceptible population for pulmonary fungal infections can be divided in two groups: Classical and newly recognized risk groups (Table 54.1). The risk factors for pulmonary mycoses in developing countries appear similar to the developed world; though certain differences are observed due to local epidemiology, including patient characteristics, cultural habitat and patient care practices.[6-8] Sub-optimum hospital care practice in the economically deprived groups and increasing medical interventions, including transplantations in the prosperous group, have led to an increase in the number of invasive fungal respiratory tract infections in both the groups. Further, the large number of untrained health care providers, misuse of steroids, intravenous drug abuse and availability of spurious infusion sets are possible additional risk factors for pulmonary mycoses in these countries. The number of persons at risk of pulmonary mycoses in developing countries is staggering.[6-8]

The growing incidence of pulmonary mycoses, which are linked to classical risk factors is in the range of 3 to 56% (Table 54.2).[9,10] The patients usually have significant neutropenia (<500 neutrophil/µl for >10d) as risk factor.

TABLE 54.1: Susceptible population for fungal respiratory tract infection

Classical risk groups:
- Cytotoxic chemotherapy for neoplastic disease
- Hematopoietic Stem Cell Transplantation (HSCT)
- Severe AIDS (CD4 cell count <100)
- Immunosuppressive therapy in autoimmune diseases
- Other transplantations
- Aging population

Newly recognized risk groups:
- Intensive care unit stay
- Chronic obstructive lung disease
- Recipients of low dose of steroids
- Cirrhotic patients
- Iron overload
- Poorly controlled diabetic patients
- Sepsis associated with immunoprophylaxis
- Malnutrition
- Moderate to severe renal or hepatic impairment

TABLE 54.2: Incidence of fungal pneumonias in classical risk factor groups (modified from Pound et al [9])

Population	*Incidence*	*Fungal pathogen*
HIV infected patients	Not known (30%-45% *Cryptococcus)*	*Cryptococcus, Aspergillus, Coccidioides, Histoplasma, Blastomyces*
Bone marrow transplant recipients		
— Allogenic	12%-56%	*Aspergillus, Scedosporium, Fusarium, Candida*
— Autologous	rare	
Solid organ transplant recipients		
— Liver	Almost 35%	*Aspergillus, Cryptococcus*
— Lung	14%-35%	*Aspergillus, Cryptococcus, Candida*
— Heart	3%-10%	*Aspergillus, Candida*
— Kidney	Not known	*Cryptococcus, Aspergillus, Zygomycetes*

The rise in number of pulmonary mycoses is partly due to increased indications of hematological transplantation procedures in recent years and evolving solid organ transplantation practices. Additionally, explosion in the number of novel biological immunesuppressant agents and widespread use of antimicrobial prophylactic regimens, including fluconazole prophylaxis, render the host at greater risk of fungal colonization and infection.[11] Other risk factors for those individuals include poor graft function, hepatic failure before transplantation, dialysis requirement, use of OKT3 antibodies, cytomegalovirus infection and thrombocytopenia.[11] Among solid organ transplant recipients, lung and liver transplant recipients appear to have a higher incidence of pulmonary mycoses (Table 54.2). In lung transplant, apart from immunosuppressant use, impairment of lymphatic drainage, blunted cough reflex and defective mucociliary clearance contribute to fungal growth in the transplanted lung.[12] Among Human Immunodeficiency Virus (HIV) infected patients, pulmonary mycoses, such as *Pneumocystis* pneumonia and *Cryptococcal* infection, are associated with peripheral CD4 count of less than 200 cells/µl. Although *Aspergillus* pneumonia occasionally occurs in advanced HIV infection, this opportunistic complication is generally uncommon.[11]

Other than classical risk factors, prolonged stay in Intensive Care Unit (ICU), corticosteroid (>4 week) treatment, Chronic Obstructive Pulmonary Disease (COPD), liver cirrhosis, individuals with systemic inflammatory disease requiring immunosuppressive therapy, poorly controlled diabetes and iron overload (Table 54.1) are newly recognized risk factors for pulmonary mycoses.[13] The incidence of pulmonary mycoses in ICUs of developing countries is expected to be higher since cofactors (multiple intravenous lines, tracheostomy, endotracheal intubation, other invasive procedures, prolonged corticosteroid and antibiotic therapy) in ICUs are either higher in numbers or misused more in developing countries due to suboptimal protocol adherence by the ICU staff. Chronic obstructive pulmonary disease is an emerging risk factor. In a recent review of 65 cases, invasive pulmonary aspergillosis was reported as a serious emerging infection in patients with COPD. The majority of the patients had advanced COPD and/or on systemic corticosteroid therapy.[14] The reports of pulmonary mycoses in solid tumor are rare. In a large series from China, approximately 3% lung cancer patients had pulmonary aspergillosis. On univariate analysis, chemotherapy, steroid use and stage IV disease were found to be the significant risk factors; on multivariate analysis only stage IV disease was the significant risk factor. Neutropenia and corticosteroid therapy correlated statistically with pulmonary aspergillosis in patients who died.[15]

AGENTS RESPONSIBLE

Although many fungi can cause respiratory infections (Table 54.3), aspergillosis is the greatest challenge in patients with prolonged neutropenia, recipients of hematopoietic stem cell transplants or solid organ transplants, and patients with advanced Acquired Immunodeficiency Syndrome (AIDS) or chronic granulomatous disease. Host factors govern both the risk and clinicopathological features of invasive aspergillosis.[16,17] Other filamentous fungi, such as *Fusarium* spp., *Pseudallescheria boydii* and *Zygomycetes* are reported with increasing frequency in patients with quantitative or qualitative defects in neutrophils.[2] Pulmonary zygomycosis is also reported in patients with uncontrolled diabetes in India.[18] The clinical presentation, radiological features and histological appearance of pulmonary

TABLE 54.3: Fungi causing respiratory tract infections

- *Aspergillus* (most common)
  - — 10% of patients with leukemia
  - — 30% of patients with solid organ transplantation
  - — 10% of HSCT
- *Fusarium* and *Pseudallescheria*
- *Zygomycetes*
- Endemic mycotic agents (*H. capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Penicillium marneffei*, rarely *Sporothrix schenckii*)
- *Pneumocystis jiroveci*
- Rarely yeasts (*Cryptococcus*, *Candida*, *Trichosporon*)
- Rarely black fungi (*Cladophialophora boppii*)

infections due to *Fusarium* spp. and *Pseudallescheria boydii* have marked resemblance to *Aspergillus* infections leading to frequent misidentification.[19] Other than these opportunistic fungal infections, endemic mycoses, including those due to *Histoplasma capsulatum, Coccidioides immitis* and *Penicillium marneffei* have increased in frequency in immunocompromised hosts in restricted geographic regions.[2] A rare case of fatal pulmonary sporotrichosis caused *S. schenckii var luriei* was reported from India.[20] *Pneumocystis jiroveci* infection had frequently been reported in patients with AIDS, but recent data showed a sharp decline in incidence after the introduction of chemoprophylaxis and tri-drug regimen in those patients.[21] Yeasts are rarely reported in respiratory tract infections.[2] Among yeasts, cryptococcal respiratory tract infections are seen more consistently. Though deep seated infections due to black mycelial fungi are increasingly reported in recent years, they rarely cause pulmonary infections. A very rare case of pulmonary *Cladophialophora boppii* infection has been reported recently in lung transplant recipient.[22]

Aspergillosis

Pulmonary aspergillosis may be classified as allergic, saprophytic and invasive (Table 54.3).

Allergic Alveolitis

The common epidemiological setting of extrinsic allergic alveolitis due to *Aspergillus* is repeated exposure in non-atopic workers to *Aspergillus* antigen in moldy hay or grain, hence, the terms “farmer’s lung” or “malt worker’s lung.” Symptoms include cough, dyspnea, fever, chills and myalgias within eight hours of exposure. A chest radiograph may reveal interstitial infiltrates. Relief of symptoms has been observed within 48 hours, while away from exposure. However, repeated exposure may lead to intractable pulmonary fibrosis.[2]

Allergic Bronchopulmonary Aspergillosis (ABPA)

Allergic bronchopulmonary aspergillosis is an allergic pulmonary disorder caused by allergic response to *Aspergillus* hyphae without direct tissue invasion by the organism. It manifests as chronic asthma, recurrent pulmonary infiltrates and bronchiectasis.[23,24] Bronchospasm in this process is thought to be mediated by an IgE (type I reaction) mediated hypersensitivity, whereas the bronchial and peribronchial inflammation appears to be induced by immune complex formation (Type III reaction) and eosinophil-rich inflammatory cell responses due to Type IV hypersensitivity. The prevalence of ABPA is claimed as 1% to 2% in patients with asthma and 2% to 15% in patients with cystic fibrosis.[25] In a recent study of patients attending chest clinic in North India, 27% of asthmatics met criteria for ABPA[26] (See Chapter 75 for details). Spectrum of *Aspergillus* pulmonary infections are given in Table 54.4.

Eosinophil-related Fungal Rhinosinusitis

Several types of sinus diseases have been attributed to the presence of fungal organisms in the nasal and sinus cavities. The incidence of Chronic Rhinosinusitis (CRS) and Fungal Rhinosinusitis (FRS) has increased over the

TABLE 54.4: Spectrum of *Aspergillus* pulmonary infections

- Allergic
  - — Allergic alveolitis
  - — Asthma
  - — Allergic bronchopulmonary aspergillosis
  - — ? Eosinophil-related sinusitis including allergic fungal rhinosinusitis
  - — ? Sino-bronchial allergic (SAM syndrome)
- Colonizing
  - — Pulmonary aspergilloma
  - — hronic cavitary
  - — Sinus aspergilloma (Fungal ball)
- Invasive
  - — Acute invasive
  - — Necrotizing tracheobronchitis
  - — Local extension
  - — Disseminated
  - — Chronic necrotizing
  - — Invasive rhinosinusitis
    - – Acute invasive
    - – Chronic granulomatous
    - – Chronic invasive

last decade. Confusion exists regarding classification, the most accepted classification divides FRS into invasive and noninvasive diseases based on histopathological evidence of tissue invasion by fungi. The invasive diseases include acute invasive, granulomatous invasive and chronic invasive FRS. The noninvasive diseases include localized fungal colonization, fungal ball and eosinophil-related FRS that includes Allergic Fungal Rhinosinusitis (AFRS).[27] The existence of allergic disease to fungi in nasal and paranasal sinus cavities was recognized about three decades ago. Allergic fungal rhinosinusitis is considered as a non-tissue invasive fungal process, representing an allergic/hypersensitivity response to the presence of extramucosal fungi within the sinus cavity, possibly akin to ABPA.[28] In western world, dematiaceous fungi, including *Alternaria sp.;* and in Middle East, Sudan and India, *Aspergillus flavus* are commonly isolated from such patients.[27-29]

It is believed that fungal allergens elicit IgE-mediated allergic and possibly type III mediated mucosal inflammation in the absence of invasion in an atopic host. Moreover, when the sensitized individuals are exposed to an environment of high fungal content, symptoms of upper and/or lower airway hypersensitiveness increase significantly. Generalized sinonasal inflammation in combination with viscid allergic mucin effectively obstructs the normal drainage pathway. Fungi persist locally, stimulating locally destructive immune response. The process then extends to involve adjacent sinuses and may produce sinus expansion and bony erosion.[29] Although, the presentation of the disease is subtle, occasional dramatic presentations of the disease in the form of acute visual loss, gross facial dysmorphia or complete nasal obstruction has been observed.

To diagnose AFRS, Bent and Kuhn proposed five diagnostic criteria:[30] Type I hypersensitivity, nasal polyposis, characteristic findings on Computed Tomography (CT) scan, presence of fungi on direct microscopy or culture and allergic mucin containing fungal elements without tissue invasion. Although the detection of fungi in allergic mucin is considered important, hyphae may be sparse in sinus content and take considerable time to visualize with the commonly used stains. This has led to confusion in the categorization of this entity, especially with the description of Eosinophilic Mucin Rhinosinusitis (EMRS).[31]

It was speculated that EMRS is a systemic disease with the dysregulation of immunological control where eosinophilic mucin could be present without the presence of fungi.[31] The definition of AFRS has faced a greater challenge with the demonstration of fungi in eosinophilic mucin independently of Type-I hypersensitivity in most of the cases of CRS. Ponikau et al. proposed a new term for this condition, namely Eosinophilic Fungal Rhinosinusitis (EFRS) to reflect the striking role of eosinophil.[32] It is proposed that high levels of Major Basic Protein (MBP) is released from eosinophils in the mucus of the patients with CRS and postulated that MBP damages the nasal epithelium from the luminal side permitting secondary bacterial infections on the damaged epithelium.[33]

Saprophytic Aspergillosis

Saprophytic or colonizing forms of aspergillosis develop in an existing pulmonary cavity, caused by old tuberculosis, emphysema or carcinoma. Children with cystic fibrosis and bronchiectasis may also have saprophytic involvement of the airway due to *Aspergillus* spp. The mass of hyphae amidst a proteinaceous matrix is called as aspergilloma. However, filamentous fungi other than *Aspergillus*, such as *Pseudallescheria boydii* and *Zygomycetes*, may also cause intracavitary fungus balls and simulate an aspergilloma.[34]

Similarly, fungal ball is described as the presence of noninvasive accumulation of dense conglomeration of fungal hyphae in one paranasal sinus cavity, usually maxillary sinus, although the disease may affect other sinuses or rarely multiple sinuses. Various terms, such as mycetoma, aspergilloma and chronic noninvasive granuloma have been used interchangeably to designate sinus fungal ball.[27] The disease is defined by the following criteria: A dense conglomeration of noninvasive hyphae in cheesy or clay-like materials within the sinus, radiological evidence of sinus opacification with or without radiographic heterogeneity, nonspecific chronic inflammation of the mucosa, no predominance of eosinophils or granuloma or allergic mucin and no histopathological evidence of fungal invasion of mucosa.[34] The disease has been found more commonly in middle-aged and elderly females.

Invasive Aspergillosis

Invasive aspergillosis occurs in patients with acquired (neoplastic diseases with persistent and profound neutropenia, receiving high doses of corticosteroids) or primary defects (chronic granulomatous disease and hyper-IgE syndrome) in neutrophil function. However, in recent years, even up to 41% of the cases of invasive aspergillosis were diagnosed in nonneutropenic patients, especially in patients with COPD, chronic liver disease, reactive airway disease and rheumatoid arthritis.[35]

Patients with HIV may develop invasive pulmonary aspergillosis when CD4 count falls less than 50 cells/cumm. Interestingly, invasive aspergillosis in patients with HIV infection remains restricted to pulmonary involvement only in majority number of cases. The various clinical manifestations of invasive aspergillosis include pneumonia, hemoptysis, invasion of contiguous intrathoracic structures and dissemination. These findings are reflection of angioinvasion, thrombosis and infarction and are not specific for aspergillosis and may be a manifestation of one of several opportunistic angioinvasive fungi like *Zygomycetes*, *Pseudallescheria boydii* and *Fusarium spp*. Fever may be the earliest manifestation of pulmonary aspergillosis.

Invasive pulmonary aspergillosis is highly prevalent in developing countries, especially in patients with malignancies and transplant recipients.[36-40] In the series of invasive aspergillosis, reported from tertiary care hospital in Thailand,[41] lung was involved in 68% cases followed by sinuses (17%), eyes (8%) and brain (5%). In an autopsy study of childhood pneumonia from Bangladesh, pulmonary aspergillosis was diagnosed in 3% of all pneumonias and 10% of necrotizing pneumonias.[42] Other than classical manifestations of pulmonary aspergillosis, certain uncommon clinical presentations have been observed in developing countries. Some of these observations include the development of invasive pulmonary aspergillosis in patients with colonizing aspergillosis (in tubercular cavity),[43, 44] ABPA or aspergilloma[45,46] and bronchial asthma.[15,43] Possibly long period of steroid therapy allowed fungal hyphae from cavitary lesion or localized mass lesion to invade lung parenchyma. Invasive pulmonary aspergillosis was also found to be associated with antineutrophil cytoplasmic antibodies positive vasculitis.[47,48] In a series of 157 patients with vasculitis, 7 (4.5%) developed invasive pulmonary aspergillosis; 2 had Wegener's granulomatosis and 5 had microscopic polyangiitis. Invasive pulmonary aspergillosis developed within 2 to 13 weeks of immunosuppressive therapy.[48]

Tracheobronchial Aspergillosis

The presence of *Aspergillus* spp. in the large airway may represent colonization or rarely, tracheobronchitis. Isolated invasive *Aspergillus* tracheobronchitis is mostly reported in patients with severely immunocompromised status due to transplantation or hematological malignancies or AIDS. Of note, 19 patients with isolated invasive *Aspergillus* tracheobronchitis were reported from China, who had impaired airway structures or defense functions rather than severely immunocompromised status. Only three (16%) patients had neutropenia. Malignancy (13 cases of solid tumor, 1 case of lymphoma) was the most common underlying disease. The disease could be classified into four different forms: Superficial infiltrative, full layer involvement, occlusion and mixed type.[49]

Chronic Necrotizing Pulmonary Aspergillosis

It is another subset of pulmonary aspergillosis. This indolent infection has been reported in elderly patients with COPD, inactive tuberculosis, pneumoconiosis or sarcoidosis. Subtle defects in systemic host defense due to malnutrition, alcoholism, diabetes mellitus or low-dose corticosteroids may also be evident. It is present as chronic refractory bronchopneumonia with fever, weight loss, cough, progressive infiltrates and evidence of invasive aspergillosis on biopsy. The infection may progress to cavitation and formation of an aspergilloma or may develop from an aspergilloma as the initial focus.[2]

Invasive Fungal Rhinosinusitis

As mentioned earlier, invasive FRS include acute invasive, granulomatous and chronic invasive FRS depending on host immune status, geographical region. Acute invasive FRS is described by a time course of less than four weeks with predominant vascular invasion occurring in patients with immunocompromised status. The histopathology demonstrates hyphal invasion of blood vessels, including carotid arteries and cavernous sinuses, vasculitis with thrombosis, hemorrhage, tissue infraction and acute neutrophilic infiltrates. Granulomatous invasive is described by a time course of less than 12 weeks with an enlarging mass in the cheek, orbit, nose and paranasal sinuses in immunocompetent hosts. Proptosis is often a prominent feature. The disease has primarily been seen in Sudan, India, Pakistan and Saudi Arabia.

Histopathologically, a granulomatous response is seen with considerable fibrosis. Hyphae are usually scanty and *A. flavus* is the primary agent isolated. Chronic invasive FRS is a slowly destructive process with a time course of less than 12 weeks that most commonly affects the ethmoid and sphenoid sinuses, but may involve any paranasal sinus. In contrast to granulomatous invasive FRS, the entity is characterized as dense accumulation of hyphae, occasional presence of vascular invasion, and sparse inflammatory reaction in association with the involvement of local structures. The disease is usually associated with AIDS, diabetes mellitus and corticosteroid treatment. *A. fumigatus* is commonly isolated from such patients.[27,29]

Zygomycosis

It is an increasingly reported polymorphic disease caused by members of the class *Zygomycetes*. The most common sites of zygomycosis are the rhinocerebral area (39%), lungs (24%) and skin (19%).[17] Pulmonary zygomycosis is most frequently observed in granulocytopenic and corticosteroid treated patients. The patients with advance AIDS are also at risk. The epidemiology of zygomycosis seems to be different between developed and developing countries. In developed countries, the disease is still a rare finding and mostly seen in patients with hematological malignancies undergoing chemotherapy, in bone marrow transplant recipients and as breakthrough infection in patients receiving voriconazole therapy or prophylaxis. However, in developing counties like India, the number of zygomycosis cases seems to be on the rise, occurring commonly in patients with uncontrolled diabetes. The number of cases with uncontrolled diabetes is so overwhelming that the other risk factors are overshadowed.[2,18,50,51]

Most of the *Zygomycetes,* causing respiratory infections in immunocompromised or debilitated hosts have a high propensity for thrombotic invasion of blood vessels, for causing a rapidly evolving clinical course, high mortality and a relative resistance to antifungal therapy. Pulmonary zygomycosis may have a wide variety of disease manifestations, including solitary nodular lesions, lobar involvement, and cavitary or disseminated form. Infiltrates or mass lesions without any specific lobar predilections are common findings. Pulmonary consolidation and cavitations are seen less frequently, though in a series from India 23% had cavitary lesions.[52] Recently, two cases of pulmonary cavitary zygomycosis due to very rare species, *Rhizopus homothallicus* have been reported.[53] It is suggested that such cavities represent the liquefaction of pulmonary infarcts. Antemortem diagnosis of pulmonary zygomycosis is difficult due to the lack of specific symptoms and signs and large numbers (44% to 100%) of cases are diagnosed postmortem. Increased awareness may improve the proportion of cases with antemortem diagnosis. Open lung biopsy, surgical extirpation and needle aspiration under image guidance provide better results.[52]

Fusarium and Scedosporium Infections

Over the past two decades, *Fusarium spp*. and *Scedosporium apiospermum* or *Pseudallescheria boydii* (sexual stage) are emerging pathogens, especially in patients with hematological malignancies undergoing chemotherapy and bone marrow transplant recipients. The pulmonary infections caused by both agents are indistinguishable many times from that caused by *Aspergillus spp*. The organisms in tissue also resemble *Aspergillus spp*., having angular, septate dichotomously branching hyphae.[2,54,55]

Fusarium solani, Fusarium oxysporum, Fusarium moniliforme and *Fusarium chlamydosporum* are the commonly isolated agents from patients with invasive *Fusarium* infection. Though invasive *Fusarium* infections produce pulmonary disease similar to that of invasive aspergillosis, pulmonary infiltrates, cutaneous lesions and positive blood culture and sinusitis characterize it. Biopsy of cutaneous lesion and advanced blood culture detection system, such as lysis centrifugation help in the diagnosis of disseminated fusariosis.[54]

Scedosporium spp. causes sinusitis, pneumonia and disseminated infections in immunocompromised hosts and fungal ball in immunocompetent patients. Pneumonia due to *Scedosporium apiospermum* is clinically indistinguishable from that due to *Aspergillus spp*. Other *Scedosporium* species, *S. prolificans* can also cause pneumonia in immunocompromised host and is considered to be mere virulent and resistant to amphotericin B. Diagnostic approaches are similar to aspergillosis or zygomycotic infections. The organism in tissue resembles *Aspergillus spp*., as angular, septate dichotomously branching hyphae. The definitive microbiologic diagnosis is established by culture.[55] Blood culture may help in *S. prolificans* isolation.

Respiratory Infections due to Dimorphic Fungi

Dimorphic fungi, including *H. capsulatum, B. dermatitidis, Coccidioides immitis, Paracoccidioides brasiliensis, Penicillium marneffei* and rarely *Sporothrix schenckii* may cause respiratory tract infection. The dimorphic fungi do appear to follow a geographically defined endemic pattern of distribution. *Penicillium marneffei,* the fungus causing penicilliosis has its environmental niche is Southeast Asia only.[56-58] Histoplasmosis, though earlier considered uncommon in Asia-Pacific region, is increasingly reported in many countries, especially in patients with AIDS.[59,60] Autochthonous cases of blastomycosis are occasionally reported from this region,[61] coccidioidomycosis and paracoccidioidomycosis are rarely reported as imported disease.[62,63] Upon entry of the conidia of the dimorphic fungi into lower respiratory tract, the interaction of host defenses and various fungal factors determines the outcome of infection. The fungi are usually contained by alveolar macrophages, resulting in a localized granulomatous reaction. Calcification develops at the site of resolving granulomatous foci of *H. capsulatum* infection.

Histoplasmosis usually presents as mild insignificant self-limiting respiratory disease in the majority of patients from endemic areas. The clinical manifestations of histoplasmosis may be classified according to the site (pulmonary, extrapulmonary or disseminated), by duration of infection (acute, subacute and chronic) and by pattern of infection (primary vs reactivation). Acute primary pulmonary histoplasmosis may develop in a normal, immunocompetent host who is exposed to a heavy inoculum. Chronic cavitary pulmonary histoplasmosis is an indolent, but progressive respiratory infection of patients with underlying COPD. Acute progressive disease is seen in immunosuppressed host. Though the number of cases of acute progressive disseminated histoplasmosis has steadily increased in the Asia-Pacific region along with the rise of AIDS population, a large number of cases are diagnosed as chronic manifestations of disseminated histoplasmosis. These cases are diagnosed as the disease frequently presented with accessible mucocutaneous lesions that can be easily biopsied.[59,60].

It is not clear whether blastomycosis is endemic in any focus in the Asia-Pacific region as there are very few autochthonous cases reported from this region. Most of those cases were reported from India.[61] The fungus was isolated from pulmonary, cutaneous and cerebral lesions. The manifestations of *B. dermatitidis* infection are protean from an asymptomatic disease, a brief influenza like illness, self-limited localized pneumonia in immune competent patients, subacute to chronic respiratory illness and fulminant infection with adult respiratory distress syndrome. The infiltrates of pulmonary blastomycosis are nonspecific and appear as bronchopneumonia or segmental consolidation.

The manifestations of pulmonary penicilliosis are little known, it is believed that the infection has a striking resemblance to disseminated histoplasmosis in HIV infected patients. The recognition of penicilliosis is sometimes difficult, especially in the area where histoplasmosis is also endemic as both diseases present with fever, weight loss, cough, anemia, lymphadenopathy and hepatosplenomegaly. However, skin lesions are more common (60 to 85%) in penicilliosis. Even laboratory findings are similar between the two groups except hyperbilirubinemia, which is more common in the penicilliosis group.[64] HIV infected patients have a higher incidence of fungemia, higher antigen titer in *P. marneffei*-specific mannoprotein Mp1p enzyme-linked immunosorbent assay and low serum antibody level.[65] All those data indicate that only high degree of suspicion among clinicians treating HIV infected patients may help in the early diagnosis of penicilliosis cases, especially when many diseases mimic similar clinical presentations.

Pulmonary Cryptococcosis

The disease is frequently associated with disseminated infection especially in immunocompromised hosts. Cryptococcosis occurs in 0.3 to 5.3% (with a mean of 2.8%) of solid organ transplant recipients and 25 to 54% of transplant recipients with cryptococcosis have pulmonary disease and the disease is limited to the lungs in 6 to 33% cases.[66] In these patients fever, cough, dyspnoea and pleural pain are common initial manifestations. Interstitial infiltrates, miliary nodules, Acute Respiratory Distress Syndrome (ARDS), hilar lymphadenopathy and pleural effusion are typical radiographic features. Pulmonary cryptococcosis is relatively common and frequent finding in patients with AIDS. In an autopsy series of 8,421 South African Miners, with an estimated HIV prevalence of 24%, 589 cases (overall prevalence of 7%) of pulmonary cryptococcosis were identified. Antemortem diagnosis for cryptococcal meningitis was in 47% of these cases and for pulmonary cryptococcosis in 1.2% cases. The remaining 52% of those cases had been misdiagnosed as pulmonary tuberculosis.[67] Therefore, pulmonary cryptococcosis is often empirically treated as pulmonary tuberculosis.

Pulmonary Candidiasis

Pulmonary candidiasis may be a secondary process arising from hematogenous dissemination or rarely a primary bronchopneumonia. Primary *Candida* bronchopneumonia may be observed in severely debilitated, neutropenic patients and very low birth weight infants and usually associated with aspiration of oropharyngeal content. The diagnosis of pulmonary candidiasis is difficult because of nonspecific clinical and radiological presentation. The presence of *Candida* in the sputum, tracheal aspiration or Bronchoalveolar Lavage (BAL) mostly represents contamination from upper respiratory tract colonization. A definite diagnosis of *Candida* pneumonia requires histopathological proof of lung invasion. Children can also be affected by pulmonary allergic reaction due to *Candida* species.[68]

Pneumocystis Respiratory Tract Infection

Pneumocystis jiroveci, formerly known as *Pneumocystis carinii*, is a major cause of opportunistic infection in respiratory tract. Pneumonia caused by this organism is an AIDS defining illness having high morbidity and mortality. Though the infection rate has come down in HIV positive patients after antiretroviral therapy, patients with inherited or other acquired immune defects and those on immunosuppressive medications are vulnerable to *Pneumocystis* infection. Patients often present initially with a history of dry cough, fever, dyspnea and difficulty in deep inspiration. Physical examination reveals varying degree of tachypnea, tachycardia, cyanosis and rales. Chest radiographs often exhibit the pathognomonic bilateral diffuse infiltrates with a ground-glass appearance; however, focal infiltrates may also occasionally be seen.

Patients with AIDS and pneumocystis pneumonia have a significantly increased number of pneumocystis organisms and fewer neutrophils in their lungs than do patients with pneumocystis pneumonia in the absence of AIDS. The smaller number of neutrophils in patients with AIDS correlates with better oxygenation and survival as compared with pneumocystis pneumonia in patients without AIDS.[69,70] The mortality rate in AIDS with pneumocystis pneumonia is 10% to 20% during the initial infection, though the rate increases substantially with the need for mechanical ventilation.[71] The mortality rate in patients with pneumocystis pneumonia in the absence of AIDS is 30% to 60% depending on the population at risk, with a greater risk of death among patients with cancer than among patients undergoing transplantation or those with connective tissue disease.[69]

The gold standard for diagnosis is a lung biopsy, though BAL fluid and induced sputum is often utilized for the diagnosis. Gömöri methenamine silver, toluidine blue, calcofluor white stains, which stain pneumocystis cysts, are commonly used to identify P. jiroveci in those samples. Trophic forms can be detected with modified Papanicolaou, Wright-Giemsa, or Gram-Weigert stains. Monoclonal antibodies for detecting pneumocystis have a higher sensitivity and specificity in induced sputum samples than conventional stains have, but the difference is much less in BAL fluid.[72,73] In patients with pneumocystis pneumonia, serum lactate dehydrogenase usually rises, but it may reflect underlying lung injury rather than any specific marker of the disease. Lower level of plasma S-Adenosylmethionine was observed in patients with pneumocystis pneumonia, but larger cohort study is required to prove its usefulness for the diagnosis of pneumocystis infection.[70]

Diagnosis of Pulmonary Mycoses

With the increase of opportunistic fungal respiratory tract infections in tertiary care centers, especially with the increase of susceptible population, the real challenge is to suspect and diagnose and treat these infections early. Otherwise, these infections are associated with very high attributable mortality. Many centers recently reported unusually high incidence of opportunistic mycoses, including *Aspergillus spp*., *Fusarium spp*., *Scedosporium spp*. and *Zygomycetes*.[5] The time period between the first evidence of fungal infections and appearance of signs and symptoms represent a window of opportunity for early treatment. However, the present status of early diagnosis of these opportunistic mycoses is dismal. The European Organization for Research and Treatment of Cancer-Mycosis Study Group (EORTC-MSG) have developed a diagnostic protocol for invasive fungal infections in immunocompromised patients as proven, probable and possible infection depending on host, clinical and microbiological criteria.[74] The diagnosis of fungal infection depends on the combination of all three, instead of one criterion in isolation, though predictive value of the same may be high. Imaging helps to increase the suspicion of fungal disease. Therefore, the mycological tools should be used in conjunction with modern imaging techniques.[5]

Among mycological techniques, conventional procedures (direct microscopy, histopathology and culture) are not sensitive enough and do not help in early diagnosis. Maximum attention has been drawn to find suitable serological or molecular diagnostic technique. Polymerase Chain Reaction (PCR) for the detection of fungal nucleic acid in specimens, though holds promise, is awaiting further standardization and validation. Therefore, the relative merits of diagnostic tests for the detection of Galactomannan (GM) and beta-D-Glucan (BDG) are being evaluated. In recent year, a lot of experience has been gained with the Platelia *Aspergillus* seroassay (Bio-Rad Laboratories). This sandwich Enzyme Immunoassay (EIA) detects galactofuranose-containing molecules (including GM), cell wall components released by *Aspergillus* species during hyphal growth. Few other fungal organisms like *Penicillium* spp. share cross-reacting epitopes with *Aspergillus* species, but fortunately, these pathogens are rare in patients at risk for fungal respiratory tract infections.

The Platelia EIA is widely used as a screening tool for the early detection of invasive aspergillosis in neutropenic patients, though sensitivity results varied in different studies.[5] A single positive assay serves as a microbiological criterion to define probable invasive aspergillosis in patients with appropriate radiographic abnormalities. Platelia EIA has been used to detect *Aspergillus* antigen not only in serum, but also in BAL and pleural fluid. Data from one major center demonstrated excellent sensitivity of the Platelia EIA when used on BAL and pleural fluid.[75] It awaits: corroboration from other centers, treating similar patients. Of note, the use of Plasma-Lyte for performing BAL and the concomitant use of semisynthetic beta-lactam antibiotics, such as piperacillin/tazobactam may result in false positive test result.

Glucans are (1–3)-beta-D-linked polymers of glucose, which are part of the outer cell wall of most pathogenic fungi (except *Zygomycetes*, *Cryptococcus* species). D-Glucan can be detected by several commercial assays (Fungitell, Association of Cape Cod; Fungi-Tec G, Seikagaku Kogyo Corporation, Japan; Wako-WB003, Wako Pure Chemical Industries, Osaka, Japan). The negative predictive value of glucan detection test by twice weekly sampling is 100% and the sensitivity is 100%, if one positive assay is considered as a positive result, though overall experience with this assay remain limited.[76] The test requires endotoxin-free and glucan-free glassware. A number of factors, including the use of albumin or immunoglobulins, exposure to glucan-containing gauze and hemodialysis, may lead to false-positive readings in glucan detection test. The assay also cross-reacts with some antimicrobial preparations and can provide false positive result in patients with gram-positive bacteremia or *Pseudomonas aeruginosa* infections. Unfortunately, none of these serological assays helps in the diagnosis of other life-threatening fungal disease, invasive zygomycosis.[5,20,77,78]

Chest radiography is not a sensitive procedure for diagnosing pulmonary mold infections at an early stage. Chest CT scan helps to pick up the lesions. Classically, these infections present as macronodular lesions or infiltrates. In neutropenic patients approximately 80% of these nodular lesions will be surrounded by areas of lower attenuation or "halo sign" that represent areas of hemorrhagic inflammation.[5] The lesions eventually may cavitate during the course of therapy and following neutrophil recovery, creating what is commonly referred to as an "air crescent sign." However, these characteristics are neither highly sensitive nor fungal specific; other infections that elicit such inflammatory responses, including bacteria and viruses, can present with halo signs.[5,7]

In the absence of specific clinical symptoms and signs or radiological evidence, the big question is "Can we minimize the number of patients on empiric therapy in the high risk patients groups?" It is well known that the systemic antifungal therapy is toxic, expensive and has many drug interactions. Emphasis should be on preemptive therapy instead of empiric therapy (Table 54.5). Though contradictory suggestions are available, at least in neutropenic patients with persistent or recrudescent fever with no other clinical or radiological evidence of fungal disease, possibly the clinicians may withhold antifungal therapy when GM and glucan tests are negative, as the serological tests have excellent negative predictive value. Conversely, in a patient population in which a positive serological test correlates with a high positive predictive value, positivity should trigger a diagnostic work up, potentially leading to early therapy.[5] However, a highly suggestive CT scan and consecutive negative serological marker should trigger an aggressive diagnostic exploration (lung biopsy and imaging guided aspiration) for invasive zygomycosis, especially in countries like India where zygomycosis rate is very high.[5,52,79]

The diagnosis of pulmonary infections due to dimorphic fungi largely depends on clinical suspicion,

TABLE 54.5: Paradigms for antifungal intervention

Intervention	*Setting*
1. Primary prophylaxis	Prevention use in patients at high risk. General principle – consider prophylaxis when fungal infection rate ≥10% (prophylaxis is not substitute to hospital care practice)
2. Empirical therapy	Preventive use in patients with prolonged (≥10 days) neutropenia (ANC ≤ 500/μL) with persistent or new fever despite adequate broad-spectrum antibacterial therapy (adequate period varies on experience of particular center)
3. Preemptive therapy	Preemptive use in patients at high risk (≥10%) of invasive fungal infections who have imaging findings (Chest CT) and/or laboratory test results (positive for antigen or fungal specific markers) or specific score results consistent with invasive fungal infection by no conclusive evidence
4. Treatment–proven invasive fungal infections	Use in patients with direct microscopy or histopathological demonstration of fungal elements and/or microscopic documentation of a fungal organism in sterile body fluid or tissue
5. Secondary prophylaxis	Continuous use in patients who had a complete or partial response to treatment of an invasive fungal infection and need to undergo further intensive anticancer treatment or immunosuppression (till reversal of immunosuppression)

direct examination of respiratory specimens, histopathological examination of paraffin-embedded tissue and culture of appropriate samples. Careful examination of fungal structure on direct microscopy helps in identification of fungus as each dimorphic fungus has distinctive morphology in tissue. In an immunocompetent host serology for antibody detection helps in the diagnosis of considerable number of cases. Conversely in immunocompromised hosts antigen detection would be preferable alternative. However, only in histoplasmosis detection of a carbohydrate antigen in serum and urine is found to be useful for diagnosis and therapeutic monitoring.[80]

Therapy of Pulmonary Mycoses

The antifungal interventions may be used in the different paradigms (Table 54.5). The spectrum of activity of antifungal agents is provided in Table 54.6. (Also see Chapter 15 on antifungal drugs).

Presently, voriconazole is considered the drug of choice for the first line therapy of invasive aspergillosis. However, particular clinical conditions favor the use of a nonazole-based primary treatment, including prior exposure to mold-active azoles, the concomitant use of prohibited medication (e.g. sirolimus), the risk of severe drug interaction, moderate to severe renal impairment or the presence of mixed fungal infections (e.g. *Zygomycetes*).[5] Multi-azole-resistant *A. fumigatus* is also described.[81] Liposomal amphotericin B is considered alternative drug of choice for the first-line therapy of invasive aspergillosis. Data regarding the use of echinocandins in the primary therapy of invasive aspergillosis is scarce. Overall, up to 50% of the patients who fail first line therapy can be salvaged with second-line use of caspofungin, posaconazole or a lipid formulation of amphotericin B.[5,82,83]

Voriconazole and amphotericin B (preferably a lipid-based formulation) are also considered drug of choice for the treatment of *Fusarium* and *Scedosporium* infections. Posaconazole may be used as salvage therapy.[84-86] For zygomycosis high dose of lipid-based formulations of amphotericin B (up to 10 mg/kg) remain the drug of choice for the first-line therapy, whereas posaconazole may be used in salvage or maintenance treatment. Surgical excision of infected lesions and reversal of underlying predisposing factors are also important in the management of pulmonary zygomycosis and should complement antifungal therapy.[52,87]

Treatment of pulmonary mycoses due to dimorphic fungi depends on the competency of the hosts and disease pattern. Self-limiting disease among immunocompetent hosts are managed with supportive care. Acute pulmonary histoplasmosis or blastomycosis is treated with itraconazole. However, profoundly immunocompromised hosts or those with severe disease are treated with amphotericin B, preferably lipid formulations. itraconazole or amphotericin B has been proven to effective also against penicilliosis.[88-91] In pulmonary cryptococcosis, if the patient is HIV infected, an initial course of amphotericin B with or without

TABLE 54.6: Spectrum of activity of antifungal agents

Organism	*AMB*	*FCZ*	*ITZ*	*PCZ*	*VCZ*	*CAS*	*ANID*	*MICA*	*5FC*
Candida albicans	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*
C. glabrata	S-I-R	SDD-R	S-I	S-I	S-I	S	S	S	S
C. parapsilosis	S	S	S	S	S	S-I	S-I	S-I	S
C. krusei	S-I-R	R	I-R	S-I-R	S-I-R	S	S	S	I-R
Cryptococcus neoformans	S	S	S	S	S	R	R	R	S
Aspergillus fumigatus	S	R	S	S	S	S	S	S	R
A. flavus	S	R	S	S	S	S	S	S	R
Zygomycetes	S	R	I-R	S-I-R	I-R	R	R	R	R
Hyalohyphomycetes	I-R	R	S-I-R	S-I-R	S-I-R	R	R	R	R
Phaeohyphomycetes	S-I	R	S	S	S	I-R	I-R	I-R	S-R
Dimorphic fungi	S	S-R	S	S	S	-	-	-	S-R

AMB = amphotericin B, FCZ = fluconazole, ITZ = itraconazole, PCZ = posaconazole, VIZ = voriconazole, CAS = caspofungin, ANID = anidulafungin, MICA = micafungin, 5FC = 5 fluorocystosine flucytosine, followed by maintenance therapy with fluconazole is recommended. Itraconazole may be used as alternative therapy in patients with the mild disease of pulmonary cryptococcosis.[92,93]

In allergic fungal pulmonary diseases like ABPA, corticosteroids are recommended. Early aggressive disease may slow down the irreversible fibrotic phase. Itraconazole may be added in resistant cases. In allergic fungal sinusitis, systemic steroids are found better than local steroids. Itraconazole may be effective in combination with corticosteroids. For fungal ball in sinuses and aspergilloma in lung, current therapeutic approaches include conservative management and surgical resection.[94-96]

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Pulmonary Mycetoma

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INTRODUCTION

The genus aspergillus includes saprophytic, ubiquitous, soil dwelling organisms that are found in organic debris, dust, compost, food items, and damp areas such as basements.[1] While there are approximately 200 species of aspergillus, only a few are known to cause disease in human beings. Among these, *Aspergillus fumigatus* is responsible for nearly 90% of all human infections. Several other important species that cause human disease include *Aspergillus flavus* and *Aspergillus niger*. Rarely, species, such as, *Aspergillus terreus*, *Aspergillus clavatus*, *Aspergillus niveus*, *Aspergillus nidulans,* among others have been implicated in the causation of human disease.[2-5]

PATHOGENESIS

Aspergillus grows at 15ºC to 53ºC and can thrive in the human respiratory tract. It is a spore-forming fungus with septate dichotomous branching hyphae. These hyphae branch at an acute angle and contain conidiophores, which harbor hundreds of conidia or spores. The spores are easily dispersed by air currents or physical contact.[1-3,6] Aspergillus infection is usually acquired from an inanimate reservoir, by the inhalation of airborne spores and these spores are common inhabitants of the airway. Even though humans may inhale hundreds of these spores daily, only some develop disease from Aspergillus manifesting as a variety of clinical syndromes.

Pulmonary mycetoma (aspergilloma), a saprophytic manifestation of aspergillosis, usually develops in a preexisting cavity in the lung and is the most common and best recognized form of pulmonary involvement due to aspergillus. Impairment or absence of normal mucociliary clearance mechanisms in a cavity may facilitate the adherence and germination of fungal conidia resulting in the formation of a pulmonary mycetoma. Some workers have also postulated that inflammatory reaction in the cavity and the ensuing secretion of toxins, enzymes and other mediators of inflammation may facilitate creation or advancement of a cavity.[7]

Pulmonary mycetomas have been most commonly reported in the cavities of pulmonary tuberculosis. They have also been described in other lung diseases associated with cavity formation (Table 55.1).[2-5,8-14] There have been case reports from India of pulmonary aspergilloma occurring in a hydatid cavity[15] and in patients with cavitary sarcoidosis.[16]

PATHOLOGY

Pulmonary mycetomas grow in the areas of devitalized lung such as a cavity, damaged bronchial tree or a pulmonary cyst. Aspergillomas have been described in cavities in the lung parenchyma, bronchi and pleura. They consist of the masses of living and dead fungal mycelia, inflammatory cells, fibrin, mucus, other blood products and tissue debris, are solid and are fragmented only with force.[2-5] Tissue invasion by the fungus does not occur in pulmonary mycetoma. Inadequate drainage is thought to facilitate the growth of aspergillus on the walls of these cavities.[2]

Earlier, aspergillomas have been classified as simple and complex aspergillomas.[17] Simple aspergillomas develop in isolated thin walled cysts of bronchial origin,

Table 55.1: Cavitary lung diseases complicated by pulmonary mycetoma

- Infections
  - Tuberculosis
  - Sarcoidosis
  - Bronchiectasis
  - Suppurative lung disease (lung abscess)
  - Hydatid cyst
  - Paragonimiasis
  - *Pneumocystis jiroveci* pneumonia
  - Cavities of other fungal infections
- Cystic lung disease
  - Lung sequestration
  - Bronchial cysts
  - Bullous lung disease
- Others
  - Pulmonary neoplasms
  - Ankylosing spondylitis
  - Cystic fibrosis

Source: references 2,5,8-14

there is little or no abnormality in the surrounding lung and the cyst wall itself is usually lined by ciliated epithelium. Complex aspergillomas develop in cavities with gross disease in the surrounding lung tissue.[17] Recently, aspergillomas have been classified as simple and chronic cavitary pulmonary aspergillosis.[18] Simple aspergillomas are encased by thin walled cysts with little surrounding parenchyma disease. Chronic cavitary pulmonary aspergillosis is associated with thick walls, multiple cavities (that may or may not contain fungal balls), and surrounding parenchymal changes (Table 55.2).[18]

Natural History

In the majority of cases, the aspergilloma remains stable, but in up to 10% of cases the lesion may decrease in size or resolve spontaneously without treatment.[2,3,19] However, rarely, progressive enlargement of a single thin walled cavity may occur slowly over months or rapidly within weeks. These patients have minor or moderate degrees of immune dysfunction, such as diabetes mellitus or corticosteroid use. This entity has been called chronic necrotizing pulmonary aspergillosis (subacute invasive aspergillosis).[18] Although aspergillomas are often thought of as benign saprophytic colonizations of the lung with *aspergillus,* invasive pulmonary aspergillosis may develop from an aspergilloma and may be often fatal.[20]

CLINICAL PRESENTATION

Patients with aspergilloma may remain asymptomatic for several years and the pulmonary mycetoma may be evident as an incidental finding on radiographic studies carried out for some other purpose.[2-5] Symptomatic patients with simple pulmonary aspergilloma commonly present with hemoptysis. The source of hemoptysis is usually bronchial artery;[2,3] rarely anastomotic plexus between pulmonary and bronchial arteries[21] has been implicated as the cause. The various causes of hemoptysis in patients with pulmonary

Table 55.2: Comparison of characteristics of simple aspergilloma and chronic cavitary pulmonary aspergillosis

Variable	*Simple pulmonary aspergilloma*	*Chronic cavitary pulmonary aspergillosis (complex aspergilloma)*
Clinical symptoms	None or minimal	Significant pulmonary and systemic symptoms
Host immunity	Not immunocompromised	Not immunocompromised; or, the immunocompromised state has remitted or is trivial
Radiographic findings	Single pulmonary cavity containing a fungal ball	One or more pulmonary cavities, which may or may not contain a fungal ball
Serological/microbiological evidence of infection with *Aspergillus species*	Yes	Yes
Progression of disease	No radiological progression over at least three months of observation	Radiological progression (new cavities, increasing pericavity infiltrates or increasing fibrosis) is evident over at least three months of observation. Hyphae are found in the cavity, but the wall of the cavity is composed of chronic inflammatory cells and fibrosis, but not tissue invasion. In some patients, a strong pleural/pulmonary fibrosis may result in chronic fibrosing pulmonary aspergillosis

Source: reference 18

Table 55.3B: Causes of hemoptysis in patients with aspergilloma

Mechanical friction of the blood vessels in the cavity wall by the moving fungal ball
Local invasion of blood vessels lining the cavity
Endotoxins released by the fungus with hemolytic properties
Release of trypsin like proteolytic enzymes
Type III (antigen-antibody) hypersensitivity reaction resulting in injury to cavity wall and hemorrhage

aspergilloma are listed in Table 55.3. Hemoptysis has been described in 69 to 91% of patients in some of the recently published studies.[11,22,23] In the series published from India,[21,24,25] this figure ranged from 65 to 93% (Tables 55.4A and B). The severity of hemoptysis may range from mild to massive and life threatening. In the series published from India, massive hemoptysis requiring bronchial artery embolization/surgery was observed in 7 to 18%[21,24,25] of patients.

Other symptoms include chronic cough and breathlessness (Tables 55.4A and B). These symptoms may probably be due to the underlying lung disease. Expectoration of blackish brown sputum (melanoptysis) has also been documented in patients with pulmonary aspergilloma.[26,27] Occasionally fever and weight loss may be present and usually signifies secondary bacterial infection.

Rare Manifestations

Coexistence of active pulmonary tuberculosis disease is uncommon in patients with pulmonary aspergilloma, but has rarely been documented.[28] The occurrence of pulmonary aspergilloma in patients with allergic bronchopulmonary aspergillosis is also uncommon.[29,30] Clinical presentation with pneumothorax has also been reported.[31]

Pulmonary Mycetoma in Special Situations

Human Immunodeficiency Virus (HIV) Seropositive Individuals

Apart from occasional case reports of aspergilloma in HIV infected individuals,[32-35] there have been few publications on pulmonary mycetoma in HIV seropositive individuals. In the series reported by Addrizzo-Harris et al.[12] 10 of the 25 patients with pulmonary aspergilloma were HIV serpositive. Seven of the ten HIV seropositive patients had a history of pulmonary tuberculosis and three of them had a history of *Pneumocystis jiroveci* pneumonia (PCP). Severe hemoptysis (>150 mL/day) occurred in 5 of 15 (33%) in the HIV negative group compared with 1 of 10 (10%) of the HIV infected group. Compared with HIV seronegative individuals, disease progression occurred more frequently among the HIV seropositive individuals with a CD4+ T-lymphocyte count <100/mm^3 (4/8, 50% vs 1/13, 8%; p=0.05). Mortality was also higher among HIV infected individuals (4/8, 50% vs 1/13, 8%; p = 0.05). More data are required to further understand these issues.

Lung Transplant Recipients

Aspergillomas have been reported in two single lung transplant recipients both of whom presented with hemoptysis in the series reported by Westney et al.[36]

Neutropenic Patients

While invasive pulmonary aspergillosis has frequently been described in patients with neutropenia, the occurrence of pulmonary mycetoma has also been occasionally described. Kibbler et al.[37] reported four such cases and reviewed the literature regarding 34 similar cases. Acute myeloid leukemia was the most common underlying diagnosis in these patients (17 of the 38 patients, 45%). Hemoptysis occurred in nearly 50% of the patients and the mortality was approximately 25%. As these pulmonary mycetomas did not develop in preexisting lung cavities, but developed in necrotic lung tissue due to fungal invasion, Kibbler et al.[36] suggested the term "mycotic lung sequestration" for this condition. Considering the potential for the progression of disease, immunosuppressed patients who have aspergilloma should be monitored closely for this complication.

DIAGNOSIS

The diagnosis of pulmonary mycetoma is usually established on the basis of clinical presentation and radiographic features, combined with serological or microbiologic evidence of infection with aspergillus species.[6,38] In patients with a past history of pulmonary tuberculosis presenting with hemoptysis, the possible differential diagnosis includes relapse, reactivation/reinfection tuberculosis, aspergilloma, scar carcinoma, among others. The diagnostic work-up should include testing for ruling out these causes.

Chest Radiograph

The chest radiograph is useful in demonstrating the presence of a pulmonary mycetoma. In a chest

TABLE 55.4A: Clinical presentation and radiological features in pulmonary aspergilloma documented in studies from India

Variable	*Akbari et al*[24]	*Pratap et al*[25]	*Shah et al*[21]
Place of study	Thiruvananthapuram, Kerala	New Delhi	Mumbai, Maharashtra
Year of publication	2005	2007	2008
No. of patients	60	72	41
Male: female	36:24	47:25	25:16
Age (years)	Mean 42.7 ± 11.8	Mean 32	Range 16–65*
Predisposing conditions (%)			
Tuberculosis	45	85	76
Bronchiectasis	28	13	15
Lung abscess	12	02	07
No associated pathology	08	ND	02
Others	05[†]	ND	ND
Salient clinical manifestations (%)			
Hemoptysis	93	65	85
Dyspnea	22	11	32
Cough	60	24	68
Chest pain	07	11	12
Weight loss	07	ND	05
Fever	ND	11	24
Type of aspergilloma (%)			
Simple	23	11	02
Complex	77	89	98
Radiological manifestations			
Location (%)			
Right upper lobe	50		ND
Left upper lobe	35		ND
Right middle lobe	03		ND
Right lower lobe	05		ND
Destroyed right lung	ND		ND
Destroyed left lung	ND		ND
Multiple	07		ND
Other findings (%)	Cavity (40) Opacity (37) Infiltrate (05) Cyst (07) Nodule (02) Mass (10)	Cavity with aspergilloma (58) Destroyed one lung (29) Localized bronchiectasis (13)	Cavity with aspergilloma (54)[‡] Only cavity (09)[‡] Destroyed one lung (09)[‡] Bronchiectasis (09)[‡] Mass (03)[‡]

All values corrected to the nearest round figure

* 21 patients were in fourth decade of life

† Acute lymphatic leukemia, chronic infiltrates, carcinoma in situ in one patient each

‡ Described in 32 patients

ND = not described

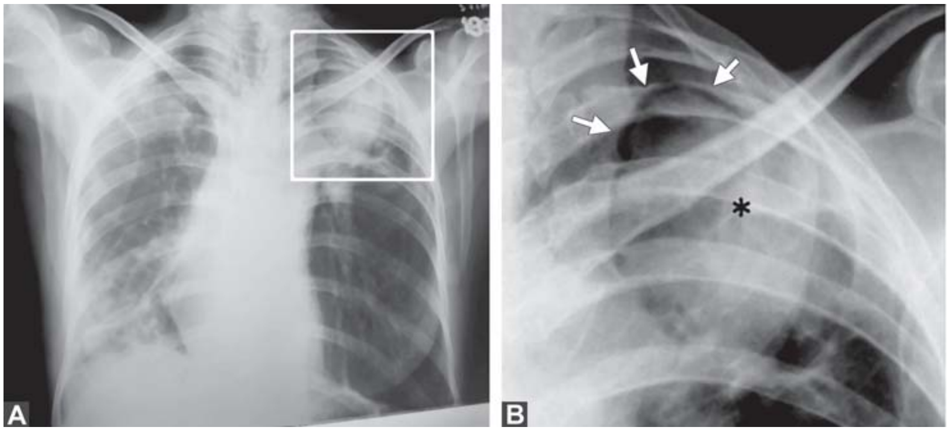
radiograph, aspergilloma appears as a mobile, spherical intracavitary mass that is separated from the cavity by an air space that appears as an "air-crescent" in the periphery (Figs 55.1A and B).[2-5,39] As these lesions usually develop in a preexisting pulmonary tuberculosis cavity, the lesions are frequently found in the upper lobes.[40] After moving the patient from supine to prone position, a change in the position of the fungus ball can be demonstrated.[2-5,39] If the lesion is peripherally located, pleural fibrosis is frequently evident. The chest radiograph may also reveal the sequelae of the pre-existing lung disease.

TABLE 55.4B: Surgical treatment, complications and mortality documented in studies from India

Variable	*Akbari et al*[24]	*Pratap et al*[25]
Place of study	Thiruvananthapuram, Kerala	New Delhi
Year of publication	2005	2007
No. of patients	60	72
Treatment	Lobectomy (n = 55), pneumonectomy (n = 02), segmental resection (n = 02), and cavernoplasty (n = 02). One patient underwent bilateral lobectomy at 14 months interval	Pneumonectomy (n = 21); lobectomy (n = 51). In 10 of the right upper lobe lesions, bilobectomies were done, by removing both the right upper and middle lobes, due to presence of adhesions
Morbidity*	12/46 complex aspergilloma patients (26%)	22/64 complex aspergilloma patients (34%)
Major complications*	Air-leak (>10 days) (n = 4), bleeding (n = 2), empyema (n = 4), respiratory problems (n = 1), wound dehiscence (n = 1)	Air-leak (>10 days) (n = 5), massive hemorrhage (n = 5), persistent pleural space (n = 3)
Mortality in complex pulmonary aspergilloma	02/46 (4%)	02/64 (3%)
Over all mortality (%)	02/60 (3%)	02/72 (3%)

All values corrected to the nearest round figure

* Morbidity and mortality were observed only in patients with complex aspergilloma. Surgery was uneventful in patients with simple aspergilloma



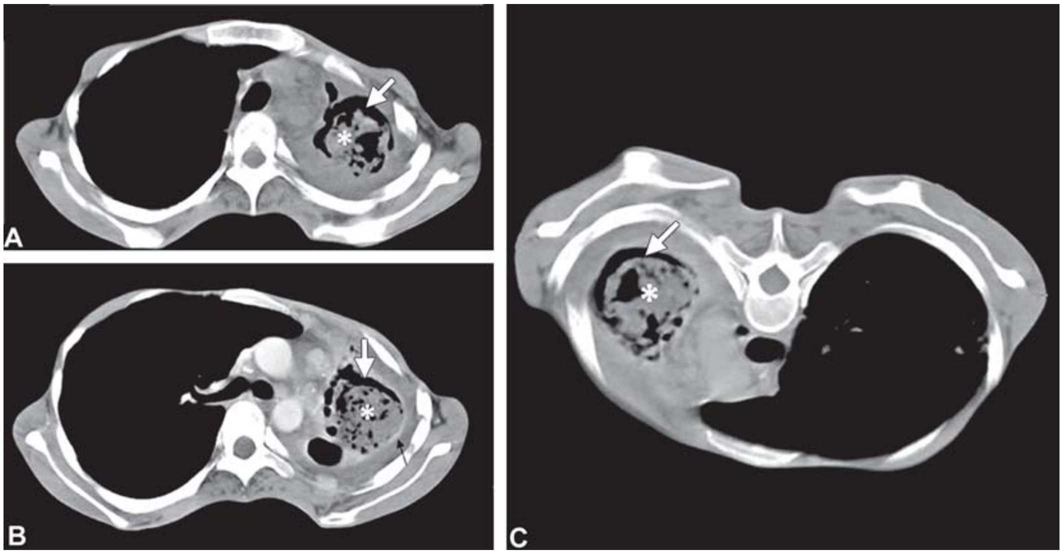
Figs 55.1A and B: Chest radiograph (posteroanterior view) (A) of a patient with past history of pulmonary tuberculosis who presented with hemoptysis showing parenchymal infiltrates in both upper zones, fibrotic changes in right lower zone. In the left upper zone, a spherical intracavitary fungal ball that is separated from the cavity by an air-space that appears as an "air-crescent" in the periphery (square) can also be seen. Close-up view of the same (B) showing a intracavitary fungal ball (asterisk) that is separated from the cavity by an air-space that appears as an "air crescent" in the periphery (arrows)

Computed Tomography

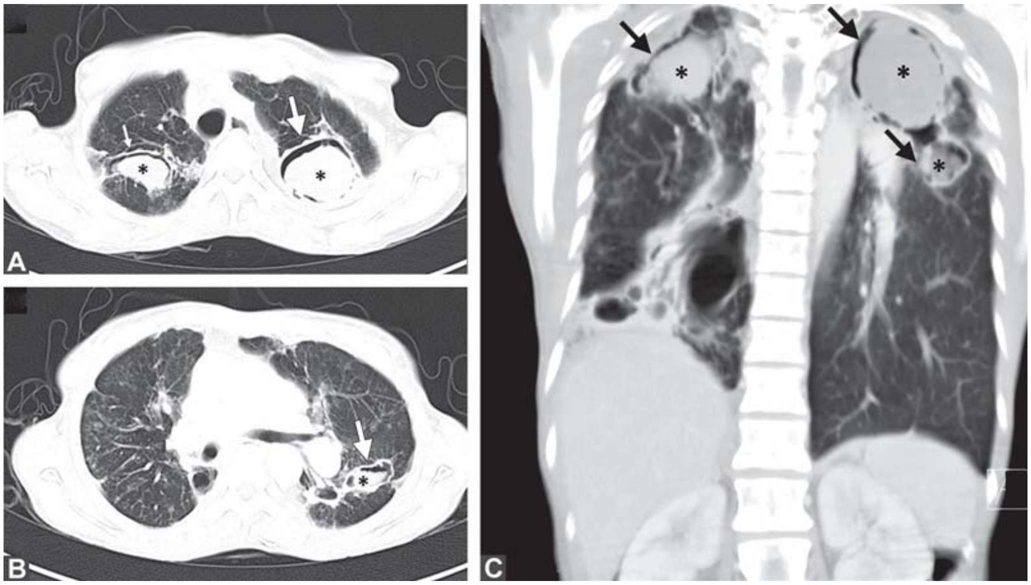
Computed tomography (CT) is increasingly being used for the evaluation of patients with pulmonary mycetoma. The CT offers the advantages of facilitating the better delineation of fungal ball and air crescent and documenting the change in the position of the fungal ball (Figs 55.2 and 55.3). The CT also facilitates the detection of fungal balls that may not be discernible on the chest radiograph. Coexistent lung disease, sequelae of previous lung disease can also be appreciated better on CT.[2-5]

Differential Diagnosis

Radiologically, aspergillomas must be differentiated from hematoma, neoplasm, abscess, hydatid cyst and Wegener's granulomatosis. However, aspergilloma may coexist with any of these conditions.[41-43] In one study[43] the mural nodules within cavitating lung cancer were more enhanced and showed a nondependent location more frequently than those of intracavitary aspergillomas. The cavitary walls were significantly thicker in cavitating lung cancer (mean thickness 5.8 mm)



Figs 55.2: Computed tomography of the chest (plain study, mediastinal window) and (A) contrast enhanced study (lung-window) (B) showing an intracavitary fungal ball (asterisk) that is separated from the cavity by an air-space that appears as an “air-crescent” in the periphery (white arrow); thickened pleura is also evident (black arrow). CECT chest obtained after moving the patient from supine to prone position (C) shows a change in the position of the fungus ball (asterisk) and the air-crescent (arrow)



Figs 55.3A to C: CECT of the chest (A) of the same patient shown in Figure 55.1A showing complex pulmonary aspergillomas (asterisk) in both upper lobes and another aspergilloma in the left upper lobe; (B) air-crescent sign (arrow) is also evident. Coronal reconstruction (C) reveals the aspergillomas (asterisks), air-crescent sign (arrow) and fibrocavitary disease. The CT was helpful in revealing several other details that were not discernible in the chest radiograph (Figs 55.1A and B)

than those in intracavitary aspergillomas (mean thickness 2.6 mm). Adjacent bronchiectasis and volume decrease of the involved lobe were observed more frequently in intracavitary aspergillomas than in cavitating lung cancers.

Serological and Microbiological Methods

Sputum, bronchoalveolar lavage (BAL) fluid culture may reveal the presence of aspergillus species in 50% of the patients with pulmonary aspergilloma.[6,38] Serum precipitins [immunoglobulin G (IgG) antibodies] against *Aspergillus fumigatus* are usually positive in almost all the cases; false-negative reports have been described in patients receiving corticosteroid treatment and in mycetomas caused by species other than *A. fumigatus*.[6,38]

Histopathology

Histopathological evidence of aspergilloma (Figs 55.4A to C) may be established in surgically excised specimens by demonstrating acute-angle branching, septate, non-pigmented hyphae measuring 2 to 4 µ in width that are best demonstrated with best detected by Gömöri methenamine silver and periodic acid–Schiff stains.[6,38] However, *Aspergillus* hyphae are histopathologically difficult to distinguish from those of *Fusarium* species, *Pseudallescheria boydii,* agents of phaeohyphomycosis, among others.

Molecular Methods

Polymerase Chain Reaction (PCR) has been used for the diagnosis of pulmonary aspergilloma. Polymerase Chain Reaction amplification of Asp fI (18 kDa) and alkaline protease (33 kDa) antigens derived from *A. fumigatus* and implicated as possible virulence factors in the pathogenesis of *Aspergillus* induced diseases has been found to be useful for the diagnosis of pulmonary aspergilloma.[44] In another study,[45] TacMAN-MGB probes, which covered the loci Gly 54, Leu 98, Glyw 138 and Met 220 of the enzyme CYP 51A coded by the gene cyp 51A, as well as the 34-bp tandem repeated sequence in the promoter region (-288 and -322 from the start codon) of this gene, was useful in detecting itraconazole resistant strains of *A. fumigatus*. These protocols need to be evaluated in the field setting.

TREATMENT

The optimal treatment strategy for patients with pulmonary mycetoma is unknown and there is no consensus regarding the choice or timing of therapy. Treatment aims at preventing life threatening hemoptysis.

Surgery

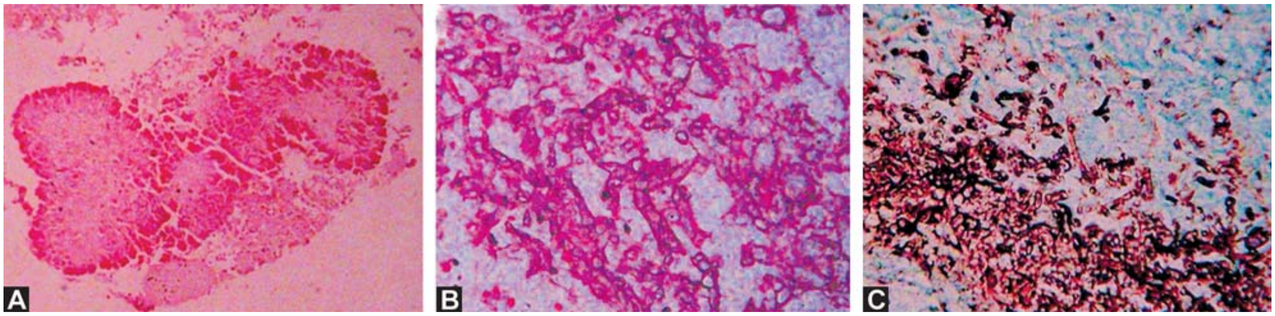
Surgical removal of aspergilloma is the definitive treatment. However, in view of the morbidity and mortality associated with the procedure, it has to be used judiciously. As per the recent Infectious Disease Society of America (IDSA) guidelines[38] surgery is indicated as the definitive treatment in patients with the episodes of life threatening hemoptysis, and those who are at risk for such a complication, like patients with underlying sarcoidosis, immunocompromised patients, and those with increasing *Aspergillus* specific IgG titres.

Morbidity

Commonly observed postoperative complications include hemorrhage, incomplete lung reexpansion, prolonged air leak, empyema and respiratory failure, wound infection, respiratory insufficiency and chylothorax.[11,46-51] Various surgical procedures used in the treatment of pulmonary aspergilloma in two studies from India[24,25] and associated morbidity are shown in Table 55.4B.

Mortality

Surgery for pulmonary aspergilloma was associated with a high mortality rate, ranging from 7 to 23% in earlier



Figs 55.4A to C: Photomicrograph of a surgically excised specimen showing an aspergilloma (A) (Hematoxylin and eosin × 100). Under high power view (B) acute-angle branching, septate, non-pigmented hyphae measuring 2 to 4 µ can be seen (Hematoxylin and eosin × 400). The fungal hyphae are better appreciated on Gömöri methenamine silver staining (× 400) (C)

(*Courtesy:* Dr KV Sreedhar Babu, Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati) studies.[11,46-51] More recent data from nine published studies[52-59] (n=456) reveal a cumulative mortality rate of 2.3%.[4] Surgical mortality has been reported to be less than 1% for simple aspergilloma.[2-5] In two large Indian studies published recently, the overall mortality rate was 3% (see Table 55.4B).[24,25] All deaths had occurred in patients with complex aspergilloma and in this group of patients, the mortality ranged from 3 to 4% (see Table 55.4B).

Since aspergilloma do not result in life threatening hemoptysis in a majority of the patients, the morbidity and the expense involved in the treatment must be weighed against the clinical benefits. Asymptomatic patients with pulmonary mycetoma should be carefully followed-up for their life time as they have a potential for developing hemoptysis.

Bronchial Artery Embolization

Patients with life threatening hemoptysis who require surgery would need to have adequate pulmonary function to undergo the operation. However, several patients are sick and may not be fit to undergo major surgery. Bronchial artery embolization may be useful as a temporary life saving procedure in patients with life threatening hemoptysis. Unlike several other conditions where bronchial artery embolization produces more favorable outcome, the results have not been as promising for patients with aspergilloma.[60] In the study reported by Kim et al.[61] (n = 118), the only significant factor associated with rebleeding one year after bronchial artery embolization was the presence of an aspergilloma (n = 32). Presently, bronchial artery embolization is not considered to be a replacement for surgery, but, is recommend by the IDSA guidelines[38] as a short-term therapy to stabilize patients for more definitive treatment, including surgery.

Medical Treatment

The role of intravenously administered amphotericin B failed to show a benefit in patients with aspergilloma.[62] Inhaled, intracavitary and endobronchial instillation of antifungal agents has been tried with limited success for the treatment for aspergilloma.[22,63,64] Intracavitary administration of transthoracic, percutaneous amphotericin B into the under CT guidance has been found to be useful in patients with massive hemoptysis, with the resolution of hemoptysis occurring within few days. While the results have been promising in some of the studies,[62,65-67] simliar success was not documented in others.[68,69]

Itraconazole has a high tissue penetration and significant itraconazole levels have been demonstrated within the cavity containing aspergilloma.[70] Oral itraconazole has been used with promising results in patients with aspergilloma with symptomatic and radiographic improvement being evident in half to two-thirds of patients; and a complete response in the occasional patient.[66-68] However, itraconazole works slowly and may not be useful in patients presenting with life-threatening hemoptysis.

According to the IDSA guidelines,[38] for patients with pulmonary aspergilloma, voriconazole (6 mg/kg IV every 12 hour for one day, followed by 4 mg/kg IV every 12 hour; oral dosage is 200 mg every 12 hour), or itraconazole (dosage for tablets is 600 mg/day for three days, followed by 400 mg/day; parenteral dosage is 200 mg every 12 hour IV for 2 days, followed by 200 mg daily thereafter are advocated as the alternatives to surgery, which is advocated as the primary therapeutic strategy. For chronic cavitary pulmonary aspergilloma, these guidelines[38] indicate voriconazole and itraconazole as the primary therapy. Potential utility of therapy with interferon-gamma in pulmonary aspergilloma has occasionally been documented[18,38] and merits further study.

PROGNOSTIC FACTORS

Factors associated with a poor prognosis in patients with aspergilloma include severe underlying lung disease, increasing size or number of lesions on imaging, presence of immunosuppression (including corticosteroid treatment), increasing *Aspergillus*-specific IgG titers, recurrent large volume hemoptysis, and underlying sarcoidosis or HIV infection.[6]

OVERALL MORTALITY

Mortality in patients who have pulmonary aspergillomas has been reported to be 5 to 6% per year.[4] In a retrospective study[22] of 85 cases over 24 years, overall mortality over 10 years was 56%, with 10 deaths directly attributable to aspergillomas. The age of the patients and underlying comorbid lung disease also seem to have a bearing on the mortality.

CONCLUSION

Pulmonary mycetomas most often develop in old tuberculosis cavities. Majority of patients with pulmonary mycetomas remain asymptomatic and the lesions may be picked up on a routine chest radiograph carried out for some other purpose. Pulmonary aspergillomas are often noticed by clinicians when patients present with hemoptysis. In patients who present with life threatening hemoptysis and are fit, surgery is the preferred treatment of choice. Bronchial artery embolization may be used as a temporary measure to control bleeding. Therapy with voriconazole and itraconazole appear to be useful. Asymptomatic patients should be carefully followed-up periodically for their lifetime as they have potential for developing life threatening hemoptysis.

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Nosocomial Pneumonia

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INTRODUCTION

Nosocomial pneumonia has been defined as an infection of the lung parenchyma that was neither present nor incubating at the time of hospital admission. It includes Hospital-Acquired Pneumonia (HAP), Ventilator-Associated Pneumonia (VAP) and Health Care-Associated Pneumonia (HCAP), which are significant problems world wide. These pneumonias are responsible for an increased mortality, hospital stay and health care costs for patients.

Definitions According to ATS/IDSA Guidelines[1]

Hospital-acquired pneumonia is defined as pneumonia occurring 48 hours after admission and does not appear to be incubating at the time of admission. Similarly, VAP is defined as pneumonia occurring 48–72 hours after endotracheal intubation. Health care-associated pneumonia is a relatively new term for pneumonia occurring in patients in the nonhospital settings, but who have got extensive health care contact. HCAP excludes HAP, VAP and Community-Acquired Pneumonia (CAP), and is associated with the following risk factors:

a. Hospitalization for more than two days in the preceding 90 days
b. Residence in a nursing home or in an extended care facility
c. Home infusion therapy
d. Patients receiving chronic dialysis or home wound care

PATHOGENESIS

The main mechanism involved in the pathogenesis of nosocomial pneumonia is through the colonization of oropharynx and Gastrointestinal Tract (GIT) with pathogenic microorganism leading to microaspiration of these contents. Colonization can occur in almost 75% of hospitalized patients within 48 hours, predominantly due to a breach of normal mucosal integrity (from numerous invasive devices—nasogastric, endotracheal tube and urinary catheter), contact through health care personnel, and colonization of endotracheal tube biofilm. Factors that lead to an increase in the gastric pH like an acute illness, or drugs can disrupt the sterility of the stomach and upper GIT and lead to colonization. There are multiple reasons for aspiration such as the altered level of consciousness, depressed gag reflex, impaired swallowing and altered gastrointestinal motility. Though endotracheal tube may prevent macroaspiration, it does not prevent microaspiration around the cuff of the tube. Sometimes, the microorganisms inhabiting the biofilm of the endotracheal tube can get dislodged and reach the lower respiratory tract. Further, it depends on the number and virulence of microorganisms, and the host defenses whether VAP develops or not. Rarely, hematogenous spread from a focus of sepsis can lead to VAP.

DIAGNOSIS

Diagnosis of HAP/HCAP is predominantly based on clinical, radiological and sputum evaluation. The data on HAP/HCAP is mainly extrapolated from studies from VAP. Ventilator-associated pneumonia should be suspected in all intubated patients who develop new onset fever, respiratory symptoms, and/or new chest infiltrates; in patients on ventilator with increased respiratory rate, increased minute volume, decreased tidal volume and increasing oxygen requirement. There are two different strategies to diagnose VAP. Clinical approach and quantitative bacteriological approach.[1]

Clinical Approach

In this approach, diagnosis of VAP/HAP is based on the presence of new radiographic infiltrate and presence of two out of three following clinical criteria—fever, leukocytosis or leukopenia, purulent lower respiratory secretions.

The specificity of the clinical criteria is increased by the addition of microscopic examination and semi-quantitative cultures of tracheal aspirate. Microscopic examination of the tracheal aspirate for gram stain and white blood cells will guide empirical treatment and prevent inappropriate therapy. A negative tracheal aspirate for gram stain, inflammatory cells and nonquantitative cultures in the absence of recent change in antibiotic therapy (within 72 hours) has a strong negative predictive value (94%) for VAP, and in such cases other noninfectious causes of pulmonary infiltrates need to be ruled out.[2] Semiquantitative cultures are reported as light, moderate or heavy growth.

Semiquantitative tracheal aspirate cultures are highly sensitive, but have low specificity and cannot differentiate colonization from infection. However, combined with clinical criteria, their specificity increases. Clinical approach hinges on the fact that failure to initiate treatment in the cases of VAP as soon as the diagnosis is suspected, will lead to increased mortality. All the patients suspected to have VAP will receive broad spectrum antibiotics according to risk factors and local microbiological epidemiology after lower respiratory tract secretions are sent for culture, but the initiation of the antibiotics should not be delayed for obtaining cultures especially in hemodynamically unstable patients. Other mimics of pulmonary infection, such as atelectasis, Pulmonary Thromboembolism (PTE), hemorrhage and congestive heart failure, which can present with similar clinical manifestations, should be ruled out before considering the diagnosis of VAP/HAP. It may sometimes lead to excessive antibiotic treatment if other mimics are not excluded before labeling a patient as having VAP.

Clinical Pulmonary Infection Score (CPIS) has been devised to increase the specificity of clinical diagnosis, it incorporates clinical, radiological, physiological (Pao_2/Fio_2) and microbiological data into a single numerical result.[3] When the score of CPIS exceeded six, a good correlation was found with quantitative cultures of specimens obtained by bronchoscopic and non-bronchoscopic methods. A CPIS score of </= 6 at 72 hours has been used to stop antibiotics without adversely affecting mortality and Intensive Care Unit (ICU) stay, but needs to be studied in a larger population.[4] However, subsequent studies did not show good sensitivity and specificity of CPIS for the diagnosis of VAP.

Clinical response after 48–72 hours in combination with semiquantitive cultures are taken into consideration to decide the further course of action regarding antibiotics.

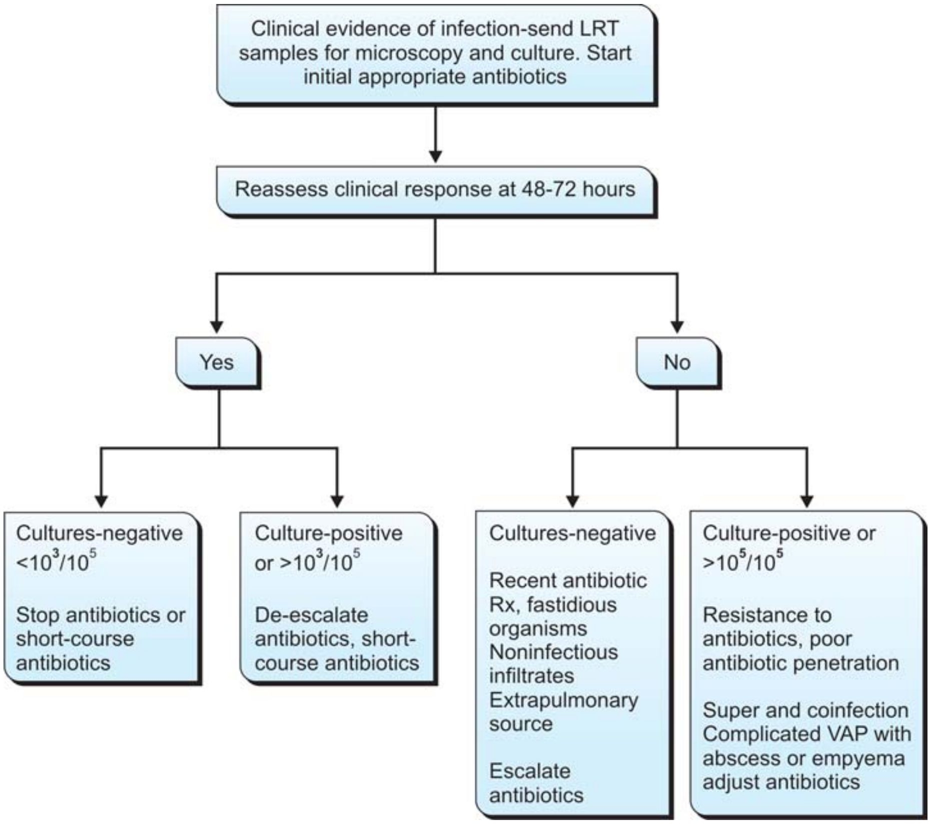
Quantitative Microbiological Approach

The Achilles heel of this approach lies in avoiding over treatment, thereby preventing resistance to antibiotics. Quantitative cultures on the other hand are more specific, but less sensitive and differentiate colonization from infection when a specific threshold is taken for diagnosis of VAP.

The growth of the bacteria in the respiratory samples above the threshold indicates infection, growth below the threshold indicates colonization. These samples can be collected bronchoscopically or blindly. The more distal the sampling from the lower respiratory tract, the more specific and less sensitive it is. So, the lower respiratory tract secretions obtained through Bronchoalveolar Lavage (BAL) and Protected-Specimen Brush (PSB) are highly specific. Mini-BAL and blind endotracheal aspirate (non-bronchoscopic) quantitative cultures have high sensitivity and low specificity, retaining the diagnostic accuracy. However, it has been shown that bronchoscopic sampling and quantitative culture techniques as compared to non-bronchoscopic and nonquantitative cultures, do not improve mortality, length of hospital stay, duration of mechanical ventilation, or length of ICU stay, but may lead to choice of narrower spectrum of antimicrobial therapy and early de-escalation of antibiotics.[5,6]

The threshold varies depending on the site from which sample has been taken. A threshold of 10^6, 10^4 to 10^5 and 10^3 cfu/ml has been taken as cut-off for blind endotracheal aspirate, BAL and PSB respectively. Patients are treated only if the quantitative cultures exceed the threshold. The main disadvantage of this approach is the failure to treat a patient with false-negative culture report, and lack of immediate availability of the culture report. To overcome this

Flow chart 56.1: An algorithmic approach to the diagnosis of VAP


Clinical evidence of infection-send LRT samples for microscopy and culture. Start initial appropriate antibiotics
Reassess clinical response at 48-72 hours
Yes
No
Cultures-negative $<10^3/10^5$
Stop antibiotics or short-course antibiotics
Culture-positive or $>10^3/10^5$
De-escalate antibiotics, short-course antibiotics
Cultures-negative
Recent antibiotic Rx, fastidious organisms
Noninfectious infiltrates
Extrapulmonary source
Escalate antibiotics
Culture-positive or $>10^5/10^5$
Resistance to antibiotics, poor antibiotic penetration
Super and coinfection
Complicated VAP with abscess or empyema
adjust antibiotics

problem, the clinician can take clues from the Giemsa or Gram-stain of the endotracheal aspirates to guide the initial appropriate therapy. False-negative cultures can occur in the cases of specific pathogen, recent start of antibiotics or cultures taken after starting antibiotics. Threshold for diagnosis may be lowered in such cases to increase the sensitivity.

A combined approach following algorithm is better in view of the short-comings of both the approaches (Flow chart 56.1).

RISK STRATIFICATION OF PATIENTS WITH VAP

Presently, there is no score to assess the severity of VAP at the time of diagnosis. APACHE II has not been shown as a good modality for risk stratifying these patients as shown in a matched cohort study.[7] Analogous to the TNM classification used in cancers, experts have come up with a relatively new concept of stratification (PIRO). This is based on predisposition (P), insult/infection (I), host response (R) and organ dysfunction (O). This concept was built upon a system of IRO during the 2001 International Sepsis Definitions Conference, which discussed the weaknesses of Systemic Inflammatory Response Syndrome (SIRS) and sepsis definitions.[8] By mixing the PIRO concept with VAP, a VAP-PIRO score was created.[9] On multivariate analysis, four variables were associated with mortality presence of comorbidities: Chronic Obstructive Pulmonary Disease (COPD); immunocompromised, heart failure, cirrhosis, or chronic renal failure (predisposition-P), bacteremia (infection/insult-I); systolic blood pressure below 90 mm Hg or need of vasopressors to maintain blood pressure (response-R); and Acute Respiratory Distress Syndrome (ARDS) (organ dysfunction-O). These results were converted into a four variable PIRO score with one point assigned to each variable, with the score ranging from 0 to 4. The mortality increased significantly as the score increased (Table 56.1).

TABLE 56.1: Categorization and mortality according to the VAP-PIRO score

Risk category	*Score*	*Mortality*
Mild risk	0–1points	9.8–17%
High-risk	2 points	52.9%
Very high-risk	3–4 points	76.5–93.3%

TREATMENT

Appropriate initial antibiotic therapy improves survival. Initial inappropriate therapy has been shown to increase the mortality in patients with severe sepsis and VAP. The most important factor for initial inappropriate therapy is the presence of Multidrug-Resistant (MDR) pathogens in culture reports obtained subsequently after admission; the mortality risk does not decrease even if antibiotics are changed subseq uently. So, the most important step in the treatment of VAP is to identify patients at risk of MDR pathogens and treat them appropriately from the beginning itself. Initial broad spectrum empirical therapy has been advocated for use in patients with risk factors, identified in the 2005 ATS/IDSA guidelines (Table 56.2).

TABLE 56.2: Risk factors for MDR pathogens

Infection occurring five days after hospitalization

High antibiotic resistance in the community/hospital

Presence of pulmonary comorbidities, immunosuppressive therapy or disease

Risk factors for HCAP leading to MDR pathogens

Antibiotic therapy in preceding 90 days

Hospitalization for more than two days in preceding 90 days

Residence in nursing home or extended care facility

Home infusion therapy, including antibiotics, recent chemotherapy

Attending hemodialysis clinic

The recent literature outlines the specific risk factors for specific pathogens (e.g. MRSA in hemodialysis patients) and also describes that the distribution of MDR pathogens is very heterogeneous and may not be present in all patients who qualify the definition of HCAP (Table 56.3).[10] Local epidemiological studies need to be done to identify infecting microorganisms in specific settings.

Empiric antibiotic treatment should be patient specific based on the individual risk factor, comorbidities and local microbiological epidemiology. Broad-spectrum empiric antimicrobial regimen should be started in patients with suspected MDR risk factors (Table 56.4).

TABLE 56.3: Some of the important pathogens responsible for nosocomial pneumonias

Non-MDR pathogens	*MDR pathogens*
Streptococcus pneumoniae	Methicillin-resistant *Staphylococcus aureus* (MRSA)
Haemophilus influenzae	*Pseudomonas aeruginosa*
Methicillin-sensitive *Staphylococcus aureus* (MSSA)	*Klebsiella pneumoniae*
-Antibiotic sensitive GNB	*Acinetobacter baumannii*
Escherichia coli	*Legionella pneumophila*
Klebsiella pneumoniae	
Enterobacter, Serratia *Proteus spp*	

TABLE 56.4: Drugs and their dosages for non-MDR pathogens

Ceftriaxone 2 gm IV 12 hourly

Ampicillin-sulbactam 3 gm IV 6 hourly

Piperacillin-tazobactum 4.5 gm IV 6 hourly

Levofloxacin 750 mg IV OD

Moxifloxacin 400 mg IV OD

Ertapenem 1 gm IV OD

Drug Regimen for MDR Pathogens (Table 56.5)

A combination regimen containing at least three drugs has to be given for patients with late onset VAP/HAP and HCAP (all cases) so, as to provide a broad spectrum antimicrobial cover, i.e. two broad-spectrum drugs with anti-pseudomonas cover and one drug with MRSA cover:

1. Anti-pseudomonas agent:
   Carbapenems: Meropenem, doripenem, imipenem
   Third-generation cephalosporin: Cefoperazone-sulbactam, cefepime, ceftazidime
   Beta-lactam antibiotics: Piperacillin-tazobactam, ticarcillin- clavulanic acid
2. Anti-pseudomonas agent: Can use either a Fluoroquinolone (FQ)/aminoglycoside
   Fluoroquinolone: Levofloxacin, ciprofloxacin
   Aminoglycoside: Gentamicin, tobramycin, amikacin
3. Anti-MRSA (Methicillin-resistant *Staphylococcus aureus*) agent vancomycin/linezolid

Newer drugs for MRSA like oritavancin, dalbavancin and telavancin have been developed, which need to be studied in larger cohort of patients. Colistin has now been used to treat MDR pathogens.

However, recent evidence does not advocate combination drug therapy for all patients with HCAP.[11]

TABLE 56.5: Drugs for MDR pathogens

		Group	*Drug and Dosage*
ANTIPSEUDOMONAS	1.	Carbapenem	Imipenem 0.5 gm 6 hourly or 1.0 gm IV 8 hourly Meropenem 1 gm IV 8 hourly
		or	Doripenem 0.5 gm IV 8 hourly
		Third-generation cephalosporin	Cefoperazone-sulbactam 2 gm IV 8 hourly–12 hourly Cefipime 1–2 gm IV 8–12 hourly
		or	Ceftazidime 2 gm IV 8–12 hourly
		Beta-lactam antibiotics	Piperacillin-tazobactam 4.5 gm IV 6–8 hourly Ticarcillin-clavulanic acid 3.2 gm IV 6 hourly
DRUGS	2.	Fluoroquinolone	Ciprofloxacin 400 mg IV 8 hourly
		or	Levofloxacin 750 mg IV OD
		Aminoglycosides	Amikacin 20 mg/kg weight IV OD Gentamicin 7 mg/kg IV OD Tobramycin 7 mg/kg IV OD
MRSA	3.	Glycopeptides	Vancomycin 15–20 mg/kg actual body weight BD (max 30 mg/kg as loading dose)
		Streptograminins	Linezolid 600 mg IV 12 hourly

Patients should be treated for MDR pathogens, if two out of three risk factors are present—[severe illness (requiring mechanical ventilation or ICU care), prior antibiotic therapy (for three days in the preceding six months) and poor functional status (ADL score>12.5)]. Limited spectrum therapy for non-MDR pathogens will suffice if these risk factors are not present. These guidelines are based mainly on consensus as there is not sufficient evidence as to whether combination therapy/monotherapy is effective. Most importantly, antimicrobial therapy has to be tailored according to local microbiological flora and their antibiotic susceptibility. Each ICU/hospital should have a protocol according to this data.

Till date, no regimen has been shown to be superior over the other. A recent meta-analysis showed no difference in the mortality and treatment failure in single versus combination therapy group concluding that single agent therapy is not inferior to combination therapy.[12] In places with high risk of pseudomonas aeruginosa and other gram-negative bacilli, local microbiological bacterial susceptibility pattern should be taken into consideration before starting empirical regimen. Institution-specific guidelines should be developed taking all these factors into account.

In a broader view for patients with early onset VAP/HAP at places where there is no increased incidence of MDR pathogens, cover should be provided for *Streptococcus pneumoniae*, *Haemophilus influenzae*, Methicillin-sensitive *Staphylococcus aureus* (MSSA) and the usual community acquired pathogens with beta-lactam and beta-lactamase inhibitor combinations (piperacillin-tazobactam, ampicillin-sulbactam), ceftriaxone, fluoroquinolones (levofloxacin and moxifloxacin) and doripenem.

For patients with late onset VAP-HAP and HCAP, combination therapy is preferable. Proposed benefits of combination therapy are prevention of emergence of antimicrobial resistance, synergism of antibiotics and for providing a broader cover for all MDR pathogens.

In addition to the appropriateness of the antibiotic therapy, there are various other host and antibiotic factors, which can lead to treatment failure.[13]

Host Factors: Many of the critically ill patients have increased third space volume secondary to hypoalbuminemia and excessive fluids, which these patients receive to correct their hypotension. The consequence of the increased third space volume is a decrease in plasma drug concentration. Hypoalbuminemia also leads to increased free drug levels, which can lead to accelerated clearance of the drug, thereby decreasing the drug $t_{1/2}$.

Antibiotic Factors: The pharmacological action of various antibiotics can be classified as either time-dependent or concentration-dependent (Table 56.6). Time-dependent antibiotics are best administered in multiple-doses as continuous infusions. These antibiotics require certain time more than Minimum Inhibitory Concentration (MIC) between doses, which usually range from 40 to 50% for their best action. It varies for different antibiotics, e.g. 30 to 40% for carbapenems and 50% to 70% for cephalosporins. On the other hand, concentration-dependent antibiotics are best administered as single daily dosage. These antibiotics require attainment of the peak concentration, many times higher than the MIC for their microbiological action, and have prolonged Post-Antibiotic Effect (PAE), which makes them effective even after their drug concentration falls below MIC.

TABLE 56.6: Various antibiotics based on time or concentration dependence

Time-dependent antibiotics	*Concentration dependent antibiotics*
Penicillins Cephalosporins Carbapenems Vancomycin, Linezolid	Fluoroquinolones-Levofloxacin Aminoglycosides

Response to Therapy

Response to therapy occurs in 48–72 hours in most (75%) of the patients who respond. Response can be assessed by the improvements in fever, oxygen requirement, tracheal secretions, leukocytosis and radiological picture. Most importantly, the fever and oxygen requirements improve after 48–72 hours, though other things take time to improve. Radiological resolution generally lags behind, there may be an initial deterioration in the radiological picture. Radiological resolution depends on the age and the associated comorbidity, e.g. COPD. Resolution is slower in elderly, patients with COPD and in patients with associated endobronchial obstruction. The presence of the following radiological features indicates rapid deterioration:

- Multilobar involvement
- More than 50% increase in infiltrates in 48 hours
- Development of cavitary or necrotizing pneumonia
- Development of large pleural effusion.

Antibiotics should not be changed in the initial 48–72 hours unless there is evidence of progressive deterioration.

Tools to Assess Clinical Response

- Combined clinical and microbiological approach (repeating quantitative cultures)
- Clinical pulmonary infection score has been used to assess the improvement of VAP.

Absence of clinical response in patients with VAP requires to be evaluated aggressively. The following factors need to be considered in the case of nonresponse:

- Wrong organism/resistant organism: Consider mycobacteria, fungus, coexisting AIDS and other viral infection
- Wrong diagnosis: Noninfectious mimics of pneumonia, pulmonary embolism with infarct, pulmonary hemorrhage, atelectasis, ARDS or presence of neoplasm
- Complications: Empyema, lung abscess, extra-pulmonary infection (e.g. Catheter-Related Bloodstream Infections (CRBSI), sinusitis, clostridium difficile colitis).

Therapy needs to be escalated to cover resistant organisms in nonresponding patients. Some clinicians wait for the response after changing treatment whereas others proceed with additional investigations. Fiberoptic bronchoscopy or even open lung biopsy may need to be considered in a subset of nonresponding patients.

PREVENTION OF HAP AND VAP

There are multiple risk factors for VAP, which are amenable for intervention by nonpharmacological measures. All the methods, which aim at preventing HAP decrease the colonization of the upper respiratory tract, oral cavity and digestive tract, thereby preventing infection.

Decontamination with Antimicrobials

Chlorhexidine: Oral decontamination with chlorhexidine (2%) solution 15 ml four times daily till after extubation has been shown to be effective in preventing VAP.[14] The principle for this effect lies in the cidal action of chlorhexidine for the microbes residing the dental and gingival plaque. From a study on the role of whole body chlorhexidine cleansing on the rates of nosocomial infections, it was concluded that the procedure lead to the reduction of CRBSI, and blood culture contamination, but did not lead to reduction in the rates of VAP.[15]

Selective Decontamination of the Digestive Tract (SDD): SDD with topical and systemic antibiotics has been shown of modest benefit in preventing VAP, but is not favored by all in view of the emergence of the resistant organisms.[16]

Hand Hygiene

Health care personnel should wash their hands before and after coming in contact with patients. They should use alcohol-based solutions for washing their hands and prevent cross-infection between patients. Hand hygiene is one of the most important and effective steps to prevent nosocomial infection. Peter Pronovost has introduced a simple checklist, which has significantly reduced the incidence of central line associated infections and deaths.[17] This checklist includes five things to adhere before each central line insertion:

i. Wash your hands;
ii. Clean the patient's skin;
iii. Put on a cap, gown and mask;
iv. Avoid placing the catheter on groin; and
v. Take out lines when you do not need them.

The checklist has saved more lives than any other scientific work has done in the recent years. Some of these hold true even for HAP.

Airway

The care of the airway is important in preventing VAP. In a cost-effectiveness study, silver-coated endotracheal tubes have been shown to be effective in preventing VAP.[18] Other measure that has been shown to be effective is the Continuous Aspiration of Subglottic Secretions (CASS). Continuous aspiration of subglottic secretions use was effective in reducing the incidence of VAP to as much as half in a meta-analysis, especially in patients requiring mechanical ventilation for more than 72 hours.[19] The most commonly used CASS device is Hi-Lo Evac. This device is costlier than routine endotracheal tubes, and the cost-effectiveness has not been assessed.

Cuff Pressure

Endotracheal tube cuff pressure should be maintained between 20–30 cm H_2O to prevent aspiration of gastric and oropharyngeal contents directly into the trachea. Excessive pressures of more than those recommended will lead to tracheal mucosal injury.

Ventilatory Circuit

Care of the whole circuit that connects ventilator to the patient, including the devices like nebulizers, which are included in the circuit, is important. Regular change of ventilator circuits has not shown to decrease the incidence of VAP and is not recommended as a measure to prevent VAP.[20] One should avoid flushing of the condensate into the lower airway, which should be emptied regularly. Passive humidifiers (HME filters) are not superior to active humidifiers, as has been reported in a large systematic review.[21] Closed suctioning system has not been shown to be superior to open system in a large meta-analysis.[22] However, it seems logical to use closed systems to avoid the risk of spraying the condensate and secretions into the ICU environment. Instead, the use of Metered Dose Inhalers (MDI) may reduce the risk of VAP. The nebulizers used for delivering aerosolized medication get contaminated rapidly. Heated circuits are not superior to the unheated circuits. Heated circuits decrease the amount of condensate, but excessive heating of inspired air can lead to the drying of tracheal secretions with the impending risk of endotracheal tube blockade with secretions.

Positioning

Semi-recumbent position at 45° is effective in preventing VAP compared to supine position. Semi-recumbent position prevents aspiration and decreases the odds of developing VAP. A randomized controlled trial comparing the rates of VAP in semi-recumbent and supine position was terminated early when it was found that the rates of VAP were significantly lower in patients in semi-recumbent position.[23]

Regular suctioning of the respiratory secretions after instilling 8 ml of normal saline showed a reduction of VAP, compared to suctioning without instilling normal saline.[24]

Role of Proton Pump Inhibitors and H_2 Receptor Blockers

Proton Pump Inhibitors (PPI) and H_2 receptor blockers have been shown to increase the gastric colonization and odds of the development of VAP and HAP due to an increasing gastric pH.[25] They should be replaced by sucralfate and antacids, which do not alter the gastric pH in non-critically ill patients. The risks of stress ulcer bleed needs to be considered when stopping these agents since the risk of gastric bleeding increases with sucralfate, though not significantly.

Miscellaneous Measures

Nasogastric and nasoduodenal tubes should be removed immediately when not required in all hospitalized patients. The nasoduodenal tube feeding group has been shown to have the lower incidence of VAP and achieved nutritional goals earlier compared to nasogastric tube group.

Preventing intubation, reintubation and decreasing the duration of mechanical ventilation and using noninvasive ventilation wherever possible, can help prevent VAP.

Certain components of ventilator bundles like sedation vacation and assessment of ability to wean daily have been shown to decrease the incidence of VAP. However ventilator bundle should be hospital specific and tailored according to the available facilities.

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Viral Pneumonias

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INTRODUCTION

Community-acquired Pneumonia (CAP) is an important cause of morbidity and mortality throughout the world in all age groups. A clear understanding of the etiology is essential for the adequate management and more importantly to prevent the use of inappropriate antibiotics thereby promoting the emergence of multidrug-resistant organisms. It is also imperative to recognize viral pneumonias as antibiotics have no effect, antivirals are few with the rapid onset of resistance if misused. Viruses, especially Respiratory Syncytial Virus (RSV), influenza A and B viruses, parainfluenza viruses and adenoviruses, are recognized as important causes of CAP in children. In adults, however, viral causes of CAP are less well characterized, and specific recommendations about the assessment and management of viral CAP are sparse. Studies have been handicapped by the difficulty in isolating the viruses and due to the presence of large number of viruses with a potential to cause pneumonia. Most studies have utilized antibody detection to confirm the etiology and hence may have compromised the ability to detect viruses as the cause of pneumonia. Most reports cite an incidence of 9% to 29% viral pneumonias among all CAPs with influenza being the most common.[1,2]

RESPIRATORY VIRUSES

Viruses of importance in the respiratory tract infection include those considered to be principally the respiratory viruses, whose replication is generally restricted to the respiratory tract, and others whose respiratory involvement is a part of the generalized infection. Classification of the viruses is dependent on the type of nucleic acid core, family of the virus, protein configuration and the lipid envelope. Postinfection immunity depends on the number of antigenic sub-types in the viral family with more effective protection amongst families with multiple immunotypes like the rhinovirus or adenovirus. Immunity is also dictated by the stability of the viral antigens, the best example is that of Influenza A, which undergoes periodic minor, as well as major changes in its surface antigens leading to susceptibility to reinfection as the acquired immunity is no longer effective. Pulmonary and systemic complications of seasonal influenza contribute to the morbidity and the mortality, especially among the elderly, the immunocompromised, those with underlying chronic lung disease and cardiovascular disease.

Resurgence of interest among the medical community in viral pneumonias has been catapulted by the outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 and more recently the pandemic of novel swine origin H1N1 influenza 2009; even as we brace ourselves for the second wave in 2010 with sporadic cases being already reported from the parts of India. On the other end of the spectrum lie the viruses with the potential to cause a pandemic with even higher mortality than H1N1 2009, like the avian influenza (H5N1). Viruses like cytomegalovirus (CMV), which were considered to affect only the immunocompromised hosts, are being identified in healthy individuals with pneumonias. Cases with dramatic presentation like Hantavirus Pulmonary Syndrome (HPS), though sporadic and geographically restricted, should be considered in this era of unrestricted globetrotting.

TABLE 57.1: Important respiratory viral infections

1. Varicella pneumonia
2. Cytomegalovirus pneumonia
3. Severe acute respiratory syndrome
4. Hantavirus pulmonary syndrome
5. Adenovirus pneumonia
6. Influenza
    i. Seasonal influenza A pneumonia
    ii. Avian influenza A (H5N1)
    iii. Swine origin influenza (H1N1) 2009.

Individual viruses (Table 57.1) will be dealt with more details after an overview of the common characteristics of viral pneumonias, including similarities in clinical presentations, radiological manifestations and pathogenesis.

PRESENTING FEATURES

Pneumonia is usually a complication of descent of infection from the upper respiratory tract, and hence, patients may give history of upper respiratory tract infection, conjunctivitis or myalgia and malaise at the onset of illness or may harbor telltale signs of the same on examination. Among patients who are not overtly immunocompromised, viral pneumonias are common among the children, the elderly, the pregnant females, patients with Chronic Obstructive Pulmonary Disease (COPD) and cardiovascular disease.

Viral pneumonia in adults is usually associated with nonproductive cough, although production of frothy, pink-tinged sputum is seen in some severely ill individuals. Cyanosis, tachypnea and use of accessory muscles are red flags indicating respiratory failure on examination. Tracheal tenderness may be present, if there is associated trachietis. Chest examination may reveal only occasional rales and wheeze in spite of an extensive disease. The clinical features of sporadic cases of viral pneumonia are usually not sufficiently characteristic to permit specific viral diagnosis or differentiation from bacterial pneumonias on clinical grounds alone. Exceptions include measles and varicella pneumonia, in which the associated rash establishes the diagnosis.

The damage to the host respiratory tract is the result of direct injury by the invading virus, unregulated immune response with the release of inflammatory cytokines and blunting of local protective mechanisms like mucociliary clearance and phagocytosis. Viruses are also known to disturb the bacterial flora of the upper respiratory tract, promoting better adhesion and thereby increasing the chances of secondary bacterial infection in the immediate postviral period. Secondary bacterial pneumonias typically occur after five to seven days of the initial onset of symptoms with usually a period of apparent improvement whereas progressive viral pneumonias have a continuous downhill course. The bacteria associated are the same as in CAP with streptococcus pneumoniae, mycoplasma and *Haemophilus influenzae* being the most common. Interestingly, Community-Acquired Methicillin Resistant Staphylococcus Aureus (CA-MRSA) is increasingly being isolated unlike in bacterial CAP.

Interstitial infiltrates rather than lobar consolidation are common but findings are nonspecific to help differentiation based on chest radiograph alone. The severity of viral CAP in normal hosts is directly related to the degree and duration of hypoxemia. The magnitude of the oxygen diffusion defect caused by viral involvement of the lung interstitium in severe viral CAPs is best assessed by the Alveolar-arterial (A-a) gradient. Patients presenting with severe viral CAP typically have increased A-a gradients of more than 35. The degree of hypoxemia is related to the degree of oxygen diffusion defect caused by interstitial pathogens. Recent studies in patients of proven viral pneumonias have identified certain patterns in High Resolution Computerized Tomography (HRCT), which may help differentiate viral pneumonias from bacterial. These include multifocal consolidation, multifocal ground-glass opacities, multifocal tree-in-bud opacities and widespread bronchial wall thickening.[3-5]

Varicella Pneumonia

Varicella-Zoster Virus (VZV) causes two distinct clinical entities: Varicella (chickenpox) and herpes zoster (shingles). Chickenpox, a ubiquitous and extremely contagious infection, is usually a benign illness of childhood characterized by an exanthematous vesicular rash. Less than 20% of all cases of VZV infection occur in adults.[6] *Varicella pneumonia*, the most serious complication following chickenpox, develops more commonly in adults (up to 20% of cases) than in children and is particularly severe in pregnant women. Pneumonia due to VZV usually has its onset three to five days into the illness and is associated with tachypnea, cough, dyspnea and fever. Varicella-Zoster Virus Pneumonia (VZVP) has a reported mortality of between 2.15% and 20% in the general population, but in pregnancy, it may be as high as 41%.[7,8]

Diagnosis

Early clues to the diagnosis of pneumonia in subjects at risk are continued eruption of new lesions, persistent fever and new onset cough. The development of VZVP in the absence of fever and after the cessation of new lesion formation is exceedingly rare. Chest radiographs of VZVP typically show ill-defined nodular or reticular densities scattered throughout both lung fields. Initially, the nodules are 2 to 5 mm in diameter and are best visualized in the periphery of the lung. With progressive disease, the nodules enlarge and coalesce, forming extensive infiltrates, especially near the hila and in the lung bases.[9,10] In the milder cases, the infiltrates may resolve in three to five days. However, in widespread severe disease, the radiographic abnormalities may persist for several weeks or months. In a few patients, the lesions calcify and remain indefinitely as numerous well defined, randomly scattered, 2 to 3 mm dense calcifications in otherwise normal lung.[9,10]

Treatment

Any adult with varicella should be closely monitored for signs of respiratory difficulty and should it occur, chest radiographs and arterial blood gases should be obtained. Supportive care with oxygen by venturi mask for maintaining saturation, adequate hydration, deep venous thrombosis and stress ulcer prophylaxis should be ensured. Intravenous acyclovir in a dosage of 10 mg/kg three times a day for 5 to 10 days is effective for VZVP or other complications in adults and children, if begun early. Patients who develop respiratory failure will require invasive mechanical ventilation with protective lung ventilation strategy for maintaining saturation. Adjunctive therapy with corticosteroids was associated with decrease in duration of mechanical ventilation and accelerated physiological recovery in a retrospective analysis of 19 patients receiving mechanical ventilation in a single center.[11] A multicenter prospective study is needed before the same can be recommended for routine management.

Cytomegalovirus (CMV) Pneumonia

Cytomegalovirus DNA viruses are of the murine and human variety. Cytomegaloviruses are DNA viruses with an icosahedral capsid with 162 capsomers and the viral particles have a diameter of 120 to 200 nm. Cytomegaloviruses are members of the Herpesviridae family, which consists of eight Human Herpes Viruses (HHVs). Morphologically, CMV resembles other herpes viruses, particularly HSV, with important cytopathic differences. Although both HSV and CMV produce intranuclear inclusions, only CMV produces cytoplasmic inclusions (dense bodies).[12] Because only CMV produces perinuclear cytoplasmic inclusions, cytopathologic diagnosis is possible. Cytopathologic changes in host tissue indicate active infection. Pneumocyctis Pneumonia (PCP) and CMVs are recognized pathogens in compromised hosts, for example, in those who undergo transplants and those on immunosuppressive drugs or steroids. However, CMV, influenza (human, avian, swine) and adenovirus are the three most common causes of severe viral CAP in immunocompetent adults.

Cytomegalovirus CAP in immunocompetent hosts is uncommon but is now being recognized more frequently, particularly when presenting as severe viral CAP. As with any respiratory virus, the severity of the disease in immunocompetent individuals varies from mild flu to acute respiratory distress syndrome, requiring mechanical ventilation. Severe CMV pneumonia may initially show minimal or no pulmonary infiltrates on chest radiograph but is accompanied by varying degree of hypoxemia. Cytomegalovirus CAP has no distinct radiologic findings on chest radiograph.

It usually is necessary to rule out other causes of respiratory failure like lobar consolidation in bacterial pneumonias or other mimics of CAP. Cytomegalovirus should be included in the differential diagnosis when there are other clinical features to suggest CMV rather than other causes of severe viral CAP. Other systemic involvement, including liver, gastrointestinal tract, central nervous system and bone marrow favors CMV. The immunomodulatory effects of CMV may precipitate a flare of underlying connective tissue disease or may be the cause of deterioration thereby making management difficult, as flare requires immunosuppression versus antivirals for CMV pneumonia.

Diagnosis

Diagnosis is established most commonly by serologic testing. The diagnosis of recent CMV infection depends on demonstrating either a single elevated CMV IgM titre or a 4-fold increase in CMV IgG titres. False positive or negative serologic results can occur in the presence of other reacting antibodies like Rheumatoid Factor (RF) or antibodies against Epstein-Barr Virus (EBV). Cytomegalovirus semiquantitative antigenemia assay is a sensitive/specific and rapid method to detect CMV activation in lymphocytes. Cytomegalovirus Polymerase Chain Reaction (CMV PCR) is very sensitive and indicates reactivation of CMV in lymphocytes.

The main difficulty in using CMV PCR is that it does not distinguish between asymptomatic or latent and active infection. Because PCR is so sensitive, serial qualitative PCR, as with semiquantitative CMV antigen levels, may be more clinically useful. Importantly, in immunocompetent hosts with primary CMV pneumonia, CMV PCR is usually negative. Virus can be isolated in human fibroblast cultures, but as the cytopathic changes are slow to occur, often cultures need to be maintained for up to three weeks before they can be declared negative. The typical cytopathic change is classically described as "owl's eye" appearance and may be identified directly in tissue specimens or in cultures.

Treatment

Treatment is the only hope for cure in immunocompromised individuals, but in immunocompetent patients the decision to treat depends on the severity of infection. Patients with hypoxemia should be treated with antivirals, but prolonged therapy usually is not required. Although acyclovir is active against other herpes viruses, it is ineffective against CMV. The mainstay of anti-CMV therapy is ganciclovir 5 mg/kg (intravenous) every 12 hours for the duration of infection.

The oral equivalent of parenteral ganciclovir is Valganciclovir. Valganciclovir is metabolized to ganciclovir *in vivo* and is as effective as parenteral ganciclovir. Oral valganciclovir may be used to complete therapy after the initial ganciclovir therapy or may be used for the entire duration of therapy. The dosage of oral valganciclovir for induction therapy is 900 mg (by mouth) every 12 hours for 21 days. In immunocompetent hosts, a complete course of therapy with ganciclovir/valganciclovir is usually not necessary because patients usually improve after one to two weeks of therapy. In such patients, anti-CMV therapy is often continued for an additional week to prevent potential relapse. Foscarnet is alternative CMV therapy, but is administered intravenously and is nephrotoxic. Unlike immunocompromised host, prognosis of CMV pneumonia in normal hosts is often good.[12]

Severe Acute Respiratory Syndrome (SARS)

From November 2002 to July 2003, SARS quickly spread from Foshan (Shunde district), Guangdong Province in the People's Republic of China to 33 other countries or regions on 5 continents.[13,14] There were 8,447 cases, 21% occurring in Health Care Workers (HCWs) and 813 deaths (9.6% overall mortality) by the time SARS was contained in July 2003. The case-fatality rate in 2003 was estimated at 13.2% for patients younger than 60 years and 50% for patients more than 60 years of age. Fifty percent of patients with Acute Respiratory Distress Syndrome (ARDS) died.[13,14]

The pathogen, the human Coronavirus (CoV) group 2b, SARS-CoV, is of animal origin. The SARS-like-CoV (SL-CoV) virus from animal hosts has a nucleotide homology greater than 99% with SARS-CoV. From virus sequence data, it seems that the masked (Himalayan) palm civet (*Paguma larvata*) acted as an amplification host. The epidemic strains (including SARS-Urbani) evolved because of civet-human interaction in Chinese animal markets. Serologic evidence of natural SL-CoV infection is also found in the Chinese ferret-badger (*Melogale moschata*).[15]

The WHO case definition for probable SARS includes:

1. Fever greater than 38°C or history of fever in the preceding 48 hours.
2. New infiltrates on chest radiograph consistent with pneumonia.
3. Chills or cough or malaise or myalgia or history of exposure.
4. One or more positive tests for SARS-CoV.

As with all epidemics, during an outbreak these points are useful in screening individuals, but outside the setting suggest only presence of common flu.

During the last epidemic, most patients presented with flu like symptoms (fever, chills, cough and malaise) and two-third of them developed dyspnea and recurrent or persistent fever. Thirty percent significantly improved within one week. Advanced age, high admission neutrophil count and initial elevated Lactic Dehydrogenase (LDH) were independent correlates of an adverse outcome. Watery diarrhea was present in more than a third of the patients and was the most common extrapulmonary symptom correlated in autopsy studies by the isolation of maximum concentrations of the virus in small bowel next only to the lungs. Cardiovascular complications in the form of hypotension and unexplained tachycardia were common. Reactive hepatitis was in 24% of the patients with up to 69% developing transient elevation of liver enzymes during their course of illness. Overall subclinical infections were very few and far apart.

Post-traumatic stress disorder and other psychiatric manifestations have been reported in survivors of intensive care. Approximately one-fifth of patients presented with a normal chest radiograph, but developed infiltrates within seven days (median three days) of onset of fever. Of the 78.3% who presented with opacities on the chest radiographs, 54.6% were unilateral and the bilateral. The involvement of more than one lung zone and bilateral versus unilateral disease were associated with a higher risk of Intensive Care Unit (ICU) admission and death.[16]

Diagnosis

Sensitivity of RT-PCR collected in the first three days of the illness was inadequate. For the emergency screening of febrile patients as per protocol, the sensitivity and specificity were 92.6% and 71.6%, respectively. Confirmation of infection was made by identifying the SARS-CoV Nucleocapsid (N) protein in the serum by N antigen-capture Enzyme-Linked Immunosorbent Assay (ELISA) and N antigen-capture chemiluminescent immunoassay. Generally, in the first four to five days of illness, nasopharyngeal aspirates and throat swabs are more useful in detecting virus, whereas stool specimens are more valuable after five days of illness (20% sensitivity).

Treatment

Suspected patients must be immediately isolated using contact, droplet and airborne isolation precautions in a negative-pressure single room. Treatment is largely based on the results of uncontrolled trials as randomized controlled trials evaluating treatment regimens are not available. Early positive outcomes using ribavirin and steroids led to widespread use of that combination. In a study of 71 cases (97% laboratory confirmed); antibiotics, ribavirin plus a 3-week step-down steroid therapy and pulse methylprednisolone "rescue" resulted in 3.4% mortality, all in patients older than 65 years.[17] Various agents have shown *in vitro* activity against the virus like indomethacin, lopinavir/ritonavir. A review in 2006 of SARS therapy administered during the epidemic revealed that finding clear-cut treatment benefits was elusive. There were 26 reports of inconclusive benefits and 4 reports of possible harm related to ribavirin therapy, 25 inconclusive reports and 4 reports of possible harm from steroid therapy, and inconclusive reports for lopinavir-ritonavir therapy (2), IFN-α therapy (3) and convalescent plasma or immunoglobulin therapy (7).[18]

Hantavirus Pulmonary Syndrome (HPS)

The hantaviruses are an enveloped genus of the family Bunyaviridae. Virions are spherical and encapsulated by a bilayered phospholipid membrane. Vascular endothelial cells are the principal target, but also infect alveolar macrophages and follicular dendritic cells. Renal tubular epithelium can also be a site for infection. Genus consists of multiple viruses, which are known to cause HPS in humans. Rodents act as reservoirs, but the virus is not pathogenic to them. Transmission largely occurs through inhalation of aerosolized urine, feces, or saliva of the rodent host. HPS is most often acquired indoors as captured animals tend to have higher rates of active infection than wild ones (25% vs 10%) and humans are more likely to encounter rodent excreta in a closed environment rather than open. Most cases reported till now have been isolated or in clusters in contrast to other epidemic viruses.

The disease has four recognized clinical phases: Prodrome, pulmonary edema and shock, diuresis and convalescence.[19] Prodrome lasts for three to six days, in which phase the onset of pulmonary edema and shock is abrupt. The second phase also lasts for three to six days with maximum mortality occurring within the first 24 hours after the onset of shock. Patients who survive this phase enter a diuretic phase with urine output ranging from 300 to 500 ml/hour and this is associated with rapid resolution of respiratory symptoms. Patients then enter a phase of convalescence, which may last a few weeks to several months before complete recovery takes place. A trio of hematologic findings, including thrombocytopenia, leukocytosis with a left shift and circulating immunoblastoid lymphocytes, is unique to HPS in the United States.

Treatment

Careful history, recognizing typical phases and a high index of suspicion are essential to achieve a diagnosis in HPS. Commercial laboratories can serologically confirm or rule out the diagnosis of HPS within 24 hours; IgM antibodies to nucleocapsid antigen are universally present in symptomatic patients and IgG antibodies are present in the most. There are no specific antiviral therapies for the management of HPS as of now and the management is supportive. Patients need admission to an intensive care unit with continuous monitoring of hemodynamic status, inotropic support and invasive mechanical ventilation with protective lung ventilatory strategy. Subset of patients may benefit from Extracorporeal Membrane Oxygenation (ECMO) in centers where it is available though there are no controlled trials in the setting of HPS.

Adenovirus Pneumonia

This is one of the common viral agents causing CAP. Clinically, it cannot be differentiated from other viral pneumonias. It was first recognized to cause pneumonia among military recruits. Subsequently, outbreaks have been reported from institutionalized populations. The severity of disease ranges from mild to severe requiring hospitalization and ventilatory support. In fatal cases, there has been extensive pulmonary damage, with death occurring two to three weeks into the illness. Intravascular coagulopathy has also been a late feature of some cases and a septic shock picture has been described. Bacterial superinfection, especially secondary to *Neisseria meningitidis* may complicate the course of the disease. There are no specific therapy and involves only supportive care.

Influenza

Influenza viruses belong to the family of Orthomyxoviridae, which are lipid-enveloped, single-stranded, negative-sense, 8-segmented RNA viruses. Serotype A and B are the frequent cause of clinical disease, serotype A has multiple subtypes based on various combination of 16 known Hemagglutinin (HA) and 9 Neuraminidase (NA) genes that code for these viral envelope or surface proteins whereas B has only a single subtype. So far, only 3 subtypes of HA (H1, H2, H3) and 2 subtypes of NA (N1, N2) have caused pandemics in humans.

Traditional pandemic surveillance has focused on monitoring the antigenic shift, the reassortment of HA and/or NA genes between human and zoonotic influenza A viruses during rare events of dual infections in a human or an intermediate host. For the surveillance of currently circulating seasonal influenza viruses, most recently the A (H3N2) and A (H1N1) viruses, viral isolates are collected throughout the year to determine the most appropriate seasonal/influenza vaccine composition for the coming influenza seasons.[20] The influenza virus associated pneumonias will be reviewed in the following sections as seasonal influenza A, avian influenza and H1N1 2009 pandemic-associated pneumonias.

Seasonal Influenza A Pneumonia

Seasonal influenza results in 2,00,000 admissions and over 40,000 deaths yearly in the United States alone. Influenza activity is generally seasonal: Activity increases during the cooler months and peaks from December to March. Virus invades and attaches to the respiratory epithelial cells of the upper respiratory tract. Dissemination occurs due to the generation of droplets ranging in size from 1 to 5 micron when the patient coughs or sneezes. Incubation period is usually one to two days, but may be up to four days. Presentation is usually with fever, myalgias and rhinitis consistent with symptoms of flu. Most cases of influenza are restricted to the upper respiratory tract and have a self-limited, benign clinical course. Severe disease with primary influenza pneumonia is more common in patients older than 65 years of age, those with underlying health conditions and young children.[2] Bilateral diffuse interstitial/alveolar infiltrates were seen as the most common radiographic abnormality (52%), followed by right lower lobe consolidation (35%).

Diagnosis

Primary influenza pneumonias are difficult to distinguish from other viral, bacterial or atypical pneumonias based on clinical radiologic or laboratory alone. The duration of shedding depends on the severity of illness and age, but generally virus can be isolated from throat and nasopharyngeal swabs obtained within two days of the onset of illness. There are several modalities to document influenza infection. These include direct viral detection (antigen tests, PCR, immunofluorescence and culture) or serologic tests. Rapid viral detection in the secretions can be achieved by commercially available antigen detection kits. Viral culture is the gold standard for the detection of virus, but takes up to 48 hours to achieve diagnosis. Serologic testing requires demonstration of fourfold rise in titre and are helpful for research purpose rather than in patient management.

Treatment

Neuraminidase Inhibitors (NAI), such as oseltamivir and zanamivir have shown to decrease the duration and severity of illness, if given within 36 hours of the onset of symptoms. In complicated influenza with primary pneumonia, studies showing efficacy of antivirals in decreasing mortality or duration of illness are less convincing. In spite of this, there is a tendency to use oral oseltamivir in patients with pneumonia and ARDS. Another member of the NAI group, peramivir, is still in clinical trials. Peramivir has an advantage over oseltamivir (taken orally) and zanamivir (taken by inhalation) as it can be given intravenously. Management is usually supportive with mechanical ventilation for respiratory failure and surveillance for the evidence of secondary bacterial pneumonia and early institution of appropriate antibiotics. Yearly vaccination has shown to decrease the incidence and severity of influenza and should be encouraged in patients over 65 years of age or in the presence of co-morbid conditions.

Avian Influenza A (H5N1)

A zoonotic virus, avian influenza A (H5N1) emerged for the first time in Hong Kong in 1997 from chickens to infect humans, infecting 18 people and killing 6 of them, a high mortality rate of more than 30%.[21] As of 2009, the World Health Organization (WHO) has reported 440 cases of sporadic H5N1 human infection, of which 262 were lethal (a 60% case-fatality rate).[22] Different viral subtypes have varied ability to cause disease in human population. Though the cases of H5N1 have been sporadic and infective potential low, fear stems from the high mortality rate among infected individuals and demonstration of certain strains of low infectivity can rapidly mutate (within six to nine months), if allowed to circulate freely among poultry to become highly virulent. The incubation period for this virus has been estimated to be up to seven days, but is more commonly two to five days after the last known exposure to sick or dead poultry. In cases where human-to-human transmission was suspected the incubation period was estimated to be between 2 and 10 days.

Diagnosis

Common laboratory findings in patients with A (H5N1) infection at the time of hospital admission included leukopenia, lymphopenia and mild-to-moderate thrombocytopenia. No distinct radiological findings help differentiate it from other viral infections. Acute respiratory distress syndrome complicated 76.5% (13 in 17) of cases in Thailand and 44.4% (8 in 18) of cases in Hong Kong.[23] Multiple organ failure, with the signs of renal dysfunction and sometimes cardiac compromise, was often noted. In fatal cases, the median time from onset to death was nine days.[24]

Treatment

High degree of resistance to amantadine has made it obsolete, NAI have been used for the treatment. Antivirals should be started within the first 48 hours before the efficacy declines. The mainstay and most effective approach to treating the disease is similar to most viral pneumonias and involves good supportive care. Intensive care during critical period of multi-organ dysfunction goes a long way in improving outcome. Adjuvant therapy with corticosteroids is not proven to improve outcome and hence is not routinely recommended.

Swine Origin Influenza (H1N1) 2009

The world witnessed the first influenza pandemic in nearly 40 years in 2009. What started as an outbreak in Mexico, soon spread to engulf the whole world with cases reported from nearly all countries by early 2010. By WHO estimates, more than 17,700 deaths among laboratory-confirmed cases had been reported by March 2010. As with any pandemic, the reported cases may have formed merely the tip of the iceberg with many subclinical cases never being reported to the health care provider.

The pandemic A (H1N1) virus originated from the triple-reassortment swine influenza (H1) virus circulating in North American pigs.[25,26] Complete genome sequencing has shown that the known molecular markers of pathogenicity (PB1-F2 and nonstructural-1 proteins) are not expressed in the pandemic A (H1N1) virus.[27] Animal studies have shown that the novel influenza virus caused increased morbidity, replicated to higher titers in lung tissue, and was recovered from the intestinal tract of intranasally inoculated ferrets in contrast to seasonal influenza H1N1 virus. This may explain why the novel virus is relatively more pathogenic than seasonal influenza viruses in its capacity to invade the lower respiratory tract and cause rapidly progressive pneumonia in humans because of our lack of background immunity to the former.

RISK FACTORS AND FEATURES OF SEVERE DISEASE

Unlike the seasonal flu, up to 40% of the patients who required hospitalization or died were previously healthy. Surprisingly, the elderly (> 65 years) are less frequently infected by the novel virus, probably because of some preexisting cross-reactive immunity against the virus due to their past exposure to previous circulating seasonal influenza A (H1N1) strains similar to the current pandemic A (H1N1) virus. Whether the components of vaccine against seasonal flu confer any cross immunity against the pandemic strain is unclear. The risk factors for severe disease include obesity, diabetes mellitus, and chronic respiratory, cardiovascular and kidney diseases, as well as diseases related to smoking, pregnancy, immunosuppression and delay in diagnosis. Diffuse alveolar damage, necrotizing bronchiolitis and diffuse alveolar damage with intense alveolar hemorrhage have been the distinct pathologic findings observed in patients who had died from H1N1 pan-demic.[28] Secondary bacterial infections were documented in 14% to 29% of patients with severe disease and require early detection with appropriate management.[29,30]

The principal clinical syndrome leading to hospitalization and intensive care is diffuse viral pneumonitis associated with severe hypoxemia, ARDS, and sometimes shock and renal failure. This syndrome has accounted for approximately 49% to 72% of ICU admissions for 2009 H1N1 virus infection.[31] Rapid progression is common, typically starting on day four to five after the onset of illness and intubation is often necessary within 24 hours after admission. Median duration of ICU care was seven days and mechanical ventilation eight days.[31] Mortality among mechanically ventilated patients ranged from 14.3% in Australia to 41.4% in Mexico[32] where access to rescue therapy were not freely available. Mortality rate among confirmed cases of H1N1 admitted at this institute in Chandigarh in 2009 was 42% (55 deaths among 131 admissions). Majority of the deaths (89.1%) occurred in the 18 to 65 years of age group with a median age of 31.5 years. The mortality among patients, receiving mechanical ventilation, was 83.1% (54 deaths out of 65) and probably represents the trend that was seen in the rest of the India during the same period.

Radiographic findings commonly included diffused mixed interstitial and alveolar infiltrates, although lobar and multilobar distributions occur, particularly in patients with bacterial coinfection (Fig. 57.1). Chest computed tomography has shown multiple areas of ground-glass opacities, air bronchograms and alveolar consolidation, particularly in the lower lobes (Fig. 57. 2).

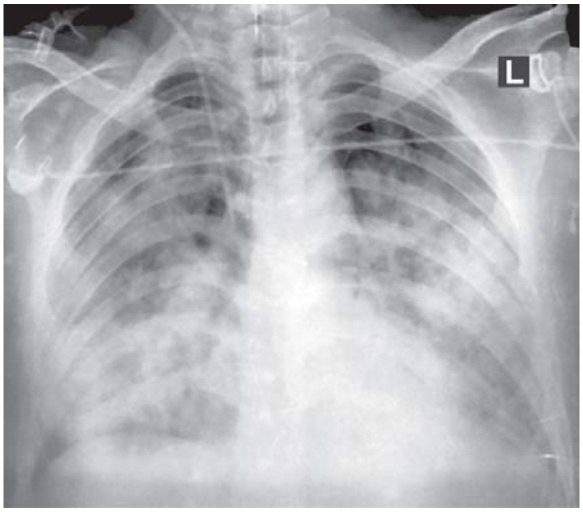

Fig. 57.1: Chest radiograph of a patient with proven severe H1N1 infection presenting with ARDS

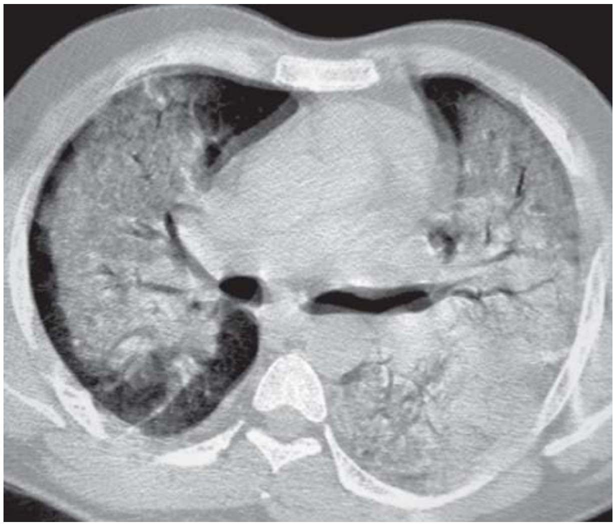

Fig. 57.2: CT of the same patient showing extensive areas of consolidation

Pulmonary thromboembolism has been reported in critically ill patients in spite of prophylaxis. Laboratory findings at presentation in patients with severe disease typically include normal or low-normal leukocyte counts with lymphocytopenia and elevations in the levels of serum aminotransferases, Lactate Dehydrogenase (LDH), creatine kinase and creatinine. Elevated creatine kinase, LDH, creatinine, metabolic acidosis and thrombocytopenia portends poor prognosis.[33] Few cases of encephalitis and myocarditis have been reported.

RESPIRATORY PROTECTION FOR HEALTH CARE PROFESSIONALS

Standard and Droplet Precautions are considered adequate to control the transmission of influenza in most health care situations. Vaccination of health care staff against seasonal and pandemic influenza strains is an essential protective strategy, but may be difficult to incorporate in practice as even with seasonal influenza the compliance among health care professionals for vaccination is only about 40%. Management principles include: Performance of hand hygiene before and after every patient contact or with the patient environment, disinfection of the patient environment; early identification and isolation of patients with suspected or proven influenza; adoption of a greater minimum distance of patient separation (2 meters) than previously recommended; use of a surgical mask and eye protection for personal protection on entry to infectious areas or within 2 meters of an infectious patient.[34]

The Centre for Disease Control (CDC) recommends the use of N95 respirators in only people involved in aerosol generating procedures like suctioning or bronchoscopy. Prophylactic antivirals should be restricted to individuals with sustained and heavy exposure. In high aerosol-risk settings, use of particulate mask, eye protection, impervious long-sleeved gown and gloves donned in that sequence and removed in reverse sequence, avoiding self-contamination should be practiced. Symptomatic staff should be excluded from discharging duties till such time criteria for non-infectivity are met. These simple precautions go a long way in conferring protection, especially in a resource constrained setting like ours.

Diagnosis

Viral RNA detection by conventional or real-time Reverse-Transcriptase–Polymerase-Chain-Reaction (RT-PCR) assay remains the best method for the initial diagnosis of 2009 H1N1 virus infection. Nasopharyngeal aspirates or swabs taken early after the onset of symptoms are suitable samples, but endotracheal or bronchoscopic aspirates have higher yields in patients with lower respiratory tract illness. Consequently, negative results in single respiratory specimens do not rule out 2009 H1N1 virus infection and repeated collection of multiple respiratory specimen types is recommended when clinical suspicion is high. Commercially available rapid influenza detection kits have poor sensitivity and cannot differentiate H1N1 2009 from seasonal influenza. Virus can be isolated in various cell cultures, but usually takes several days for diagnosis.

Antiviral Therapy

H1N1 2009 is susceptible to neuraminidase inhibitors, such as oseltamivir and zanamivir, but is almost universally resistant to amantadine and rimantadine. Early institution of oseltamivir results in the reduction of duration illness, severity and clearance of virus from the upper respiratory tract. Progression of disease and death can occur despite early therapy and even administration of oseltamivir after 48 hours of the onset of symptoms have been associated with reduced mortality among hospitalized patients. One should not wait for test results for starting antivirals and even if negative, should be continued on oseltamivir until an alternate diagnosis is achieved. In severely ill patients, viral RNA may be detectable in endotracheal aspirates for several weeks after the initiation of oseltamivir therapy.

An increased dose of the drug (e.g. 150 mg twice daily in adults) and particularly an increased duration of therapy (e.g. a total of 10 days) with the avoidance of treatment interruptions are reasonable in patients with pneumonia or evidence of clinical progression. A *His275Tyr* mutation in viral neuraminidase confers high-level resistance to oseltamivir, but not to zanamivir. Most oseltamivir-resistant 2009 H1N1 viruses have been sporadic isolates from treated patients, particularly those with immunosuppression who received prolonged oseltamivir therapy or those in whom post-exposure oseltamivir chemoprophylaxis failed, but few cases of *de novo* resistance have been reported, which is a cause for concern.[35] Inhaled zanamivir has not been adequately studied in influenza, but it is the only drug that can be used in oseltamivir resistance.

Intravenous peramivir and zanamivir have shown good efficacy in seasonal influenza, but *His275Tyr* mutation also confers resistance to peramivir. Intravenous zanamivir is the drug of choice in the presence of oseltamivir resistance. Food and Drug Administration (FDA) recently approved intravenous peramivir for emergency use in hospitalized patients.

Management of Critically Ill Patients with H1N1 Influenza 2009 (Table 57.2)

Severe respiratory insufficiency necessitating mechanical ventilation was encountered in 10% to 30% of hospitalized patients with H1N1 influenza 2009.[36] Noninvasive Positive Pressure Ventilation (NPPV) relieves hypoxemia, decreases work of breathing and therefore tachypnea, but does not alter the course of

TABLE 57.2: Management of critically ill H1N1 influenza 2009 patients

Definite benefit in all critically ill patients	*Benefit in subgroup of patients not responding to standard care*	*Potential or unproven benefit*
Oseltamivir, zanamivir	Activated protein C	Pooled hyperimmune serum
Low tidal volume ventilatory strategy and conservative fluid management.	ECMO, high frequency oscillatory ventilation, prone ventilation	Noninvasive positive pressure ventilation (NPPV)
DVT and stress ulcer prophylaxis.	Recruitment maneuvers	IvIG, statins and N-acetyl-L-cysteine
	Corticosteroids in shock and persistent ARDS	Corticosteroids upfront in the absence of shock

illness. As with other cases of ARDS, NPPV is not routinely recommended for the management of hypoxemic individuals as it may delay intubation and inadvertently increase mortality. Noninvasive Positive Pressure Ventilation may be used under controlled circumstances, with the knowledge that most people would require invasive ventilation and early decision to intubate, if no improvement occurs in the first hour.

The WHO interim guidelines on the prevention and control of acute respiratory diseases in healthcare have included NPPV among those aerosol generating procedures in which there is possibly increased risk of respiratory pathogen transmission. Invasive Mechanical Ventilation (IMV) should be with low tidal volume (6 ml/kg IBW), lung protective ventilation (plateau pressures < 30 cm H_2O)[37] and conservative fluid strategy.[38] In ICUs where the infrastructure is available, Extracorporeal Membrane Oxygenation (ECMO) has been shown to improve survival in patients with refractory hypoxemia.[31,39]

Deep Venous Thrombosis (DVT) prophylaxis with subcutaneous heparin and stress ulcer prophylaxis should be given to all critically ill patients, unless contraindicated. Corticosteroids have not shown to improve survival, carry risk of increased viral replication, dissemination and prolonged shedding when given early in the course of illness. Steroids in stress dose (hydrocortisone 200 to 300 mg/day) should be given in the presence of co-existent shock and may be considered in patients with persistent ARDS (no improvement in lung injury score after day seven). Activated Protein C (APC) should be considered early in patients with more than two organ system involvement or a baseline APACHE score more than 25. Immunomodulation with statins, use of convalescent hyperimmune serum, intravenous immunoglobulin and N-acetyl-L-cysteine have a potential for improving outcomes in patients with severe disease, but are not of proven value to merit their usage in practice at this point of time.

TABLE 57.3: Priority groups for vaccination against H1N1 influenza

- Healthcare professionals and paramedical staff
- Pregnant women
- Individuals between 6 months to 24 years of age
- Those above 25 years of age with underlying cardiopulmonary disease, diabetes mellitus and renal disease
- Household contacts of infants younger than 6 months of age.

H1N1 Influenza 2009 Monovalent Vaccine

Greenberg et al. and Clark et al. established the efficacy of monovalent vaccine against H1N1 influenza 2009 in two separate trails published recently. There has been ambiguity regarding the dosage of vaccine (15 vs 7.5 microgram) and whether one or two doses are needed for adequate immune response. Based on the pandemic proportion of the current influenza, time needed for eliciting immune response and need versus availability of vaccine, it is been recommended that a single dose of 15 microgram of monovalent vaccine should elicit seroprotective levels of antibodies in at least 80% of recipients. CDC recommends vaccination for the defined groups of individuals (Table 57.3).[40]

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58

Pulmonary Manifestations of Human Immunodeficiency Virus (HIV) Infection

Zarir F Udwadia

INTRODUCTION

Ever since the first description of the Human Immunodeficiency Virus (HIV) infection, the lung has been the most commonly affected organ. Early autopsy studies in the mid-eighties showed that there was pulmonary involvement in 90% of Acquired Immunodeficiency Syndrome (AIDS) patients with a widespectrum of infectious and noninfectious complications. Both HIV1 and HIV2 have been isolated from the lung, it is clear that the lungs are an important organ of viral replication. There is a widespectrum of pulmonary problems encountered in HIV (Table 58.1). The type of complication depends upon several factors related to the host, the organisms and the environment (Table 58.2). (Details of individual problems are available in the respective chapters on the subjects).

TABLE 58.1: Important pulmonary complications observed in HIV-infected patients

1. Respiratory infections
    - i. BACTERIAL:
        - *M.tuberculosis*
        - *Strep. pneumoniae*
        - *H. influenzae*
        - *Staph. aureus*
        - *Nocardia,*
        - *Listeria*
        - *Klebsiella spp*
        - *Pseudomonas spp*
        - *Rhodococcus equi*
    - ii. FUNGAL:
        - *Pneumocystic jiroveci*
        - *Cryptococcus neoformans*

Contd...

Contd...

        - *Histoplasma capsulatum*
        - *Candida albicans*
        - *Coccidioides immitis*
        - *Aspergillus spp*
    - iii. PARASITIC:
        - *Toxoplasma gondii*
        - *Cryptosporidium spp*
        - *Microsporidium spp*
        - *Leishmania spp*
        - *Strongyloides spp*
    - iv. VIRAL:
        - Cytomegalovirus
        - Herpes simplex
        - Varicella zoster
        - Epstein-Barr virus
        - Human Herpesvirus Six (HHV-6)
        - JC virus
        - Respiratory Syncytial Virus (RSV)
        - Human Herpesvirus 8 (HHV-8) (KSAHV)
2. Malignancies
    - Kaposi's sarcoma
    - B-cell lymphoma
    - Bronchogenic carcinoma
3. Idiopathic
    - Interstitial lung disease (Lymphocytic interstitial pneumonia, nonspecific interstitial pneumonia)
    - Airway disease; bronchiolitis, emphysema
    - Diffuse infiltrative CD8 lymphocytosis
    - Sarcoidosis
    - Organizing pneumonia
    - Primary pulmonary hypertension
    - Alveolar hemorrhage

TABLE 58.2: Factors on which the type of pulmonary disease in the HIV +ve patient depends

1. Geographical distribution
2. Severity of immunocompromise
3. Use of disease (such as Pneumocystis jiroveci) prophylaxis
4. Use of anti-retrovirals (ARVs).

Indian Epidemiology

Data from India on pulmonary complications in HIV patients is limited. An early autopsy study showed that tuberculosis accounted for 61% of all pulmonary diseases while bacterial pneumonias featured second at 18% in the terms of frequency.[1] In this study, Pneumocystis Jiroveci Pneumonia (PJP) infection accounted for only 5% of all cases. A more recent study of all hospitalizations for HIV in a tertiary center in Mumbai for over two years (2002-2003), which looked at 300 consecutive HIV-positive admissions revealed that the lungs were most commonly affected (120 of 300 admissions, 40%). In this study, tuberculosis (pulmonary and extrapulmonary) was the most common pulmonary cause of admissions (40%). The novel information that emerged from this study was that Pneumocystis Carinii Pneumonia (PCP), previously considered rare in the Indian context, ranked second in importance in this study (30%). Bacterial infections (pneumonia) ranked third with 30 cases (25%). Malignancies and miscellaneous conditions accounted for 4% each.[2]

PNEUMOCYSTIS JIROVECI PNEUMONIA (PJP)

The long-standing controversy about whether to place PCP in the parasitic or fungal families was finally settled by elegant gene sequencing studies by Edman incontrovertibly linking PCP to the fungal family.[3] The term PCP was subsequently changed to Pneumocystis Jiroveci Pneumonia (PJP) after the name of Czech parasitologist, Otto Jírovec. The new name first proposed by Frenkel, has now been accepted by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) since 2002 onwards.

Globally, PJP accounted for almost 2/3rd of the AIDS index diagnoses in the first decade of the HIV pandemic. It still remains the most prevalent Opportunistic Infection (OI) in patients with HIV. Considered rare in the Indian, Asian and African context, it was probably being under diagnosed in the developing world due to the lack of a wider availability of special diagnostic facilities like High Resolution Computed Tomography (HRCT) scanning, bronchoscopy and Bronchoalveolar Lavage (BAL) studies and special immunofluorescence staining.[4] This study not only showed it to be common when diligently searched for, but also revealed that almost half of all cases (49%) would have been missed without access to the sophisticated diagnostic techniques. Earlier deaths from diseases caused by more pathogenic organisms may also have been partly responsible for less prevalence reported from Africa and India. In this series, PJP infection occurred at a low mean CD4 count of 96.

In the developed world, whilst PJP remains one of the common opportunistic infection, there is little doubt that the incidence is declining in the West. There are two reasons for this decline: Firstly, effective Trimethoprim-Sulfamethoxazole (TMP-SMX) prophylaxis used in almost all patients with CD4 counts less than 200 who are otherwise almost nine times more likely to develop PCP; secondly, the widespread availability of Antiretroviral (ARV) therapy. PJP however retains its importance in HIV and continues to develop in patients who are unaware of their HIV status, in those with no access to care, and those who are unwilling or unable to adhere to therapy, nonresponders, or in failures with ARV therapy.

Clinical Features

Dyspnea and cough are the most common symptoms and tachypnea is the most common sign. A study from Zimbabwe established that a respiratory rate more than 40/min is the single best clinical predictor of PJP infection in HIV-positive patients.[5] Crackles and rhonchi are infrequent. Whilst hypoxia is common, it is by no means universal. In our series at Hinduja Hospital, Mumbai, India, 50% of patients had a normal SaO_2 at rest and 15% had completely normal clinical examination. The mean duration from the onset of symptoms to final diagnosis averaged as long as 30 days. In fact, the rapid onset of symptoms, high fever and rigors, which are commonly encountered in pyogenic infections are all rare in PJP.

Radiology

In the early stages, bilateral mid-zone interstitial shadows are seen. These are often subtle, normal chest radiographs have been reported in 5 to 34% of series. In our own series, 10% of patients had normal radiographs, HRCT greatly increases the diagnostic rate. The commonest CT pattern consists of the bilateral patchy areas of ground glass density, which are centrally located. Air-filled cysts or pneumatoceles may be seen in the upper lobes in approximately 10% of cases. A variety of atypical radiographic features have been reported, which include:

Upper lobe infiltrates (especially in patients on nebulized pentamidine prophylaxis), cystic changes, pneumothorax, pleural effusions, focal nodular lesions, cavitation and adenopathy. It may be pointed out that effusions, upper lobe infiltrates and adenopathy are all more often secondary to TB than to PJP especially in the India and other countries where TB prevalence is high.

Of importance is the fact that whilst the evolution of the shadows is often rapid, they are slow to resolve. In an earlier report on 104 PJP patients, only 35% of patients' radiographs had actually improved at three weeks, complete resolution had occurred in only 43% at five months.[6]

Of other diagnostic tests, LDH estimation and desaturation with exercise are both sensitive, but not specific for PJP infection. Microbiology is crucial to make a diagnosis. Sputum is often not produced, hence induced by nebulization with hypertonic saline. The yield can be improved by the examination of BAL/fluid. A transbronchial biopsy is seldom performed, but further increases diagnostic yield. The organisms are best seen on staining with Gomori methenamine, calcofluor white and immunofluorescence staining, which are sensitive and highly specific for identifying trophic and cystic forms.

Treatment

Trimethoprim-sulfamethoxazole remains the treatment of choice. Unfortunately, side effects are common at the high doses required for PJP infection. As many as 50% of patients develop major side effects, which demand temporary or permanent discontinuation of treatment.

Clindamycin plus primaquine is a reasonable alternative that is better tolerated. A large multicenter study, which compared clindamycin plus primaquine with TMP-SMX in 87 patients found it better tolerated with similar success rates.[7] Other drugs which are used include nebulized and intravenous pentamidine, dapsone and atovaquone.

Role of steroids: Steroids are unequivocally useful in moderate to severe PJP. Their use should be reserved for PJP patients who are hypoxic (PaO_2 < 70 mm Hg). Steroids are shown to reduce the rate of worsening respiratory failure and death by as much as 50% in some series. They are most effective when given within 72 hours of onset of disease. They act by blunting the inflammatory response, used in a dose of oral prednisolone 20 mg twice daily, 40 mg once daily for five days, or 20 mg once daily for 11 days.

Antiretroviral Therapy (ARV): The timing of ARV in relation to PJP is controversial. Whilst it was earlier felt best to complete the TMP-SMX therapy before commencing ARV therapy, evidence from the Adult and Adolescent Spectrum of HIV Disease Project showed that the concurrent prescription of ARV was associated with improved early survival.[8]

Outcome: There is little doubt that the outcome of PJP has improved. In the Adult and Adolescent Spectrum of HIV Disease Project, which looked at 4,412 patients with 5,222 episodes of PJP infection, survival at one year improved from 40% in 1992 to 63% in 1998, despite the emergence of antibiotic resistant PJP strains.[8] This improvement in survival is attributable to widespread use of steroids, better ICU care of these patients and earlier introduction of ARV therapy.

COMMUNITY-ACQUIRED PNEUMONIAS (CAPs)

CAPs which dominates PJP in all African and most Western series is 10 times more common in HIV-positive patients.[9] The incidence of CAP increases with declining CD4 counts. Bacteremic pneumococal pneumonia accounted for 26% of all CAPs in Nairobi.[10] Gram-negative bacilli and *Staphylococcus aureus* increase in importance as immunosuppression increases. Atypical pathogens are relatively uncommon. The mortality of CAP is approximately four times higher in HIV-positive patients. Relapses are also more frequent, occurred in 22% of Nairobi sex workers with CAP.[10] TMP-SMX prophylaxis is useful not just for PJP prophylaxis, but also for prevention against bacterial pneumonia. It was associated with a 67% reduction in the incidence of bacterial pneumonia in patients receiving this drug. Pneumococcal vaccine is recommended, but may be ineffective in preventing disease; the 23 polyvalent vaccine actually increased the risk of developing CAP.[11]

Malignancies

Lymphomas, Kaposi's sarcoma and bronchial carcinoma are the malignancies, which are more frequently reported in patients who are HIV positive.

1. *Kaposi's sarcoma (KS):* Kaposis sarcoma was one of the initial pulmonary complications. It is now known to be associated with human herpesvirus type 8 (HHV8) infection. HIV is believed to activate this virus, which lies dormant in the endothelial cells, acts as the trigger for angiogenesis, which results in the development and proliferation of this vascular tumor.[12] KS becomes

more prevalent as the CD4 declines. In the United States, it is strikingly more homosexual population. The prevalence has dropped dramatically in the Western world after the introduction of ARV therapy. KS is considered rare in India apart from a few, scattered case reports. Typical radiographic features of KS include nodules and pleural effusions. In the setting of the typical KS skin lesions, the diagnosis is often presumptive. The diagnosis can be made more definitely if similar raised purple plaques are seen on bronchoscopic examination. These lesions are highly vascular and distinctive, they are best not biopsied for the fear of bleeding. Treatment involves the combination of ARVs and chemotherapy in systemic disease.

2. *Non-Hodgkins Lymphoma (NHL):* HIV-positive individuals are almost 500 times more at the risk of developing NHL compared to the normal population. NHL too occurs with an increasing frequency as the CD4 counts reduce. Epstein Barr Virus (EBV) may be implicated in the pathogenesis of many cases.[13] In the HIV-infected patients, NHL is aggressive and usually Stage 4 at presentation. The outlook, despite aggressive chemotherapy, is poor. ARV therapy is responsible for the reducing prevalence of NHL in the developed world. ARV combined with chemotherapy has been responsible for an improved survival, which is now reported.
3. *Bronchogenic carcinoma:* HIV-positive patients are at the greater risk of developing lung cancer. Some studies suggest that adenocarcinomas are more frequent. As in NHLs, lung cancers in the HIV-positive population tend to be present in more aggressive and advanced forms. Unlike with NHL or KS, the CD4 counts tend to be well preserved in patients with HIV-associated lung cancer.[14]

Miscellaneous Nonmalignant Conditions

1. *Pulmonary hypertension:* HIV is an important cause of pulmonary hypertension. HIV infection must be excluded before a young adult is labeled to have primary pulmonary hypertension. HIV is believed to result in an increased expression of endothelin.[1] HIV-Related Pulmonary Hypertension (HRPH) can occur at all stages of HIV disease and at any level of CD4 count. Prognosis is guarded and treatment is administered as for any other patient with pulmonary hypertension, though interactions between sildenafil and protease inhibitors should be borne in mind.[15]
2. *Lymphocytic Interstitial Pneumonia (LIP):* LIP, may be EB virus related, is more common in children with HIV infection. It is now increasingly encountered in adults as well. The CT appearance with interstitial shadowing may be confused with PJP infection, however the symptoms are more insidious. Thoracoscopic biopsy is usually needed to make a definitive diagnosis. Treatment consists of a combination of ARVs and steroids.

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59

Lung Abscess

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DEFINITION

Latin word "abscessus" means collection of pus that has accumulated in a cavity formed by the tissues on the basis of an infectious process. Lung abscess is defined as severe, localized suppurative infection in the substance of the lung, associated with necrotic cavity formation.[1] The lesion is usually surrounded by a fibrous reaction, forming the abscess wall. Failure to recognize and treat lung abscess is associated with poor clinical outcome. The formation of multiple small (< 2 cm) abscesses is occasionally referred to as necrotizing pneumonia or lung gangrene. Both lung abscess and necrotizing pneumonia are the manifestations of a similar pathologic process. In the last two decades, the increasing use of corticosteroids, immunosuppressive agents, and chemotherapeutic drugs has changed the natural milieu of the oropharyngeal cavity and contributed to the mounting frequency of opportunistic lung abscesses.

EPIDEMIOLOGY

Lung abscesses are uncommon in the West with an incidence of 4 to 5 cases per 10,000 hospital admissions. But lung abscess continues to pose a major problem in the developing countries. In a retrospective study of 1,150 consecutive patients with thoracic and cardiovascular diseases 75 patients (16%) had lung abscess, 53 of whom were treated medically with 8 deaths, while 22 had emergency resection for massive hemoptysis with 9 deaths. The mortality from lung abscesses also has decreased, but remains between 2 and 10 percent for community-acquired lung abscess and 60 percent for hospital-acquired lung abscess.[2] Majority of patients with primary lung abscess improve with antibiotics, with cure rates documented at 90 to 95%. Host factors associated with a poor prognosis include an advanced age, debilitation, malnutrition, Human Immunodeficiency Virus (HIV) infection, or other forms of immunosuppression, malignancy and duration of symptoms more than 8 weeks.[3,4] The mortality rate for patients with underlying immunocompromised status or bronchial obstruction who develop lung abscess may be as high as 75%.[5] A retrospective study reported the overall mortality rate of lung abscesses caused by the mixed gram-positive and gram-negative bacteria at approximately 20%.[4] One hundred eighty-four patients with lung abscess, admitted to the Hospital of the University of Mississippi between 1960 and 1982, were studied and data from the different decades show a mortality rate of 22% in the 1960s, 25% in the 1970s, and 28% in 1980–1982.[6]

CLASSIFICATION

Lung abscess is considered acute if the duration of symptoms at the time of presentation is less than six weeks and chronic if it exceeds six weeks.[7] Primary lung abscesses are commonly observed in patients who are predisposed to aspiration or in otherwise healthy individuals, whereas secondary lung abscesses represent complications of a preexisting local lesion, such as a bronchogenic carcinoma or a systemic disease (e.g. HIV infection) that compromised immune function[8] (Table 59.1). In a retrospective review of 23 children with documented lung abscess, 11 cases were of primary lung abscess, and 12 of secondary lung abscess.[9]

TABLE 59.1: Factors contributing to the development of lung abscess

1. Oral cavity disease
   - Periodontal disease
   - Gingivitis
2. Altered consciousness
   - Alcoholism
   - Coma
   - Drug abuse
   - Anesthesia
   - Seizures
3. Immunocompromised host
   - Steroid therapy
   - Chemotherapy
   - Malnutrition
   - Multiple trauma
4. Esophageal disease
   - Achalasia
   - Reflux disease
   - Esophageal obstruction
5. Bronchial obstruction
   - Tumor
   - Foreign body
   - Stricture
6. Generalized sepsis

ETIOLOGY

Lung abscesses have numerous infectious causes[10-22] (Table 59.2). Anaerobic bacteria continue to account for most cases.[10] Aspiration lung abscesses are mostly caused by anaerobic bacteria. In one report from India, the anaerobes accounted for about 38 percent of 198 cultures from 100 patients of pleuropulmonary infections, of whom all the 13 patients of lung abscess had anaerobic infection either in isolation or along with aerobic bacteria.[11] These bacteriae predominate in the upper respiratory tract and are heavily concentrated in the areas of oral-gingival disease. Other bacteria involved in lung abscesses are aerobic gram-positive and gram-negative organisms.[12-15] Among the aerobic organisms, *Staphylococcus aureus, Klebsiella pneumoniae, E. coli* and Type III *Streptococcus pneumoniae* are frequently associated with lung abscess formation.[12-15] Rarely fungi like basidiobolus (Figs 59.1A to C) can also produce lung abscess, especially in an immunocompromised host.[16-18]

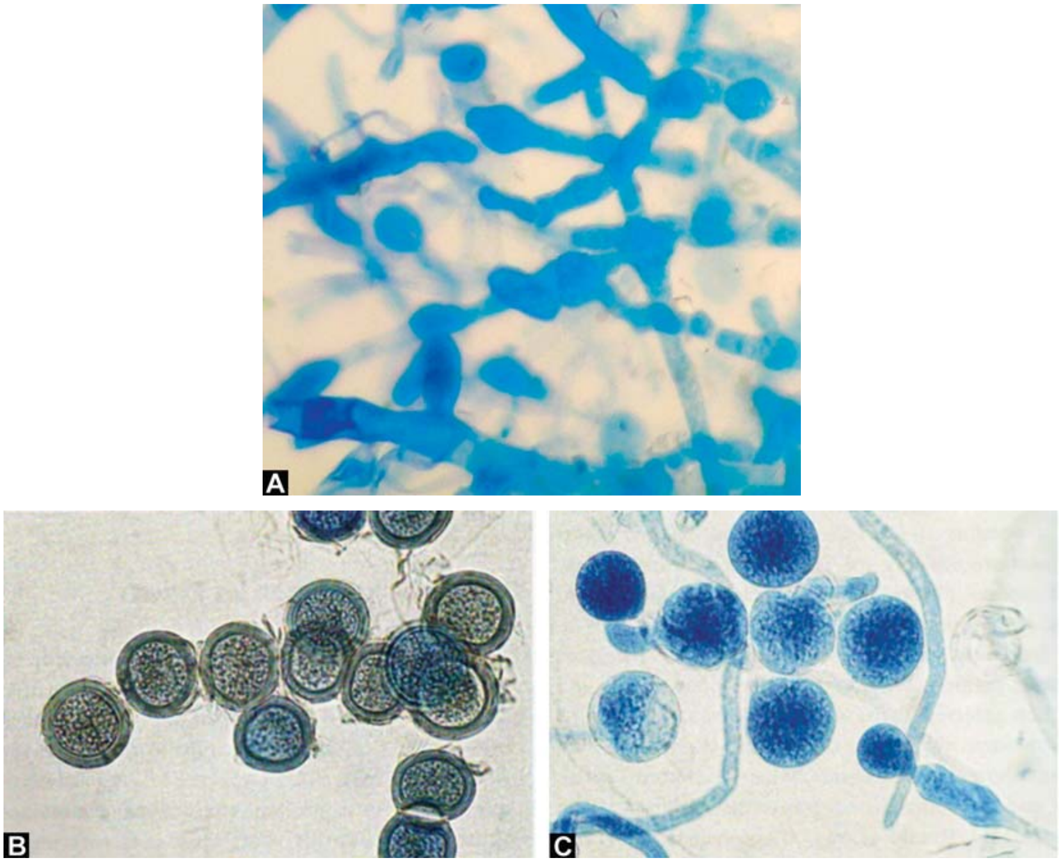
The organisms are aspirated to lower respiratory tract due to many factors, which may be local or general (Table 59.1). Other routes of the spread of infection to lungs include infected chest wall foci, infradiaphragmatic abscesses and hematogenous spread.

TABLE 59.2: Microorganisms responsible for lung abscess

Group	*Organism*
Aerobic organisms	*Klebsiella pneumoniae* *Nocardia sp.* *Pseudomonas aeruginosa* *Staphylococcus aureus* *Burkholderia pseudomallei*[19,20,21] (Fig. 59.2) *Pasteurella multocida*[22] *Streptococcus milleri* *Other streptococci*[11]
Anaerobic organisms	*Bacteroides sp.* *Fusobacterium sp.* *Clostridium sp.* *Peptostreptococcus sp.* *Actinomyces sp.* *Prevotella sp.*
Fungi	*Aspergillus sp.* (aspergillosis) *Blastomyces dermatitidis* (blastomycosis) *Coccidioides immitis* (coccidioidomycosis) *Cryptococcus neoformans* (cryptococcosis) *Histoplasma capsulatum* (histoplasmosis) *Pneumocystis jiroveci* *Rhizomucor* (mucormycosis) *Rhizopus sp.* (mucormycosis) *Sporothrix schenckii* (sporotrichosis) *Basidiobolus sp.*
Mycobacteria	*Mycobacterium avium-intracellulare* *Mycobacterium kansasii* *Mycobacterium tuberculosis*
Parasites	*Entamoeba histolytica* (amebiasis) *Echinococcus granulosus* (echinococcosis) *Echinococcus multilocularis* (echinococcosis) *Paragonimus westermani* (paragonimiasis)

PATHOGENESIS

Aspiration of infectious material is the most frequent etiologic mechanism in the development of pyogenic lung abscess. Aspiration due to dysphagia (e.g. achalasia) or compromised consciousness (e.g. alcoholism, seizures, cerebrovascular accident, head trauma) appear as important predisposing factors. Poor oral hygiene, dental



Figs 59.1A to C: Basidiobolus

infections and gingival disease are also common in these patients. Patients with alcoholism and those with chronic illnesses frequently have oropharyngeal colonization with gram-negative bacteria, especially when they undergo prolonged endotracheal intubation and are administered agents that neutralize gastric acidity. A pyogenic lung abscess can also develop from the aspiration of infectious material from the oropharynx into the lung when the cough reflex is suppressed in a patient with gingivodental disease.

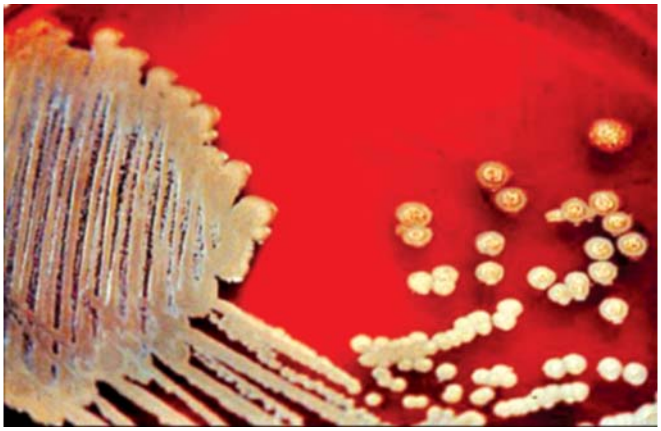


Fig. 59.2: Dry wrinkled colonies with metallic sheen of *Burkholderia pseudomallei* in blood agar

PATHOLOGY

Brock[23] in 1942, illustrated the mechanism of aspiration and abscess formation, which most often follow the dependent course. In the supine position, these are most often located in the posterior segment of the upper lobes and superior segment of the lower lobes. In the more upright position, materials flow into the basal segments of the lower lobes. When a person is in the lateral decubitus position, the axillary branches of the sub segments of apical and posterior upper lobe bronchi are favored.[24] Lung abscess that occurs as a part of hemetogenous spread may be found in any part of lung. Initially, the aspirated material settles in the distal bronchial system and develops into a localized pneumonitis. Within 24 to 48 hours, a large area of inflammation results, consisting of exudate, blood, and necrotic lung tissue. Multiple areas of liquefactive necrosis ("cross-country" pattern)[24] can occur secondary to bacterial proliferation.

This type of necrosis involves destruction of lung parenchyma, bronchi and arteries. In contrast, cavities that are more chronic and more slowly formed, such as the tuberculous cavities, often have remnants of fibrotic bronchopulmonary bands coursing through the cavity.[24] But most of the abscesses in the lung have an acute phase that destroys all the tissues in the area. Later, these areas coalesce to form a large abscess. The abscess frequently connects with a bronchus allowing drainage of the necrotic material leaving an empty or partially empty cavity with or without fluid level. The infection may extend into the pleural space and produce an empyema without rupture of the abscess cavity. The infectious process can also extend to the hilar and mediastinal lymph nodes, and these too may suppurate.

Sometimes, septic emboli may reach the lungs from right-sided bacterial endocarditis, which commonly complicates intravenous drug abuse, the usual organism being *Staphylococcus aureus*. Septic emboli may arise from the infected intravenous cannulae or from thrombophlebitis of the deep veins of the legs or pelvis or in relation to superficial cutaneous cellulitis. Gram-negative sepsis elsewhere, such as the urinary tract, the abdominal or the pelvic cavities may also contribute to the development of abscess. Alternatively, an abscess may develop as an infectious complication of a preexisting bulla or lung cyst or secondary to carcinoma of the bronchus.

CLINICAL FEATURES

Symptoms

Onset of symptoms in lung abscess is often insidious. This is more acute following pneumonia, where it begins with spiking temperature, rigors and night sweats followed by cough with sputum production. The expectorated sputum characteristically is foul smelling and bad tasting and often blood stained. Abscesses due to organisms other than anaerobes (e.g. *Mycobacteria*, *Nocardia*) do not demonstrate putrid respiratory secretions. There will be associated pleuritic chest pain and breathlessness.[25] In a series of 252 consecutive patients studied by Moreira and associates,[26] 70.2% were alcoholic. Cough, expectoration, fever and overall poor health were observed in 97% of patients, chest pain was reported by 64%, 30.2% presented digital clubbing; 82.5% had dental disease; 78.6% reported having lost consciousness at least once, and 67.5% presented with foul smelling sputum.[26]

TABLE 59.3: Differential diagnosis of a cavitary lung lesion

1. Cavitating lung cancer
2. Localized empyema
3. Infected bulla containing a fluid level
4. Infected bronchogenic cyst or sequestration
5. Pulmonary hematoma
6. Cavitating pneumoconiosis
7. Hiatus hernia
8. Lung parasites (e.g. hydatid cyst, *Paragonimus* infection)
9. Actinomycosis
10. Wegener's granulomatosis and other vasculitides
11. Cavitating lung infarcts
12. Cavitating sarcoidosis

Signs

There are no specific signs for lung abscess. Patients usually have signs of periodontal disease or a condition causing impaired consciousness. Patients are often febrile and tachypnic. Those with an abrupt onset lung abscess are often sick. Clubbing of fingers may be present, which may develop within a few weeks and this is reversible as the abscess resolves. If the abscess is localized there will be crackles on auscultation. If it is secondary to pneumonia, it is associated with dullness on percussion, bronchial breathing, egophony and crackles. There will be dullness on percussion and reduced breath sound if associated with pleural effusion. Primary lung abscesses that occur following staphylococcal suppurative pneumonia in infants and children tend to be abrupt and more threatening.[27]

Laboratory Diagnosis

A large number of conditions may present with a cavitary lung lesion (Table 59.3). Several different laboratory investigations are therefore required for the differential diagnosis of a lung abscess.

Hematological

A complete and differential white blood cell count will reveal leukocytosis and a left shift.

Microbiological Diagnosis

i. Sputum for Gram stain, culture and sensitivity. Expectorated sputum and other methods of sampling the upper airway do not yield useful results for anaerobic culture because the oral cavity is extensively colonized with anaerobes. Diagnostic material as below, uncontaminated by bacteria colonizing the upper airway may be obtained for culture[28-30] (Table 59.4).

TABLE 59.4: Uncontaminated pulmonary samples for microbiological demonstration and culture

- Transtracheal aspirate[28,29]
- Transthoracic pulmonary aspirate
- Fiberoptic bronchoscopy with protected specimen brush[30]
- Bronchoalveolar lavage fluid for quantitative culture
- Surgical specimens
- Pleural fluid (if empyema present)

ii. Bronchoscopy using a protected brush[30] to obtain a specimen uncontaminated by the upper airway or quantitative culture of organisms from the bronchoalveolar lavage fluid has been advocated to establish bacteriologic diagnosis of lung abscess. However, the experience with this technique in the diagnosis of anaerobic lung infections is limited and the diagnostic yield is uncertain.[31] But more importantly, cultures obtained by any of these methods are unlikely to be positive after the initiation of antibiotics.

iii. Blood culture: Blood cultures are infrequently positive in patients with lung abscess.

iv. If tuberculosis is suspected, acid-fast bacilli staining and mycobacterial culture also required.

v. Obtain sputum for ova and parasite whenever a parasitic cause for lung abscess is suspected.

Imaging Studies

i. *Chest radiograph:* A typical chest radiographic appearance of a lung abscess is an irregularly shaped cavity with an air-fluid level inside.[32] Lung abscesses as a result of aspiration most frequently occur in the posterior segments of the upper lobes or in the superior segments of the lower lobes (Fig. 59.3). Klebsiella lung abscess usually develops in the right upper lobe and is characterized by the bulging fissure sign. Lung abscesses due to Staphylococcus species are often multiple and bilateral. The wall thickness of a lung abscess progresses from thick to thin as it evolves. The cavity wall can be smooth or ragged, but is less commonly nodular, which raises the possibility of cavitating carcinoma. The extent of the air-fluid level within a lung abscess is often the same in posteroanterior and lateral views.[32] The abscess may extend to the pleural surface, in which case it forms acute angles with the pleural surface.[33]

Anaerobic infection is suggested by cavitation within a dense segmental consolidation in the dependent lung zones[34] (Figs 59.4 and 59.5). Lung

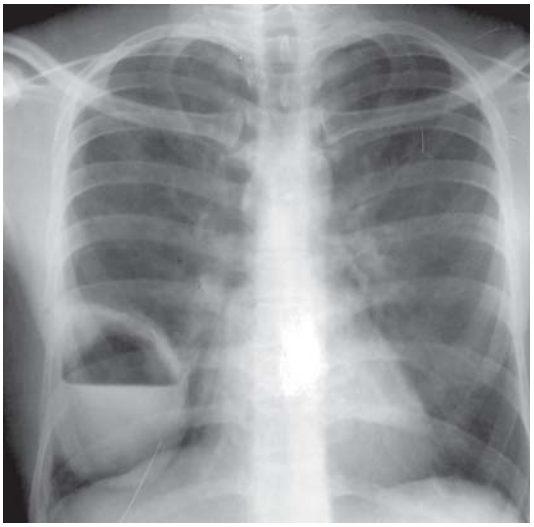


Fig. 59.4: X-ray Chest PA showing lung abscess right lower lobe

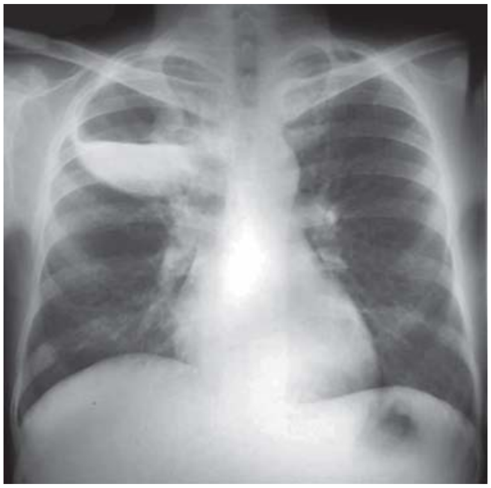


Fig. 59.3: X-ray Chest PA showing lung abscess right upper lobe

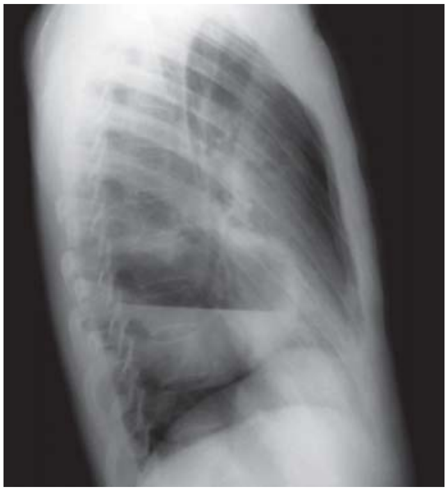
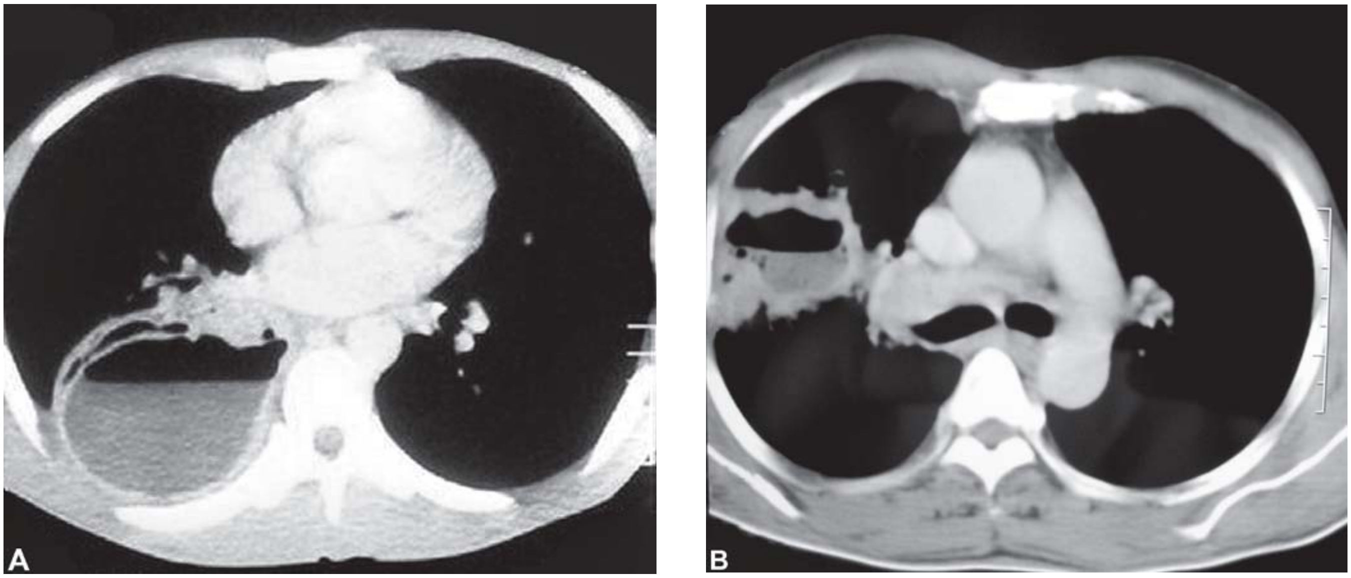


Fig. 59.5: X-ray Chest right lateral showing lung abscess right lower lobe



Figs 59.6A and B: CT thorax showing lung abscess

infection with a virulent organism results in more widespread tissue necrosis, which facilitates progression of the underlying infection to pulmonary gangrene. Up to one third of lung abscesses may be accompanied by an empyema.

ii. *Computed tomography (CT):* CT scanning of the lungs may help visualize the anatomy better than the chest radiography.[32] CT scanning is very useful in the identification of concomitant empyema or lung infarction.[32] On CT scan, an abscess often is a rounded radiolucent lesion with a thick wall with ill-defined irregular margins (Fig. 59.6A). Abscess walls are typically irregular in width and have regular luminal margins and exterior surfaces (Fig. 59.6B). Infected bullae may mimic an abscess especially when there is adjacent pneumonia; however, a smooth luminal margin on plain film[35] or CT suggests the correct diagnosis. The vessels and bronchi are not displaced by the lesion, as they are by an empyema.[33] The lung abscess is located within the parenchyma compared with loculated empyema, which may be difficult to distinguish on chest radiographs.[33,36] The lesion forms acute angles with the pleural surface chest wall.

iii. *Ultrasound (US) examination:* Ultrasound and ultrasound-guided transthoracic aspiration is an alternative method for CT thorax and guided aspiration. In a case series of 35 patients, 33 of the abscesses (94%) were demonstrated at ultrasound, while two lesions were not depicted. On ultrasound examination, lung abscesses were depicted as hypoechoic lesions with irregular outer margins and an abscess cavity that was manifested as a hyperechoic ring. Ultrasound-guided transthoracic needle aspiration of fluid from the abscess cavity was performed successfully in 31 of 33 patients (94%). A total of 65 pathogens were isolated from 31 aspirates (41 anaerobes and 24 aerobes).[37]

Bronchoscopy

Flexible fiberoptic bronchoscopy is performed to exclude bronchogenic carcinoma whenever bronchial obstruction is suspected or less commonly, to identify and remove a foreign body.[38] Bronchoscopy also helps to retrieve uncontaminated specimen for culture, as well as to remove pus.

COMPLICATIONS

Lung abscess if not diagnosed and treated early is met with few complications. Approximately one third of lung abscesses are complicated by empyema. This may be observed with or without bronchopleural fistula. Hemoptysis is a common complication of lung abscess. Occasionally, the hemoptysis can be massive, thus requiring urgent surgery. Spread of infection to other parts of same lung and to the opposite lung is possible. Bacteremia and metastatic abscesses, including brain abscess may also occur in patients who receive inadequate treatment. Metastatic brain abscess most frequently involve temporal lobe and cerebellum. Rarely, it may rupture into the mediastinum causing acute mediastinitis. Poor treatment response may lead on to bacteremia and septicemia.

TREATMENT

Treatment of lung abscess is guided by the available microbiology and knowledge of the underlying or associated conditions. Once the clinical diagnosis of lung abscess is made and the respiratory secretions sent for culture and drug sensitivity tests, patient should be initiated on broad spectrum antibiotics. Antibiotics with a spectrum covering gram-negative aerobes and anaerobes are preferred. This may be modified once drug sensitivity results are available.

Antibiotic Therapy

Most patients, even with necrotizing pneumonia, respond well to high-dose penicillin[39] and show clinical improvement within a week to 10 days. Clindamycin is preferred in the cases of severe underlying disease or when penicillin fails to yield signs of recovery.[40,41] The presence of empyema not only increases the duration of therapy, but also carries a higher mortality rate (20% vs 5%).[42]

- Standard treatment of an anaerobic lung infection is clindamycin (600 mg IV q8h followed by 150–300 mg PO qid). This regimen has been shown to be superior than parenteral penicillin. Several anaerobes may produce beta-lactamase (e.g. various species of *Bacteroides* and *Fusobacterium*) and therefore, develop resistance to penicillin.[43]
- Although metronidazole is an effective drug against anaerobic bacteria,[44,45] the experience with metronidazole in treating lung abscess has been rather disappointing because these infections are generally polymicrobial. A failure rate of 50% has been reported in the past.[44,45] Necrotizing pneumonia and pulmonary abscess that develop in the nursing home or in the hospital setting require a more aggressive diagnostic approach, and broad-spectrum antibiotic coverage. Inspite of these measures and appropriate antibiotic selection, nosocomial-acquired disease carries a mortality rate of 30 to 50%.[42]
- Ampicillin plus sulbactam is well tolerated and is as effective as clindamycin with or without a cephalosporin in the treatment of aspiration pneumonia and lung abscess.[46]
- Moxifloxacin is clinically effective and is as safe as ampicillin plus sulbactam in the treatment of aspiration pneumonia and lung abscess.[47]

Duration of Therapy

- Although the duration of therapy is not well established, most clinicians generally prescribe antibiotic therapy for 4 to 6 weeks.
- It generally suggests that antibiotic treatment should be continued until the chest radiograph has shown either the resolution of lung abscess or the presence of a small stable lesion.
- The extended treatment is recommended since there is a risk of relapse with a shorter antibiotic regimen.

Response to Therapy

- Patients with lung abscesses usually show clinical improvement within 3 to 4 days of initiating the antibiotic therapy. Clinical resolution is expected in 7 to 10 days. Persistent fever beyond this time indicates a therapeutic failure, and these patients should undergo further diagnostic studies to determine the cause of failure.
- Considerations in patients with poor response to antibiotic therapy include bronchial obstruction with a foreign body or a neoplasm or an infection with resistant bacteria, mycobacteria or fungi.
- Large cavity size (> 6 cm in diameter) usually requires prolonged therapy.[48]
- The infection of a preexisting sequestration, cyst or bulla may also be responsible for the delayed response to antibiotics.[49]

Physiotherapy

Physiotherapy is useful in helping the patient to clear the purulent material. Postural drainage can be given keeping the affected pulmonary segments uppermost. However, chest physical therapy and postural drainage are not widely recommended because of the fear of spillage and extension of infection.

Surgical Care

Surgery is very rarely required for patients with uncomplicated lung abscesses. The usual indications for surgery are failure to respond to medical management, suspected neoplasm or congenital lung malformation.[50] The surgical procedure is either lobectomy or pneumonectomy. When surgery is necessary, lobectomy is the most common procedure; segmental resection may suffice for small lesions (< 6 cm diameter cavity). Pneumonectomy may become necessary for multiple abscesses or for pulmonary gangrene, unresponsive to drug therapy.

Percutaneous Drainage

Percutaneous drainage of a complicated abscess (i.e. one associated with fever and signs of sepsis) is beneficial in selected patients who do not respond to adequate medical therapy.[15] They are ventilator-dependent patients who are not candidates for extensive thoracic procedures. Other indications for drainage include ongoing sepsis despite adequate antimicrobial therapy, a progressively enlarging lung abscess in imminent danger of rupture, failure to wean from mechanical ventilation, and contamination of the opposite lung. Results achieved with percutaneous drainage show it to be safe and effective method when compared with surgery. Percutaneous drainage is rarely complicated by empyema, hemorrhage or bronchopleural fistula.[51] Although, a few patients who undergo percutaneous drainage develop bronchopleural fistulas, most of these fistulae close spontaneously with the resolution of the abscess cavity. Percutaneous drainage may be used to stabilize and prepare critically ill patients for surgery. Percutaneous or surgical drainage of lung abscesses is necessary in roughly 10% of patients.[52] Aggressive interventional therapy can be diagnostic and therapeutic in the infected lung abscess. But interventional therapy can be harmful in the case of postinfectious necrotizing pneumonia.[53]

In current practice, most of the lung abscesses are drained under CT guidance. CT allows optimal placement of catheter and hence enables the safe and effective percutaneous evacuation of lung abscess. The morbidity and mortality of patients with percutaneous catheter drainage is lower than that with surgical resection.[54] Hence, CT-guided drainage should be considered the first therapeutic choice in most patients of lung abscess who do not respond to medical therapy. Endoscopic lung abscess drainage is considered if an airway connection to the cavity can be demonstrated. Success of this treatment represents an additional option other than percutaneous catheter drainage or surgical resection.[55-58] Recently the technique of passing angiography catheters through the rigid bronchoscope into the abscess cavity, to facilitate the bacteriological diagnosis and drainage of the cavity is being successfully adopted.[55,58] Endobronchial catheters with the use of laser appear to be relatively safe and effective for the treatment of lung abscess in selected patients in whom the abscess is adjacent to the central airway.[59] When necessary, a bulge in an adjacent airway can be perforated with laser.

PROGNOSIS

The prognosis of patients with lung abscesses depends on the underlying or predisposing pathologic event and the speed with which appropriate therapy is established. Negative prognostic factors include a large cavity (>6 cm), necrotizing pneumonia, multiple abscesses, immunocompromised state, age extremes, associated bronchial obstruction, and aerobic bacterial pneumonia.[3] The prognosis associated with amebic lung abscess is good when treatment is prompt.

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60

Bronchiectasis and Cystic Fibrosis

David Honeybourne

BRONCHIECTASIS

Introduction

Bronchiectasis is a chronic condition with a variable clinical course that may include acute exacerbations and also chronic deterioration in some cases. Bronchiectasis was first described by Laënnec in 1812. Clinical features in a patient present with bronchietasis include presence of frequent productive cough often accompanied with the shortness of breath on effort. The prevalence of bronchiectasis in populations has been found to be very variable and many older studies were carried out before High Resolution Computed Tomography (HRCT) thoracic scans were available. Prevalence figures have varied between 4 per 1,00,000 population and 272 per 1,00,000 population, partly dependent upon the age range studied.[1,2] There are sparse data on the prevalence of bronchiectasis in the Indian subcontinent.

Bronchiectasis is not infrequently misdiagnosed as chronic bronchitis and/or chronic obstructive pulmonary disease with 15 to 30% of patients, diagnosed with COPD having the evidence of bronchiectasis on high resolution CT lung scans. [3,4]

There is some evidence that in populations with poor access to health care and high rates of lower respiratory tract infections, particularly during childhood, there may be a higher prevalence of bronchiectasis.[5]

Pathology

Until recently, the original definition of bronchiectasis was based on the pathological findings. Pathologically bronchiectasis is defined as permanent dilatation of the bronchi.[6] Further morphological definition has classified bronchiectasis as cylindrical or tubular, which involves dilatation of the airways and also varicose bronchiectasis. There are, in addition, focal areas of narrowing within the dilated airways. A further type is saccular or cystic bronchiectasis, which is characterized by the progressive dilatation of the bronchi with collection of large clusters of cysts. However, morphological subtyping of bronchiectasis is of little practical value in the terms of patient management. Figure 60.1 shows changes of advanced bronchiectasis.

The airways in bronchiectasis show evidence of chronic inflammatory changes with high sputum concentrations of substances such as elastase, interleukin 8 and other proinflammatory agents. It is thought that

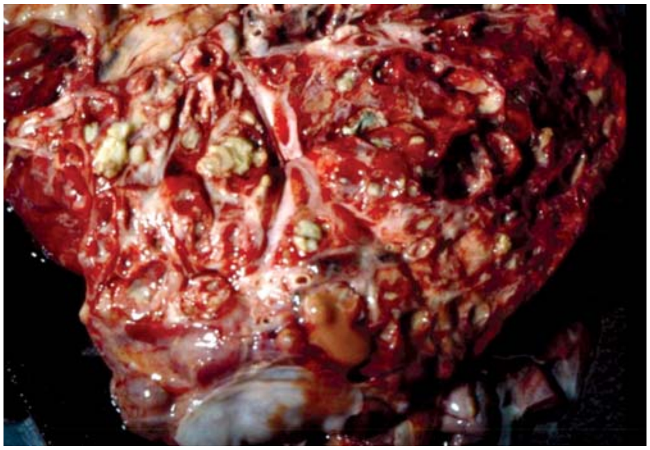

Fig. 60.1: Extensive advanced bronchiectasis

an increase in the levels of these agents is driven by recurrent bacterial infections.

Physiology

Classically, patients with bronchiectasis show the evidence of airflow obstruction. Around 40% of cases may show significant improvement in FEV_1 after using a beta-2 bronchodilator.[7] Also a significant number of patients show evidence of bronchial hyperreactivity.[8] Patients may also have a restrictive defect due to fibrotic changes associated with bronchiectasis.

Etiology

Table 60.1 shows a list of causes or conditions associated with bronchiectasis.

Childhood viral or bacterial infections particularly in malnourished children are known to predispose to lung damage within the growing lung and lead to the emergence of bronchiectasis. The increasing use of immunization against whooping cough (*Bordetella pertussis*) and measles has led to a reduction in such cases. In countries, where there is a high incidence of pulmonary tuberculosis, there are also likely to be many cases of patients with subsequent bronchiectasis secondary to fibrotic damage caused by tuberculosis. Other bacterial infections are known to be involved in both the early and later stages of bronchiectasis, e.g. *Pseudomonas aeruginosa* and *Haemophilus influenzae.*

Atypical mycobacteria are being increasingly recognized in patients with bronchiectasis and infection with these atypical organisms may initiate bronchiectasis or colonization and further tissue damage may occur in patients with preexisting bronchiectasis.

TABLE 60.1: The etiology of bronchiectasis

- Postinfectious, e.g. tuberculosis, whooping cough, pneumonia
- Cystic fibrosis
- Connective tissue diseases, e.g. SLE, rheumatoid arthritis,
- SLE, Sjögren's syndrome, relapsing polychondritis
- Allergic bronchopulmonary aspergillosis
- Ciliary defects, e.g. primary ciliary dyskinesia, Young's syndrome, Kartagener's syndrome
- Immune deficiency, e.g. IgA deficiency, X-linked agammaglobulinemia, common variable immunodeficiency, secondary to chronic lymphatic leukemia
- Congenital defects, e.g. tracheobronchomegaly (Mounier-Kuhn syndrome), pulmonary sequestration
- Secondary to inhalation or aspiration, e.g. due to a foreign body
- Inflammatory bowel disease, e.g. ulcerative colitis

Aspergillus fumigatus is commonly found in the environment and in susceptible patients, may lead to an allergic reaction, causing the clinical condition Allergic Bronchopulmonary Aspergillosis (ABPA). Allergic reactions to the fungus in the airways may cause inflammation and collateral damage to the airway walls as a result. Occasionally invasive aspergillosis may also occur.

Patients who are Human Immunodeficiency Virus (HIV) positive may also develop bronchiectasis related to their reduced immunity.

Genetic and congenital conditions may lead to bronchiectasis. These include cystic fibrosis (see later part of this chapter for further description) and primary ciliary dyskinesia. Primary ciliary dyskinesia is an inherited autosomal recessive condition with a birth frequency of approximately 1 in 30,000. In this condition bronchial cilia are unable to beat normally. This is due to an absent or shortened dynein arm within the cilia. Some of these patients also have Kartagener's syndrome where there is bronchiectasis, situs inversus and chronic sinusitis. This condition causes a lack of correct rotation of organs in the fetus and hence there is often association with situs inversus and dextrocardia. Some progress has recently been made in identifying the underlying genetic mutations. Another uncommon condition is Mounier-Kuhn syndrome, which causes tracheobronchomegaly. Bronchiectasis has also been reported to be found in associated with alpha 1-antitrypsin deficiency and Marfan's syndrome.

It is important to think of the possibility of an underlying immune deficiency causing an increased risk of lung infections leading on to the development of bronchiectasis. Such immunodeficiency disorders include X-linked agammaglobulinemia, IgA deficiency, Severe Combined Immunodeficiency of Childhood (SCID) and Common Variable Immunodeficiency (CVID).

In some subjects with bronchiectasis, there may be a history of aspiration of a foreign body, such as a peanut during childhood or sometimes aspiration of food may cause a foreign body to be lodged in an airway, which may then gradually result in the development of bronchiectasis over a long period of time. Aspiration will typically, but not invariably, involves the right middle or right lower lobe.

Bronchiectasis may be associated with connective tissue diseases especially rheumatoid arthritis, but also systemic sclerosis, systemic lupus erythematosus or ankylosing spondylitis.

Clinical evidence of bronchiectasis has been reported in around 3% of patients with rheumatoid arthritis. More detailed investigations, including high resolution CT scanning have reported much higher levels.[9,10]

There is an association between inflammatory bowel disease and bronchiectasis particularly in patients with chronic ulcerative colitis.[11] Airway inflammation may be exacerbated by effector lymphocytes. Sometimes immune modulating drugs may result in an exacerbation of lung symptoms. It is interesting that in some patients, who have a bowel resection for ulcerative colitis, the respiratory symptoms may increase postoperatively.

The proportion of bronchiectasis patients with underlying disorders detailed in Table 60.1 will vary according to the population studied. Clearly in a population, where there is a high prevalence of pulmonary TB, postinfectious bronchiectasis will be relatively common. Also, the availability of complex immune testing may be limited in some countries and therefore, this cause may remain underdiagnosed. However, in many published series, around 50% of patients with bronchiectasis will have no definite identified cause.

Bronchiectasis is often diffuse, but sometimes may be local. A good example of local bronchiectasis is the one which occurs after an inhaled foreign body and may lodge in the right middle or right lower lobe.

Cases of bronchiectasis may be identified in association with nail dystrophy often with yellow discoloration called "yellow nail syndrome" and is usually associated with sinusitis, pleural effusions and primary lymphedema.

Young's syndrome is a combination of bronchiectasis, obstructive azoospermia and chronic sinusitis.

There is some emerging evidence that there may be an association between asthma and bronchiectasis. A history of asthma usually occurs first and then evidence of bronchiectasis occasionally emerges many years later. Some of these cases may be related to ABPA.

Symptoms and Signs

Recurrent cough with sputum production may be an indication of underlying bronchiectasis in children. There should also be a high index of suspicion for underlying bronchiectasis in children with chronic respiratory symptoms. Furthermore, the finding of persisting inspiratory crackles over the lungs should raise the possibility of bronchiectasis.

In adults, similar symptoms to those in children, i.e. a chronic productive cough with shortness of breath and occasionally wheezing may occur. Also, the patient may have recurrent hemoptysis and fever at times of acute infective exacerbations. Pleuritic chest pain may also occur occasionally. Frequent respiratory infections may be associated with weight loss. Based on appearance, sputum can be classified into mucoid, mucopurulent or purulent types. A higher proportion of patients with varicose or cystic bronchiectasis have purulent sputum compared to those with tubular bronchiectasis as assessed by high resolution CT lung scans.[4]

Dyspnea correlates with the degree of impairment of FEV_1, sputum volume and extent of changes seen on HRCT scans. Dyspnea occurs in around 72% of cases.[12] Chest pains, usually nonpleuritic, may occur in around one-third of patients. Hemoptysis occurs in around half of cases and in a small proportion of cases, may be massive and life threatening.

There is, however, a form of bronchiectasis in adults where there may be daily nonproductive chronic cough. Therefore, the absence of purulent sputum production does not exclude the possibility of underlying bronchiectasis.

A full assessment of symptoms should include: An estimated or measured 24-hour sputum volume when clinically stable, a record of the number of infective exacerbations that the patient has per year, the extent of the use of antibiotics and also assessment of the effects of the symptoms on activities of daily living. The St. George's respiratory questionnaire has been used to assess the quality of life in the adult patients with bronchiectasis.[13]

Classical sign on examination is the presence of coarse inspiratory crackles over the affected lungs especially in the lower zones, which may be present in about 70% of patients. Crackles may often extend into expiration. Coughing may temporarily lessen the crackles. Wheezing may be heard in around 45% of cases. Finger clubbing has been reported to occur in around 40% cases, although this has been less frequent in some reports.[12]

Diagnosis

Prior to CT lung scanning, bronchograms were the definitive way of diagnosing and delineating the extent of bronchiectasis. The advent of HRCT lung scanning has revolutionized the diagnosis of bronchiectasis.[14] CT scanning has been shown to be the most sensitive and specific way of diagnosing the condition. In particular, the HRCT is superior to a plain chest X-ray. CT scan appearances (Fig. 60.2) may include ring-like shadows where airways are seen in cross-section or a tramline appearance where airways are seen in longitudinal section. Modern high resolution CT scanners can produce 3-D reconstruction of affected areas (Fig. 60.3).

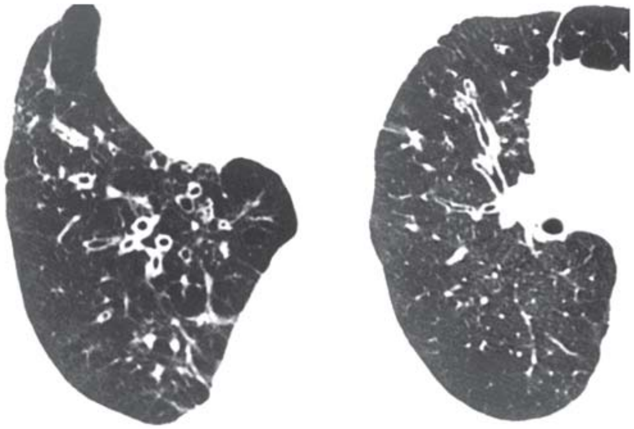

Fig. 60.2: High resolution CT scans showing the signs of signet ring shadowing and tramline changes typical of bronchiectasis

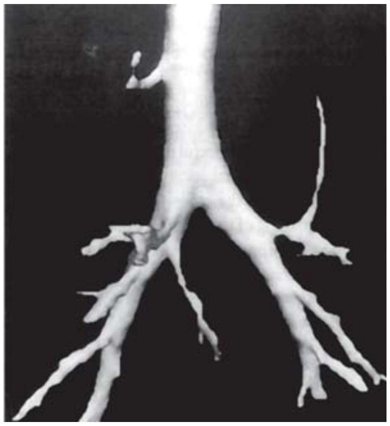

Fig. 60.3: 3-D reconstruction from a CT scan showing bronchiectasis

Nonspecific findings include focal pneumonitis or areas of atelectasis. CT scanning may also visualize varicose constrictions. The distribution of abnormalities seen on the CT scan may occasionally give some clue as to the underlying etiology. For instance, localized bronchiectasis in the right middle or right lower lobe suggests a foreign body aspiration, cystic fibrosis and ABPA, which tend to have an initial predilection for the upper lobes.

Other investigations include (after taking a careful history and performing a thorough examination) assessment of sputum samples for bacterial infections, including mycobacteria and also fungal infections such as aspergillus. The possibility of ABPA should be investigated by measuring the total serum IgE and looking for specific IgE and IgG to *Aspergillus fumigatus*. Immune deficiency may be detected by looking at serum IgG, IgA and IgM levels, IgG subclasses and also an assessment of functional antibody levels, particularly antibody levels against *Hemophilus influenzae* and *Streptococcus pneumoniae*. In some cases, investigations for possible underlying cystic fibrosis may be appropriate (see later in this chapter). In selected patients, studies of cilial function will be appropriate particularly looking for primary ciliary dyskinesia. They will usually require referral to a specialist center where mucosal biopsies are examined by ultramicroscopy. Also investigations should look for the possibility of an associated underlying connective tissue disease.

Microbiology

Patients with established bronchiectasis may have a wide range of respiratory pathogens in the sputum. Common causes of bacterial exacerbation in bronchiectasis include *Haemophilus influenzae, Staphylococcus aureus,* MRSA, *Streptococcus pneumoniae*, coliforms (e.g. Klebsiella, Enterobacter) or *Pseudomonas aeruginosa*. Assessment of sputum samples, over the course of weeks or months at clinic visits, often provides invaluable information. Patients may eventually become colonized by one or more organisms and occasionally the numbers of those organisms increases and initiates an acute exacerbation requiring antibiotics. In particular, *Pseudomonas aeruginosa* is likely to cause chronic colonization in more severe cases and may lead to progressive lung damage as part of a "vicious circle" of recurrent infection, tissue damage, predilection to further infection and then, further tissue damage. Specific treatment for chronic pseudomonas colonization is detailed below.

Specific sputum testing for mycobacteria should be carried out, firstly to exclude the possibility of tuberculosis, and secondly to look for colonization and possible infection with atypical mycobacteria such as *Mycobacterium avium-intracellulare, Mycobacterium kansasii or Mycobacterium abscessus*. The finding of atypical mycobacteria on two samples of sputum will then indicate the need for prolonged multiple antibiotic therapy.[15]

Treatment

Treatment can be divided into two areas. Firstly for an exacerbation of bronchiectasis and secondly for long-term maintenance treatment.

An exacerbation causes the patient to have symptoms of one or more symptoms such as increasing frequency of cough, sputum volume and sputum purulence. Initially the treatment depends partly on the previous microbiology results. If the patient is colonized with

Pseudomonas aeruginosa, then treatment can be done with an oral agent, such as ciprofloxacin 500 mg twice a day; for more severe exacerbations, intravenous antibiotics may be more effective. If two different types of intravenous antibiotics are used at the same time, then this will help in reducing the risk for emergence of antibiotic resistance. Also intravenous therapy would be indicated, if there was a failure of improvement on oral treatment. There are currently very few oral agents available, which are effective against *Pseudomonas aeruginosa*. Ciprofloxacin is often the first choice of oral agent and in some countries chloramphenicol is an alternative, but it needs to be explained to the patient that there is a rare possibility (approximately 1 in 25,000) of the patient developing severe aplastic anemia from the drug.

If infection is found due to other bacterial agents such as *Streptococccus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* or *Staphylococcus aureus*, then an oral agent may be sufficient, or alternatively a single intravenous agent may be effective. If the exacerbation is caused by MRSA, then often two antibiotics are recommended either orally or intravenously. (Table 60.2)

Due to difficulties with antibiotic penetration into the damaged lung and airways,[16] a prolonged course of antibiotics is often required. The optimum duration of such a course is unclear, however if there is a clinical improvement with a fall of serum inflammatory markers, such as C-reactive protein, then this would indicate improvement and often such a course of antibiotics would last for 10 to 14 days.

Another important treatment option for an exacerbation includes physiotherapy. There has been some recent evidences that physiotherapy is effective in acute exacerbations.[17] Also patients may benefit from nebulized bronchodilators during an exacerbation and may later be transferred back to regular treatment. It is unclear, whether a course of steroids given at the same time, as the course of antibiotics has any beneficial effect. Theoretically, it may reduce the inflammatory response in the lung, but the possibility of side-effects also needs to be considered.

The choice of intravenous agents for an exacerbation due to *Pseudomonas aeruginosa* includes ceftazidime, aztreonam, tazobactam, meropenem, colistin, and aminoglycosides such as tobramycin or gentamicin. Availability of these drugs will vary between different countries. If intravenous aminoglycosides are used, then monitoring of blood levels is essential to reduce the risk of renal or auditory side effects. For instance, if tobramycin is given two or three times per day then pre-dose and post-dose levels should be measured to assess the trough and peak levels. If a single daily dose of aminoglycoside is used,[18] e.g. a 30 minute infusion of tobramycin, then monitoring of just trough levels may be sufficient.

Also with acute exacerbations, it is of utmost importance to address general issues such as maintaining adequate hydration and maintaining oxygen saturation.

Noninvasive ventilation may be useful for those patients who slip into type 2 respiratory failure.[19]

Long-term Management of Stable Disease

The general advice about stopping smoking and improving nutrition applies to bronchiectasis patient. Also annual vaccination against seasonal influenza is advised as is pneumococcal vaccination, approximately every 10 years. Patients with significant bronchiectasis should receive instructions from a respiratory physiotherapist about the choice of different airway clearance techniques and should be strongly advised to carry out home physiotherapy regularly. There is currently no good evidence to use nebulized recombinant human DNase as a mucolytic agent, although further larger studies may be required.[20] There have been some studies recently looking at nebulized hypertonic saline[21] and also inhaled mannitol[22] as agents to help aid sputum production and it is likely that further evidence about their possible value will emerge in the near future. Lung function tests should be carried out before and after bronchodilators use to look for evidence of reversibility of airflow obstruction with both inhaled β-agonists and anticholinergic agents. Sometimes exercise tolerance and

TABLE 60.2: Recommendation of antibiotics to be used for these infections

Bacterial infection	*First choice*	*Second line treatment*
Haemophilus influenzae or *Moraxella catarrhalis*	Co-amoxiclav	Doxycycline, ciprofloxacin
Streptococcus pneumoniae	Amoxicillin	Clarithromycin
MRSA	Rifampicin and trimethoprim or IV vancomycin or teicoplanin	Rifampicin and doxycycline or linezolid
Pseudomonas aeruginosa	Ciprofloxacin	Ceftazidime and tobramycin or colistin

symptoms may improve with these agents despite there being no significant improvement in lung function measurements. The evidence base for using inhaled corticosteroids is limited.[23,24] There have been some studies that have shown a reduction in sputum volume and an improvement in quality of life measurements without any obvious effects on lung function or exacerbation rates. Some patients may benefit from a trial of inhaled steroids for several months.

In patients who are colonized with *Pseudomonas aeruginosa*, the use of long-term nebulized antibiotics may be helpful in reducing the bacterial load in the airways. This, in turn, may reduce chronic inflammation and hence reduce lung damage. The inhaled antibiotics, however, have the drawback of being expensive and sometimes may cause wheezing even after pre-dosing with inhaled β-2 agonists. There is some limited evidence in the literature of benefit from long-term nebulized antibiotics in patients with more severe bronchiectasis colonized with pseudomonas.[25] On first isolation of *Pseudomonas aeruginosa* in the sputum, attempts should be made to eradicate the infection to try and stop chronic colonization.

In a small number of patients with very localized bronchiectasis, the possibility of surgery should be considered.[26] They apply for instance to those patients who have localized bronchiectasis following aspiration of a foreign body or related to previous localized tuberculosis. Surgery with localized lung resection may benefit selected patients with hemoptysis, chronic debilitating cough or a lung abscess unresponsive to antibiotic treatment.[27]

Lung transplantation may also be considered, but the capacity to do this developing countries is currently very limited.

The role of long-term oral antibiotics in bronchiectasis, perhaps given as a rotation of different antibiotics, is uncertain. However, there is some evidence in the literature regarding benefit of such an approach in patients with severe bronchiectasis in terms of reduced sputum volume, number of days absent from work due to ill health and reduction in exacerbation frequency. Recently there has been some evidence of the potential benefit of reducing exacerbation frequency by using long-term oral azithromycin as an anti-inflammatory agent in bronchiectasis.[28]

Noninvasive ventilation can improve quality of life in some patients with chronic type 2 respiratory failure due to bronchiectasis.[29]

Complications

Hemoptysis is a rare, but potentially life-threatening complication of bronchiectasis. Severe hemoptysis (defined as more than 300 mls) of blood coughed up per 24 hours may occur. Whenever possible, the bleeding site should be identified by a combination of bronchoscopy, CT lung scanning and angiography. Often bleeding occurs from a bronchial artery and an interventional radiologist may be able to embolize the vessel.[30] Occasionally with severe hemoptysis, surgery may be necessary.

Amyloidosis is an occasional complication of chronic severe bronchiectasis. A lung abscess may develop due to bronchiectasis and this may be refractory to prolonged antibiotic therapy.

Prognosis

The prognosis of bronchiectasis is very variable, depending upon any underlying cause, particularly immunodeficiency, the extent of the bronchiectasis and also the type of bacterial colonization. Generally, colonization with *Pseudomonas aeruginosa* is linked to a worse prognosis.

Research into different treatments of non-cystic fibrosis bronchiectasis has lagged behind treatments for cystic fibrosis related bronchiectasis and further trials are required for new emerging drug treatments to establish whether they have a role in non-cystic fibrosis bronchiectasis.

CYSTIC FIBROSIS

Epidemiology

Cystic Fibrosis (CF) is a disease caused by an autosomal recessive mutation on chromosome 7. In UK, there are about 8,000 people who have this diagnosis (now with improved prognosis the proportion of adults is slightly higher than those in children). In European populations, CF affects approximately 1 in 2,500 live births. In some countries there is now a national screening program to detect such cases soon after birth. Again in European populations, approximately 1 in 25 live births carries 1 mutation. There is some speculation in the literature that heterozygotes may possibly have a survival advantage when faced with other gastrointestinal infections such as cholera or typhoid. This may explain why the disease has not become gradually rarer over the centuries. However, in the Indian subcontinent, CF is less common. The exact incidence and prevalence figures are unknown. However, in European countries like the United Kingdom with significant number of immigrants from the Indian subcontinent, there are a substantial number of cystic fibrosis patients that are now being recognized.

The prevalence of CF in Asian immigrants in Britain has been estimated at around 1 in 10,000 and the clinical course tends to be more severe than matched non Asian controls.[31]

Genetics and Cellular Dysfunction

The CF mutation on chromosome 7 leads to an abnormality in a protein that is called Cystic Fibrosis Transmembrane Regulator (CFTR). This defective protein leads to the disruption of ion transport in epithelial lined organs, particularly the airways, but can also involve the sweat ducts, pancreatic ducts, bile ducts and the intestine. The genetic abnormality was isolated on chromosome 7.[32] This led to a great hope that gene therapy would eventually become a cure. Since 1989,over a 1,000 different mutations have been identified, any of which may produce the CF phenotype. Some of these mutations are extremely rare, however. The commonest mutation in the UK is deletion of phenylalanine (delta F508). A recent paper by Shastri et al. (2008) has described the commoner genetic mutations in India.[33]

Patients who are homozygous for delta F508 tend to have severe respiratory and pancreatic involvement although occasionally exceptions may occur. Indeed there is sometimes a discrepancy between the known genotype and the phenotype. There is increasing evidence of influence of other genes on different chromosomes, so called "modifying genes" and extensive research work is currently being carried out to identify such genes with potential implications for treatment. Potential modifying genes include mannose-binding lectin, transforming growth factor beta and protease inhibitors.

The CFTR is a 1,480 amino acid product coded for the long arm on chromosome 7. It is a glycoprotein and its function is to mediate ATP related chloride conductance. Deficiency of the CFTR causes reduced chloride conductance and consequent changes in sodium absorption by the cells. In the airways, excess sodium and water is absorbed across the cell membrane into the cell and this leads to a concentration of macromolecules and mucus in the airways. This, in turn, acts as a magnet for pathogens such as *Pseudomonas aeruginosa*. There is also some evidence that the defective CFTR may also be proinflammatory leading to airway damage in early childhood.

The CFTR mutations have been divided into five groups:

1. No synthesis, e.g. the nonsense mutation G542X
2. A block in processing, e.g. delta F508
3. A block in regulation, e.g. missense G551D
4. Altered conductance, e.g. missense R117H
5. Reduced synthesis, e.g. missense 455E.

Generally, groups 4 and 5 are associated with a mild phenotype. Some of these mild phenotypes may only present in adult life; in males they may be diagnosed first in the infertility clinics.

Diagnosis

Diagnosis is usually made in early childhood either by neonatal screening or by the development of symptoms such as failure to thrive or intestinal obstruction in neonates.

The diagnosis of cystic fibrosis depends upon a positive sweat test, gene analysis and also the clinical picture. Sweat testing classically involves pilocarpine iontophoresis, which is applied to the skin to stimulate sweat production, usually on the forearm. A 5 millivolt electric charge is then applied to the skin for 10 minutes and sweat is collected on a tiny piece of gauze. The chloride content of the gauze is then analyzed together with the difference in weights before and after sweat simulation. This then allows a sweat chloride level to be calculated. Normally, sweat chloride levels are less than 30 millimoles/liter. The diagnostic level for classical cystic fibrosis is a chloride level of 60 or more millimoles/liter. The sodium content will also be increased although usually not to quite such a high level as the sweat chloride level. If an abnormal sweat test is recorded it is usual to repeat the test to ensure accuracy. A small number of individuals will have a borderline sweat test between 30 and 59 millimoles/liter and this may be associated with the condition called "atypical cystic fibrosis." These tend to be patients, who have mild symptoms and who are often diagnosed in late childhood or as adults. Patients with atypical cystic fibrosis are less likely than classical CF patients to have pancreatic insufficiency.

Clinical Features

Cystic fibrosis is a multiorgan disease. The lungs bear the brunt of the disorder with eventual recurrent severe respiratory infections leading to bronchiectasis. However, 85% of CF patients have pancreatic insufficiency and around 5 to 10% have significant cystic fibrosis related liver disease. The liver disease occurs due to chronic inflammation of the bile ducts which may eventually lead to biliary cirrhosis. Many patients with CF have a low bone mass, partly due to the effects of chronic infection, but also partly due to the presence of the CFTR mutation itself. The sweat glands function abnormally and paradoxically produce a rise in sweat chloride and sodium levels, which is used (as detailed above) to diagnose the condition. Male patients are usually infertile due to inability of sperm to pass through the blocked vas deferens. With modern fertility treatments, sperms may be aspirated from the testes of such patients and *in vitro* fertilization may be possible. Generally, females with CF are fertile. Patients with CF are at increased risk of pneumothoraces (Fig. 60.4).

The CFTR abnormality leads to the development of thick and highly viscous sputum in the airways, which is very difficult for the patient to expectorate and also is an ideal area for bacterial colonization. The bacteria involved in respiratory infections in CF patients vary according to age. *Haemophilus influenzae* and *Staphylococcus aureus* are typical bacterial infections in earlier childhood. As the patient grows older, it is more likely that *Pseudomonas aeruginosa* will become the predominant pathogen and by late teens, over 50% of patients will be colonized with this organism. Chronic colonization may then lead to intermittent acute exacerbations leading to increasing shortness of breath and increased purulent sputum volume.

Infections and Treatment

The cornerstones of treatment are techniques to reduce the viscosity of sputum, improve airway clearance, treat lung infections vigorously and use anti-inflammatory agents. There is a considerable amount of research currently underway looking at the possibility of gene therapy and also drugs to influence ion transport.

An essential part of treatment is modifying and improving the nutrition of CF patients. Pancreatic insufficiency leads to poor fat absorption, which in turn, leads to abdominal symptoms of distension, diarrhea and malabsorption. Consequently, malnutrition leads to a stunting of growth and increased risk of severe lung infections.

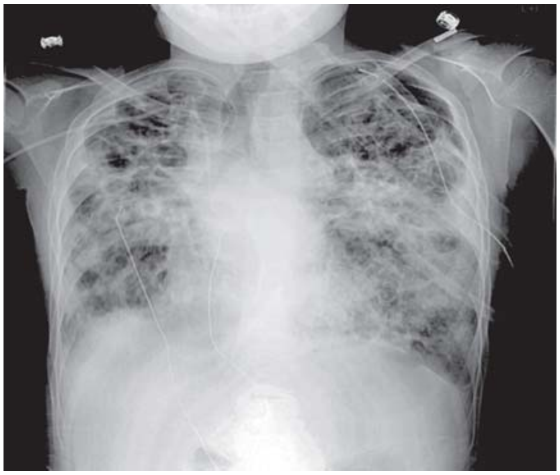

Fig. 60.4: Chest X-ray showing extensive bronchiectasis changes in a patient with cystic fibrosis. Intercostal tubes following a pneumothorax

In the early 1970s, a radical change in approach was made initially in Toronto, Canada, when a combination of high fat, high energy diets were used in combination with pancreatic enzyme supplements. Nowadays, this is the norm for managing such patients. This is extremely important because poor nutrition leads to an energy deficit with weight loss, poor respiratory muscle strength, increased pulmonary infection with increased lung damage and a vicious cycle of further lung infections.

Some patients with more advanced disease are helped by nasogastric feeding or feeding through a Percutaneous Endoscopic Gastrostomy (PEG) tube.

Other pathogens in cystic fibrosis, which are less common than *Pseudomonas aeruginosa* include the *Burkholderia cepacia* complex. These include around 14 different species or genovars. Genovars 2 and 3 are particularly infectious and damaging to the lung. Genovar 3 is called *B. cenocepacia* and this tends to be associated with the worst prognosis of patients infected with this complex. The Burkholderia complex is highly infectious and damaging to lung tissues and patients may deteriorate rapidly once they acquire this infection. Other gram-negative organisms, which may be isolated from the sputum include *Stenotrophomonas maltophilia*, Acinetobacter and Pandorea species. Some of these relatively rare gram-negative organisms may emerge due to the long-term effects of antibiotic pressure caused by the need for recurrent courses of intravenous antibiotics in CF patients. *Aspergillus fumigatus* may cause a direct necrotizing infection in the lungs, but more commonly some patients with CF may develop allergic bronchopulmonary aspergillosis.

An increasing problem in CF patients is the appearance of atypical nontuberculous mycobacteria especially Mycobacterium abscessus, but also occasionally *Mycobacterium avium-intracellulare* and *Mycobacterium kansasii*. These nontuberculous mycobacteria are usually extremely difficult to eradicate. The presence of such infection, particularly *Mycobacterium abscessus*, may be a relative contraindication to patients subsequently being accepted for lung transplantation.

CF patients have no detectable immune deficiency and bacteremia is uncommon. The altered airway secretions lead to increased sputum viscosity and then colonization with bacteria. There is a defect in the mucociliary escalator due to highly viscous sputum. Chronic infection causes collateral damage to lung tissue. The sputum itself consists of a large amount of bacterial DNA and phagocytic debris.

Exacerbations of lung infection in CF are diagnosed partly on a clinical basis in the terms of symptoms and signs, but also on evidence of a reduction in lung function particularly the FEV_1% predicted, sputum bacteriology sometimes, including bacterial counts and also X-ray or CT lung scan evidence.

Specific treatments of known bacterial infections in CF are as follows:

Staphylococcus aureus is usually treated with drugs such as flucloxacillin or fusidic acid. Some patients acquire MRSA and may require intravenous vancomycin, teicoplanin or oral/IV linezolid.

Haemophilus influenzae is often treated with co-amoxiclav.

Pseudomonas aeruginosa may be sensitive to oral ciprofloxacin and in some countries oral chloramphenicol is used (although there are concerns about its side effect of aplastic anemia). Often, *Pseudomonas aeruginosa* treatment requires intravenous antibiotics. The usual practice is to give at least two intravenous antibiotics together to reduce the risk of emergence of bacterial resistance.

High doses of intravenous antibiotics are often required in CF because of increased renal clearance of some antibiotics and also concerns about antibiotic penetration into the mucoid forms of *Pseudomonas aeruginosa* often with associated biofilms. Typical combinations for IV antibiotic use in CF include: Ceftazidime plus tobramycin or ceftazidime plus colomycin/colistin. Alternative to ceftazidime include meropenem, Tazocin or aztreonam.

If tobramycin or gentamicin is used, it is essential to check blood levels particularly the trough levels, to make sure that excessive doses are not leading to accumulation in the blood which may lead to toxicity to the inner ear and/or the kidneys.

Increasingly long-term nebulized antibiotics are used in CF patients who are colonized with *Pseudomonas aeruginosa*. The aim is to reduce the bacterial load in the lungs and delay tissue damage. Typical examples of nebulized antibiotics that are currently in use include tobramycin and colistin. Other nebulized forms of antibiotics are also currently being assessed, e.g. aztreonam, meropenem and ciprofloxacin.

Duration of IV antibiotic treatment is often around 14 days for pseudomonal infections. The dose and frequency of dosing with antibiotics depends partly on the type of antibiotic used. Some antibiotic effects are concentration dependent, i.e. the higher the peak blood level, the more effective it is, e.g. tobramycin. The idea here is to give high infrequent doses. Recently, single daily doses of tobramycin have become the norm rather than dosing two or three times per day. Other beneficial antibiotic effects depend upon the time above the minimum inhibitory concentration of that antibiotic for a particular bacterial infection. An example of this is ceftazidime. In this case, it is better to give frequent doses or even a continuous infusion rather than a single daily dose.

Lung function testing in CF usually occurs at each outpatient visit. Spirometry is the usual measurement made. As the disease progresses, the FEV_1% predicted progressively deteriorates. A decline in FVC is less rapid. It is important to recognize and to treat lung infections at an early age in children to try and delay airway colonization and to delay the rate of lung function decline with age.

The commonest way of now assessing pancreatic dysfunction is to measure fecal pancreatic elastase-1 levels in a small sample of feces rather than carrying out three or five day fecal fat collection. The more advanced the pancreatic disease, the lower the fecal 1 elastase level becomes.

Nutrition in CF usually aims for a high calorie, high fat diet often with additional food supplements. Sometimes, in addition, nasogastric or gastrostomy feeding is used. It is important to give oral fat soluble vitamin supplements to patients with CF related pancreatic deficiency, i.e. vitamins A, D, E and K.

Some older children and adults may develop abdominal distension and blockage due to Distal Intestinal Obstruction Syndrome (DIOS), previously called meconium ileus equivalent. Clinically, the patient complains of abdominal pain, bloating, vomiting or constipation. On examination, there may be a palpable lump in the right iliac fossa and a plain abdominal X-ray may show fecal loading and sometimes fluid levels. Treatment involves the use of bowel cleansing solutions.

CF related liver disease can lead in severe cases to biliary cirrhosis, which may then lead to portal hypertension. There are lung complications associated with severe liver diseases, including intrapulmonary shunting, pulmonary hypertension and respiratory muscle weakness due to poor nutrition. Also hepatomegaly may cause the right diaphragm to be raised and low blood albumin levels may lead to the onset of ascites and/or pleural effusions. Treatment includes the daily use of oral ursodeoxycholic acid. In severe cases, liver transplantation may be indicated.

The management of CF is based around a multidisciplinary team approach. The CF team consists of doctors, nurses, physiotherapists, dieticians and clinical psychologists with additional input from specialists in diabetes, liver disease, infertility, etc.

Chest physiotherapy is essential to help the patient clear the airways and there are a variety of physical maneuvers and mechanical devices, which aid sputum production. Nebulized bronchodilators are often used to help as well. Also many patients use a nebulized drug called DNase (dornase alfa), which is a drug that acts by cleaving bacterial DNA in the sputum, making it less viscous. The usual dose in adults is 2.5 mg nebulized once daily.

Other Treatments

There has been considerable interest in the development of anti-inflammatory drugs. Initially ibuprofen was used, but a significant number of patients suffered from side-effects from this medication. More recently, the macrolide antibiotic azithromycin has been used in a single daily dose of 250 mg in adults for its anti-inflammatory effects. Several studies have shown an improvement in lung function, quality of life and fewer infective exacerbations. Oral steroids may also have a beneficial effect in some patients, but of course this needs to be weighed against the problems of long-term side effects, particularly osteoporosis.

Cross infection between CF patients can be a serious problem. This was first recognized with *Burkholderia cepacia* infections, but more recently epidemic forms of *Pseudomonas aeruginosa* have been described and some of these epidemic forms may be more pathogenic than sporadic forms. Therefore, in outpatient clinics, both spacial and temporal separation of patients is required.

Lung transplantation should be considered when the patient's lung function has declined with an FEV_1% predicted of 30% or less.[34] When patients reach that level of lung function, the two year survival is around 50% and the potential advantages of lung transplantation should then be discussed with the patient.

Gene therapy is also being investigated in research trials at the moment. The main problem has been finding a suitable vector, which enables sufficient epithelial cells to become transfected with subsequent incorporation of the normal gene into the host's genome. Initial results appear very promising.

Prognosis

The median survival for cystic fibrosis has shown a remarkable improvement over the past few decades. For instance in the United States in 1985, the median survival was 25.5 years and in 2001, it was around 37 years. Generally, survival is better in patients who are pancreatic sufficient. Median survival is slightly better in males in comparison to female patients and is better in patients who have group 4 or group 5 CF mutations. There is also a close correlation between survival and poor nutritional status. Around 40% of adults with cystic fibrosis have CF-related diabetes. There is some evidence that raised airway glucose concentrations may increase the likelihood of frequent and more severe respiratory infections.

Finally, the story of the unraveling of the pathogenesis of cystic fibrosis and subsequent development of effective treatments has been one of medicine's great success stories during the past few decades. The management of the condition also serves as a model for multidisciplinary team working.

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Rare Respiratory Infections

Mohankumar Thekkinkattil, S Arulmozhi

INTRODUCTION

There is an increased recognition of new and rare respiratory infections in clinical practice. These are attributed to the emergence of new pathogens especially in the immunocompromised patients.

VIRAL INFECTIONS

Several viruses complicate the course of Chronic Obstructive Pulmonary Disease (COPD), bronchial asthma and in patients in Intensive Respiratory Care Unit (IRCU). Immunosuppressed patients are susceptible to infections from cytomegalovirus, herpes viruses, adenoviruses and paramyxoviruses. Infections from hantaviruses, human metapneumoviruses, avian influenza A viruses and viruses of Severe Acute Respiratory Syndrome (SARS) and their mutations have been reported in the recent years. Upper respiratory tract infections due to viruses present with well-defined clinical syndromes according to the virulence and the dose of the viruses, and the resistance of the host.[1,2]

Human Metapneumovirus

Human Metapneumovirus (HMPV) is a human pathogen, which resembles Respiratory Syncytial Virus (RSV), causes respiratory illness in all age groups.[3-5] HMPV infection in children often exists with other respiratory virus infections especially the RSV. Maximum number of cases occurs during winter.[6,7] Clinical presentation varies from very mild to severe bronchiolitis and pneumonitis. The clinical features are often mistaken as RSV infection in children. It is common to have bronchiolitis, wheezing and severe hypoxemia, in children who are hospitalized. Nasal secretion levels of the virus chemokines RANTES are reported as suppressed whereas levels of IL8 are increased.[8]

Hantavirus Pulmonary Disease (HVPD)

Hantavirus pulmonary disease or Hantavirus hemorrhagic fever is an endemic zoonosis, which affects both adults and children in Europe and Asia. It has been also reported from India.[9] The causative agents belong to the genus hantavirus, of family Bunyaviridae.[9,10] It is carried by specific rodent host species, but host switches have been reported.[10,11] The clinical picture varies from place-to-place with the type of infection. Hemorrhagic complications like disseminated intravascular coagulopathy, severe thrombocytopenia, shock, oliguric renal failure, pleural effusion, ascites, neurological complications like hemiparesis, epilepsy and seizures are possible in this virus infection.[12-14] These infections are usually diagnosed by using IgM capture test and/or RT-PCR detection of viral RNA. Neutralization tests and gene sequencing are required for genotyping and serotyping. Immunofluorescence Immunoassay (IFA) or Enzyme-linked Immunosorbent Assay (ELISA) are also done in some cases.[15]

BACTERIAL INFECTIONS

Reye's-like syndrome associated with pertussis infection is generally seen in woman in coma with acute liver dysfunction, severe hypoglycemia and prolonged prothrombin time, may be mistaken for aspirin-induced Reye's syndrome.

Hemolytic-uremic syndrome in streptococcal pneumonia, is mainly seen in the young children, the morbidity and mortality are high. Pneumonia, disseminated intravascular coagulopathy, chronic renal and respiratory failure are important clinical features.[15] Lemierre's syndrome can rarely produce complications like septic arthritis, sternoclavicular joint sepsis and cavitating pneumonia.[16] The clinical features include fever, myalgia, tachypnea and tachycardia. Sometimes *Salmonella* can also involve the lungs.

Salmonella infections apart from the usual pneumonitis, can also produce myocarditis. Multiple organ failure in a previously healthy adult with or without fever, diarrhea, and shortness of breath, altered sensorium, acute pulmonary edema and respiratory failure should warrant a differential diagnosis of *Salmonella* infection. In some patients, hepatic and muscular enzymatic surge, rhabdomyolysis and disseminated intravascular coagulation have been reported.[17]

Streptococci in rare cases produce severe bacteremia and toxic shock syndrome in adults. High fever and tonsillopharyngitis, are often observed.

Community-acquired pneumonia by **Acinetobacter baumannii** is rare though an important example of nosocomial pneumonia. In subtropics, this is one of the causes of severe community-acquired pneumonia. The pathology consists of prominent cellular alveolar exudates with partial hyaline membrane and suppurative pneumonia.

RARE FORMS OF TUBERCULOUS INFECTIONS

Human tuberculosis typically caused by *Mycobacterium tuberculosis* complex, can rarely occur due to **rare genetic variants** such as *M. canettii*, *M. microti* and *M. pinnipedii*. The natural reservoir, mode of transmission and host factors are not well studied. So far, there is no drug resistance and the species are susceptible to rifampicin, pyrazinamide and ethambutol. Delayed growth on the solid media, contact with animals and special phenotypic pictures should be borne in mind for the diagnosis of these forms.[18]

Mycobacterium asiaticum was reported first in 1982. Chronic lung disease was a risk factor for pulmonary infection. It can produce both pulmonary and extrapulmonary disease. It responds well to standard anti-TB regimens.[19]

CHLAMYDIAL INFECTIONS

Chlamydia psittaci on intracellular gram-negative bacterium, which causes psittacosis has seven genotypes, A to F, which can be transmitted to humans from the bird's feces. The incidence seems to increase in the Western world . Clinical presentation varies from febrile episodes to the occurrence of severe pneumonia.[20] Pleuritic pain and dyspnea are common. Chest radiography shows ground-glass opacity with small areas of radiolucency. Hilar lymph nodes are involved in most of the cases.

Nocardia asteroides, an aerobic nonspore-forming bacterium can produce pulmonary nocardiosis. Clinical features include the presence of cough, increased sputum production, pleural pain and microabscesses. X-ray findings show air space consolidation and multilobar, nonsegmental nodules. True infection may involve the pleural space with effusions and empyema. The prognosis is good with treatment.[21]

Pulmonary actinomycosis is a relatively rare disease caused by *Actinomyces israelii*. Though they are gram-positive bacteria, the characteristic branching filaments clustered with neutrophils (sulfur granules) usually require special stain to diagnose. Coinfection with *S. aureus* increases the pathogenicity. It usually presents with pneumonia, mass-like consolidation will mimic malignancy. Airway obstruction is common.[22] Penicillin is the mainstay of treatment. Periodic therapeutic bronchoscopy may felicitate medical treatment.

Melioidosis (Whitmore's Disease)

Melioidosis is caused by *Burkholderia pseudomallei*, a bacterium. It is an infectious disease seen in humans, as well as in animals such as sheep, goats, horses, cattle, dogs and cats. Humans with underlying chronic illnesses through direct contact with the contaminated soil and water in endemic areas are more at risk of acquiring the infection. Pulmonary melioidosis may present as an acute or a chronic suppurative form. In acute pulmonary infection, the onset is associated with high-grade fever, headache, anorexia, chest pain, generalized myalgia, and productive cough with normal sputum production or with nonproductive cough. Patient may present with the symptoms of mild bronchitis to those of severe pneumonia. Lung abscess and empyema may also occur. Melioidosis is diagnosed from the blood, sputum or skin lesions by serology or by isolating *Burkholderia pseudomallei*. Radiological investigations like chest X-ray and CT thorax may show features of pneumonia. Treatment with antibacterials should be started as early as possible to prevent the progression. Drugs like penicillin, doxycycline, amoxicillin-clavulanic acid, imipenem, aztreonam or ceftriaxone are given intravenously for treatment.[23]

Tularemia (Rabbit Fever)

Francisella tularensis is a gram-negative facultative intracellular bacteria, which causes tularemia in animals. The organism that spreads by aerosol transmission, is highly virulent. Tularemia can be transmitted to humans by contact with infected animals or blood sucking arthropods like ticks, deer flies and mosquitoes. Pneumonic tularemia follows inhalation of *F. tularensis* during lawn mowing or bush cutting, which disturbs the carcasses and facilitate the release of bacterial aerosols. Patients present with cough, dyspnea, fever, chills, headache and pleurisy. Chest X-ray shows bronchopneumonia, hilar node enlargement with or without pleural effusion. Treatment with streptomycin or gentamicin subsides the symptoms.[24]

Rhodococcus equi

Formerly recognized as *Corynebacterium equi*, an opportunistic pathogen, causes pneumonia. It was commonly found in animals such as horses and cattle. In immunocompromised patients, R. equii causes pulmonary manifestations without any animal contact. In immunocompetent individuals, exposure to animals or soil contaminated with the animal waste is important to cause *Rhodococcus* disease. Patients usually present with the symptoms of pneumonia. Erythromycin, rifampicin and fluoroquinolones are recommended for treatment.

Moraxella catarrhalis

Moraxella catarrhalis was initially recognized as a commensal of pharynx. In recent years, it is shown to have significant pathogenicity in humans. *M. catarrhalis* requires iron for its growth in tissues. This organism utilizes hemoglobin as the source of iron.[25] Expression of type IV pillai, which in turn are affected by iron deficiency is required for natural persistent colonization of *M. catarrhalis* on mucosal surface.[26] The iron deficiency or inadequate heme component of hemoglobin is the vital factor for *M. catarrhalis* to become invasive.[27]

Meningococcal Pneumonia

Neisseria meningitidis colonizes the nasopharyngeal mucosa in 5 to 10% patients, but invasive disease is rare. Preceding viral respiratory infection facilitates the invasion. Patients present with fever, chills productive cough and pleuritic pain. Radiographic picture shows focal pneumonia. Rarely, *N. meningitidis* may cause interstitial pneumonitis, and the clinical picture resembles that of viral pneumonia. Histopathologically, the lung shows diffuse generalized, inflammation of the alveolar septa with intra-alveolar edema. The bacteremia results in lodging of the organisms and of meningococcal antigens in the interstitial capillaries of the lung. Diagnosis is made by immunohistochemical analysis and real time PCR assays. Antibiotics of penicillin group and cephalosporins are used for treatment. immunoprophylaxis is advisable for high-risk groups.[28-30]

PARASITIC INFECTION

Balantidium coli, a ciliated protozoan commonly causes intestinal infection. There are some rare cases of lung involvement. Thick-walled upper lobe cavity in a farmer with exposure to pig manure was reported with the disease. Bronchoalveolar lavage fluid showed trophozites of *B. coli*.[31] Doxycycline is the drug of choice.

Parasitic Pneumonias

Parasitic pneumonias are seen in many protozoan and helminthic infections. During the larval stage, the parasite passes through pulmonary circulation, gets sequestered resulting in pneumonia. Sometimes, pneumonia may result from direct extension from the contiguous sites. If left untreated, it may result in life threatening problems.[32] Due to the wide travel across continents and globalization, the parasitic diseases are now reported from all over the world, not only from the tropical and the subtropical regions. Parasitic pneumonias can be caused by protozoa, trematodes, cestodes and nematodes. *Leishmania donovani* causes pulmonary leishmaniasis in lung transplant patients and in other immunocompromised patients. *Entamoeba histolytica* infection results pulmonary amebiasis.

Tropical pulmonary eosinophilia present as chronic mild interstitial lung disease is caused by *Wuchereria bancrofti* and *Brugia malayi*.

Pulmonary dirofilariasis is caused by *Dirofilaria immitis* and *Dirofilaria repens*.

Pulmonary Malaria

Plasmodium falciparum, as well as *Plasmodium vivax* can cause pulmonary manifestations, in the severe forms of malaria. There is no typical malarial pneumonitis, and it may occur due to secondary bacterial or viral infections. The clinical symptoms consist of fever, cough and respiratory distress. Noncardiogenic pulmonary edema may sometimes occur. Diffuse interstitial edema, lobar consolidation, pulmonary edema and pleural effusion are important radiological findings. Treatment for severe malaria consists of injectable artemisinin, parenteral chloroquine, quinidine gluconate, and quinine hydrochloride. In severe respiratory distress conditions mechanical ventilation is recommended.[32]

ZOONOTIC BACTERIAL PNEUMONIAS

Yersinia enterocolitica of Enterobacteriaceae, commonly results in gastroenteritis. It can rarely cause pneumonias in immunocompromised individuals. Bacteremia causes spontaneous pleural empyema. Children are equally affected as adult. Treatment consists of third-generation cephalosporins, quinolones and chloramphenicol. Management of empyema may also require intercostal tube drainage and intrapleural fibrinolysis.[33-37]

Pasteurella multocida Infection

P. multocida may cause infection in humans following animal bite, scratch or lick, but may occur even without animal contact. Upper respiratory tracts are colonized by the *Pasteurella multocida* as commensals in cats and dogs, poultry, and domestic pet animals. *P. multocida* infection may occur in healthy, as well as immunocompromised persons. It affects all age groups, but more commonly in young children who have contact with pet animals. Elaborate history is needed to elicit exposure to animals. Skin manifestations, following animal bite mimic *Streptococcus pyogenes* infection. Pulmonary manifestations consist of sinusitis, otitis media, pharyngitis, mastoiditis, epiglottitis and Ludwig's angina. In cases with pre-existing chronic pulmonary disease, *P. multocida* may cause pneumonia, tracheo-bronchitis, lung abscess and empyema. Chronic obstructive pulmonary disease increases the mortality by 30%. The clinical presentation consists of hoarseness of voice, sinus tenderness and pharyngeal erythema. In addition to routine wound care for animal bite and vaccination prophylaxis, empirical antibiotic therapy is recommended for treatment. Oral antimicrobials like amoxicillin, amoxicillin-clavulanic acid combination, second-generation cephalosporins, carbapenems and fluoroquinolones are effective. In severe infections, parenteral antibiotics are recommended.[38-41]

Yersinia pestis

Yersinia pestis, a rod-shaped (safety pin appearance) facultative gram-negative anaerobe, can infect both humans and animals.[42] Commonly, rodents are the reservoir host for *Y. pestis*. In human plague outbreaks, fleas from other mammals may also have some role.[43] The vector, fleas acquires *Y. pestis* during feeding on an infected rodent.[44] Transmission of *Y. pestis* infection from rodents to humans occurs by skin contact. Human-to-human infection spreads by sneezing, coughing or through direct contact with the infected tissue. *Y. pestis* infection may clinically present in three forms: Bubonic plague, septicemic plague and pneumonic plague.

In pneumonic plague, the symptoms of the other two types are not always seen. Patients are present with various symptoms such as cough, dyspnea, fever, chills, chest pain, hemoptysis, hypotension, lethargy and shock. During severe bacteremia, several organs are affected resulting in disseminated intravascular coagulation and bleeding. Necrosis of skin and soft tissue, increases the mortality by over 20%. Early diagnosis of plague is difficult since the initial symptoms may mimic many other diseases.[45] Treatment is given with intravenous antibiotics for pneumonic plague. Streptomycin, gentamicin, chloramphenicol and fluoroquinolones are the first-line drugs used for the treatment.

In conclusion, the diagnosis of rare respiratory diseases requires taking a good clinical history, awareness of these diseases and appropriate diagnostic procedures. The list is not complete. The emergence of new pathogens, with modified lifecycles, newer genetic transformations, and mutations make rare infections a difficult proposition in the terms of diagnosis and treatment.

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Parasitic Lung Diseases

VK Vijayan

INTRODUCTION

Lung diseases due to parasitic infections are common in tropical regions of the world.[1] However, these diseases are now being increasingly reported from many parts of the world due to globalization and travel across the continents.[2] The emergence of Human Immunodeficiency Virus (HIV) infection/Acquired Immunodeficiency Syndrome (AIDS), the frequent use of immunosuppressive drugs in many diseases and organ transplantations have also resulted in resurgence of parasitic lung infections.[3,4] Though many parasitic infections have a benign course, a large number of parasitic infections may cause considerable morbidity and mortality.[5] The important pulmonary diseases that can occur due to parasitic infections are listed in Table 62.1.

Pulmonary Amebiasis

Amebiasis is one of the most common infections in the world. It has been estimated that approximately 50 million cases of invasive amebiasis occur worldwide each year, with up to 100,000 deaths. Ingestion of mature *Entameba histolytica* cysts through fecal contaminated food, water or hands causes infection. The trophozoites released in the intestine pass through the bloodstream to reach extraintestinal sites, such as liver, and lungs resulting in pathological lesions. Pulmonary amebiasis occurs primarily due to extension of the amebic liver abscess.[6] The main manifestations of pleuropulmonary amebiasis are fever, right upper quadrant abdominal pain, chest pain and cough. Hemoptysis and expectoration of "anchovy sauce-like" pus indicates amebiasis.

The diagnostic findings in pleuropulmonary amebiasis are elevated hemidiaphragm, tender hepatomegaly, pleural effusion and basal pulmonary involvement. Active trophozoites of *E. histolytica* can be demonstrated in the sputum or pleural pus. Microscopic examination of stool samples may reveal cysts or trophozoites of amebae. The presence of ameba in the stool does not signify that the disease is due to *E. histolytica* as two nonpathogenic species found in humans (*E. dispar* and *E. moshkovskii*) are indistinguishable morphologically. Other diagnostic tests include culture of *E. histolytica* and serological tests [indirect hemagglutination test, Enzyme-linked Immunosorbent Assay (ELISA) and indirect fluorescent antibody test.]

Nitroimidazoles (metronidazole or tinidazole) are the main drugs used for the treatment of invasive amebiasis.[7] Metronidazole is given in a dose of 750 mg orally three times a day for 7 to 10 days. Tinidazole can be prescribed in a dose of 800 mg orally three times a day for 10 days. Treatment with nitroimidazole should be followed by treatment with a luminal amebicidal drug (paromomycin or diloxanide furoate) to cure intestinal luminal infection. Paromomycin is given as the total amount of 25 to 35 mg/kg per day in three divided doses for seven days or diloxanide furoate in a dosage of 500 mg orally three times a day for 10 days.

Pulmonary Leishmaniasis

The important protozoan parasites that cause leishmaniasis are *Leishmania donovani*, *Leishmania tropica*,

TABLE 62.1: Pulmonary diseases caused by parasitic infections

Diseases	*Parasites*
I. Protozoa	
1. Pulmonary amebiasis	*Entamoeba histolytica*
2. Pulmonary leishmaniasis	*Leishmania donovani*
3. Pulmonary malaria	*Plasmodium vivax*
	Plasmodium falciparum
	Plasmodium malariae
	Plasmodium ovale
	Plasmodium knowlesi
4. Pulmonary babesiosis	*Babesia microti*
	Babesia divergens
5. Pulmonary toxoplasmosis	*Toxoplasma gondii*
II. Helminths	
a) Cestodes	
1. Pulmonary cystic hydatidosis	*Echinococcus granulosus*
2. Pulmonary alveolar echinococcosis	*Echinococcus multilocularis*
b) Trematodes	
1. Pulmonary schistosomiasis	*Schistosoma haematobium*
	Schistosoma mansoni
	Schistosoma japonicum
2. Pulmonary paragonimiasis	*Paragonimus westermani*
c) Nematodes	
1. Pulmonary ascariasis	*Ascaris lumbricoides*
2. Pulmonary ancylostomiasis	*Ancylostoma duodenale*
	Necator americanus
	Ancylostoma ceylanicum
3. Pulmonary strongyloidiasis	*Strongyloides stercoralis*
4. Tropical pulmonary eosinophilia	*Wuchereria bancrofti*
(Filarial infection)	*Brugia malayi*
5. Pulmonary dirofilariasis	*Dirofilaria immitis*
	Dirofilaria repens
6. Visceral larva migrans	*Toxocara canis*
	Toxocara cati
7. Pulmonary trichinellosis	*Trichinella spiralis*

Source: Vijayan VK. Parasitic lung infections. Curr Opin Pulm Med 2009; 15(3):274-82.

Leishmania major and *Leishmania infantum*.[8] Various species of female *Phlebotomus* (the sand fly) transmits infection to man.[9] Leishmaniasis is endemic in Bangladesh, India, Nepal, Sudan and Brazil. It is seen predominantly in North Bihar, adjoining districts of West Bengal and eastern districts of Uttar Pradesh. Leishmaniasis and HIV infections often coexist in a deadly synergy and leishmaniasis accelerates the onset of AIDS in persons infected with HIV.[10] Visceral leishmaniasis is characterized by irregular fever, weight loss, enlargement of liver, and spleen and anemia. Pneumonitis, septal fibrosis, pleural effusion and mediastinal adenopathy are reported in patients coinfected with HIV. Leishmaniasis has also been reported in lung transplant patients.[11] *Leishmania* amastigotes can be found in the alveoli, pulmonary septa and Bronchoalveolar Lavage (BAL) fluid.

Diagnosis of leishmaniasis is by the demonstration of the parasites in bone marrow aspirates and by the demonstration of specific DNA sequences in tissues by molecular biology techniques. The treatment of leishmaniasis includes use of drugs such as amphotericin B, especially the liposome formulations and pentavalent antimonials.[12]. Liposomal amphotericin B is prescribed in a dosage of 3 mg/kg/day intravenously on days 1, 5, 15 and 21. Sodium stibogluconate is given in a dosage of

20 mg/kg daily intravenously or intramuscularly for 28 days.[8] Miltefosine, the first oral drug used for the treatment of visceral leishmaniasis is prescribed in a dosage of 2.5 mg/kg daily orally for 28 days and the maximum daily dose is 150 mg.[13] A single infusion of liposomal amphotericin B (in a dose of 10 mg/kg body weight) has been found to be as effective as conventional therapy with amphotericin B deoxycholate.[14]

Pulmonary Malaria

The malarial parasites that may infect humans are *Plasmodium vivax, P. falciparum, P. malariae, P. ovale and P. knowlesi* and are transmitted primarily by the bite of an infected female *Anopheles* mosquito. Falciparum malaria is the most deadly type of malaria infection.[15] The pulmonary manifestations range from cough to severe and rapidly fatal noncardiogenic pulmonary edema and Acute Respiratory Distress Syndrome (ARDS). Acute lung injury and ARDS have also been reported to occur in 3 to 30% of patients with severe malaria and has been described with falciparum, vivax and ovale malaria.[16,17] Acute lung injury and ARDS usually occur within a few days of onset of the disease, and even after initial response to antimalarial treatment and clearance of parasitemia. Pulmonary manifestations are common in children, pregnant women and travelers with malaria.[18] Pneumonia in malaria is also due to secondary bacterial infection. Pleural effusion is rarely reported in malaria. Light microscopy of stained thick and thin blood smears is the gold standard for the diagnosis of malaria. Thin smears allow identification of malaria species. Radiological findings in severe falciparum malaria include lobar consolidation, diffuse interstitial edema, pulmonary edema and pleural effusion. A polymerase chain reaction detection of *Plasmodium falciparum* in human urine and saliva samples has also been described.[19]

The drugs used for the treatment of severe malaria are quinine dihydrochloride, quinidine gluconate and injectable artemisinin derivatives. Artemisinin-based combination therapies (artesunate and sulfadoxine-pyrimethamine, artesunate and amodioquine, artesunate and mefloquine or artemether and lumefantrin) are amongst the best antimalarial drugs.[20] Quinine dihydrochloride is given Intravenously (IV) as a loading dose of 20 mg salt/kg body weight (bw) diluted in 10 ml/kg bw of 5% dextrose or dextrose saline over four hours. It is followed by the administration of maintenance dose of 10 mg/kg salt diluted in 10 ml/kg bw of 5% dextrose saline IV over four hours repeated every eight hours until the patient can swallow. Then quinine tablets are prescribed in a dose of 10 mg salt/kg bw every eight hours in combination with doxycycline or clindamycin to complete a seven-day-treatment course. Quinidine gluconate reconstituted in normal saline is infused IV in a dose of 10 mg/kg bw over one to two hours followed by a maintenance dose of 0.02 mg/kg per minute continuous infusion for at least 24 hours followed by oral medication. Artesunate is given as a loading dose of 2.4 mg/kg IV bolus at 0, 12 and 24 hours followed by the maintenance dose of 2.4 mg/kg daily for seven days. Artesunate is dispensed as a powder of artesunic acid and this is dissolved in 5% sodium bicarbonate to form sodium artesunate. The solution is then diluted in 5 ml of 5% dextrose which is given by IV injection. Once the patient can tolerate oral therapy, parenteral therapy is switched to a complete treatment course of an Artemisinin-Based Combination Therapy (ACT). Artemether is given as a loading dose of 3.2 mg/kg IM followed by the maintenance dose of 1.6 mg/kg IM daily.

The patients presenting with ARDS require invasive mechanical ventilation with intensive care management.[21] Early positive-pressure ventilation with lung protective strategy using low tidal volumes and appropriate Positive End Expiratory Pressure (PEEP) in volume assist control mode help to prevent the high mortality associated with ARDS in severe malaria.

Pulmonary Babesiosis

Babesiosis is caused by hemoprotozoan parasites, *Babesia microti* and *Babesia divergens.*[22] Man gets the infection by the bite of an infected tick, *Ixodes scapularis* and can also be infected from a contaminated blood transfusion. The parasite attacks the red blood cells and can be misdiagnosed as malaria. The risk factors for systemic infection are immunosuppression, advanced age and splenectomy. The symptoms are fever, drenching sweats, cough, tiredness, loss of appetite, myalgia and headache. Acute respiratory distress syndrome occurring a few days after initiation of medical therapy is an important pulmonary manifestation.[23] Chest radiological features include bilateral infiltrates with an alveolar pattern and thickening of the septa. Specific diagnosis is made by the examination of a Giemsa-stained thin blood smear, DNA amplification using PCR or detection of specific antibody. The peripheral blood smears may show, in addition to ring forms, tetrads inside the red blood cells. These tetrads known as Maltese cross formations are pathognomonic of babesiosis and are not seen in malaria.[24] Treatment is with a combination of clindamycin (600 mg every 6 hours) and quinine (650 mg every 8 hours) for 7–10 days or Atovaquone (750 mg every 12 hours) and azithromycin (500–600 mg on first day and 250–600 mg on subsequent days) for 7–10 days.[25]

Pulmonary Toxoplasmosis

Toxoplasmosis is caused by the protozoan parasite, *Toxoplasma gondii*. Cats are the primary carriers of the organism.[26] Human gets the infection by eating parasitic cystcontaminated raw or undercooked meat, vegetables or milk products. The symptoms of toxoplasmosis are flu-like syndrome, enlarged lymph nodes or myalgia. Pulmonary toxoplasmosis has been reported with increasing frequency in patients with HIV infection. Toxoplasma pneumonia can manifest as interstitial pneumonia/diffuse alveolar damage or necrotizing pneumonia. Diagnosis of toxoplasmosis is based on the detection of the protozoa in body tissues. A real-time PCR-based assay in BAL fluid has been reported in HIV-positive patients.[27,28] Toxoplasmosis can be treated with a combination of pyrimethamine (25–100 mg per day orally) and sulfadiazine (1–1.5 gram four times a day orally) for three to four weeks.[8]

TABLE 62.2: Rare pulmonary protozoal infections in immunocompromised individuals

Diseases	*Parasites*
1. Pulmonary acanthamebiasis	*Acanthamoeba castellanii* *Acanthamoeba polyphaga*
2. Pulmonary balamuthiasis	*Balamuthia mandrillaris*
3. Pulmonary naegleriasis	*Naegleria fowleri*
4. Pulmonary trichomoniasis	*Trichomonas vaginalis* *Trichomonas tenax* *Trichomonas hominis*
5. Pulmonary lophomoniasis	*Lophomonas blattarum*
6. Pulmonary trypanosomiasis	*Trypanosoma cruzi* *Trypanosoma brucei gambiense* *Trypanosoma brucei rhodesiense*
7. Pulmonary cryptosporidiosis	*Cryptosporidium parvum* *Cryptosporidium hominis* *Cryptosporidium meleagridis*
8. Pulmonary cyclosporiasis	*Cyclospora cayetanensis*
9. Pulmonary encephalitozoonosis	*Encephalitozoon cuniculi* *Encephalitozoon hellem* *Encephalitozoon intestinalis*
10. Pulmonary entercytozoonosis	*Enterocytozoon bieneusi*
11. Pulmonary balantidiasis	*Balantidium coli*

Source: Vijayan VK. Parasitic lung infections. Curr Opin Pulm Med 2009; 15(3):274-82.

Rare Pulmonary Protozoal Infections

Free living *Acanthameba* species can cause systemic disease with pulmonary manifestations of nodular infiltrates, pneumonitis and respiratory failure in immunocompromised patients.[29] *Cryptosporidium parvum* infection has been reported to produce interstitial pulmonary infiltrates and focal areas of consolidation in AIDS patients.[30] Recurrent aspiration secondary to mega esophagus can lead to pneumonitis, lung abscess and bronchieactasis in *Trypanosoma cruzi* infection (Chagas disease). Cardiogenic pulmonary edema and pulmonary hypertension secondary to cardiac failure and dilated cardiomyopathy have also been reported in Chagas disease.[31] East African trypanosomiasis due to *Trypanosoma brucei rhodesiense* has been reported to cause noncardiogenic pulmonary edema and ARDS in acute stage. Other rare pulmonary protozoal infections that have been reported in immunocompromised individuals are listed in Table 62.2.[8]

Pulmonary Cystic Hydatidosis

Cystic hydatidosis or hydatid cyst caused by *Echinococcus granulosus* is a serious health problem in most parts of the world particularly in sheep-raising areas of the Mediterranean countries, Middle East, the Balkan, South America, Australia and New Zealand. Dogs are the definitive hosts and sheep the main intermediate host. The liver is the primary location followed by the lungs.[32] Typically, the larvae that pass through or bypass the liver filter are trapped in pulmonary arterial capillaries. The entrapped larvae develop into hydatid cyst that grows gradually and often complicate by rupturing in the airway or less commonly in the pleural space. Secondary pulmonary hydatidosis may occur by rupture of a liver cyst in vena caval circulation or a heart cyst in the right ventricular cavity or primary lung cyst in the bronchi, and then seeding the protoscolices along the bronchial tree. In the majority of cases, primary lung hydatidosis is single. Multiple hydatidosis may be unilateral or bilateral. Patients are asymptomatic in the initial stages of infection. Chest pain, hemoptysis, dyspnea or allergic reaction may appear subsequently. Bronchial rupture of the cyst can result in the vomiting of contents of hydatid cysts. Intrapleural rupture may be acute leading to hydropneumothorax or empyema, or insidious with the delayed development of secondary pleural hydatidosis.

Secondary metastatic hydatidosis is often associated with the obstruction of pulmonary artery branches resulting in chronic hydatid cor pulmonale. Vomiting of small or entire hydatids is a specific sign called "hydatidoptysis."

Diagnosis of pulmonary hydatid cyst is still based on radiography and non-complicated cyst presents as well defined homogenous hydrous round ("cannon ball") opacity that may be lobulated by contiguous bronchovascular axes. Fissured or ruptured cyst in the bronchi may have the characteristic findings of "air crescent," pneumocyst, floating membrane, ring within a ring or completely empty cavity images. Thoracic ultrasonography may be useful if the cyst is accessible to ultrasound examination. It may confirm the cystic structure showing the characteristic double contour aspect (the pericyst and the parasite membrane endocyst) in non-ruptured cysts. Detached or retracted membrane may be observed in ruptured cysts. Daughter cysts are diagnostic in lung hydatidosis. Liver and abdomen ultrasound study is generally systematically performed to search for associated abdominal hydatid cysts. CT is helpful in doubtful cases, as it can analyze the internal structure of the cyst and measure the density; and evaluate the state of the neighboring parenchyma, the whole thorax and abdomen for associated cystic lesions or anomalies (Fig. 62.1).[2,33] Laboratory tests are complementary to clinical and imaging investigations. Eosinophils can be slightly increased in complicated cysts. Serological tests are less sensitive in patients with lung hydatidosis (65%) than in those where hydatid cysts are localized in liver (80% to 94%).[34]

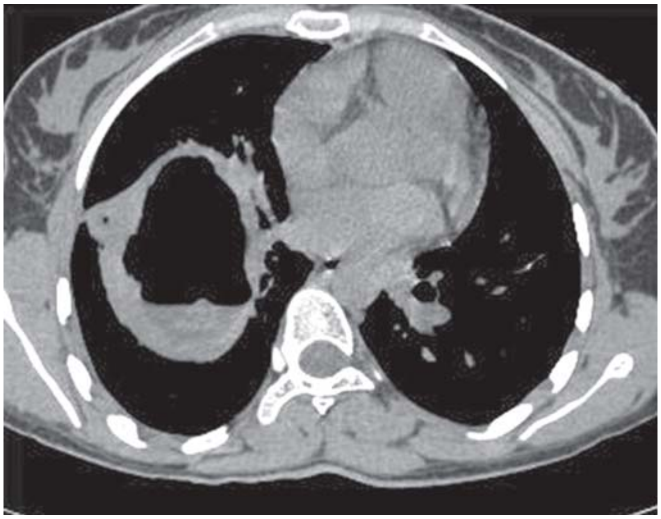

Fig. 62.1: Thoracic CT scan in a patient with cystic hydatid disease *(Source: Vijayan VK. Parasitic lung infections. Curr Opin Pulm Med 2009; 15(3):274-82).*

Surgery is the main treatment for pulmonary hydatidosis and aims to remove the parasite and treat associated parenchymal, bronchial or pleural disease. During surgery, spillage of hydatid fluid must be avoided to prevent secondary hydatidosis. Relapse rates up to 11.3% have been reported. Surgery must be as conservative as possible and resection is necessary in cases with severe and irremediable lung damage. Bilateral lung hydatidosis, present in 4 to 26% of operated cases, may be treated with one- or two-stage surgery either by bilateral thoracotomy or sternotomy. Video Assisted Thoracoscopic Surgical (VATS) approach can be safely used in selected cases with the same surgical rules as in open surgery.[35,36] Long-term treatment with benzimidazole carbamates (albendazole or mebendazole) has not been found to be very effective in lung hydatidosis. Treatment with benzimidazole has been suggested to prevent recurrences, though there is no evidence of their efficacy.[37,38] Treatment with these drugs has also been found to be associated with alopecia and hepatic and hematologic toxicity. Therefore, the medical therapy must be reserved for inoperable or complex cases. Percutaneous treatment by Puncture Aspiration Injection Reaspiration (PAIR) or percutaneous thermal ablation is used in hepatic hydatidosis. PAIR has been rarely used for lung hydatidosis because of the risk of anaphylactic shock, pneumothorax with pleural spillage and bronchopleural fistulae.

Pulmonary Alveolar Echinococcosis

Alveolar echinococcosis caused by *Echinococcus multilocularis* is a rare, but severe, highly pathogenic and potentially fatal form of echinococcosis. Wild canines especially the foxes are the definitive hosts and other hosts include dogs, cats and wolves. Small animals mainly rodents are the intermediate hosts. Alveolar echinococcosis is restricted to northern hemisphere (Europe, North America, some regions of China and Japan).[39] The liver is the first target of the parasite with a silent and long incubation period (5–15 years). Exogenous proliferation causes the infiltration of adjacent tissues and pressure necrosis. It can metastasize to distant organs mainly lungs, brain and bones. Lung involvement results from metastatic dissemination or direct extension through the diaphragm such as in case of hepatic echinococcosis with intrathoracic rupture into bronchial tree, pleural cavity or mediastinum. Direct extension to the right atrium through the inferior vena cava with recurrent episodes of pulmonary embolism has also been reported.

Imaging studies with radiography, ultrasonography, CT and Magnetic Resonance Imaging (MRI), may help in the diagnosis of metastatic lung disease. Biopsy may be needed to confirm the diagnosis.[40,41] Serologic tests, ELISA and Indirect Hemagglutination Assay (IHA) are available and are of great value for early detection in endemic areas to confirm diagnosis and to plan early surgery.[41] The radical resection of localized lesions is the only curative option for alveolar echinococcosis, but it is rarely possible in case of invasive and disseminated disease. Medical treatment is with mebendazole 40 to 50 mg/kg/day in three divided doses or with albendazole 10 to 15 mg/kg/day orally in two divided doses for a long period (minimum of two years) after radical surgery. Life-time treatment with medicines may be required for nonresectable or incompletely resected lesions.[38]

Pulmonary Schistosomiasis

The schistosomes that cause human disease are *Schistosoma haematobium*, *Schistosoma mansoni* and *Schistosoma japonicum*. The schistosome eggs are passed in urine (*S. haematobium*) or in feces (*S. mansoni* and *S. japonicum*) by the infected humans. The eggs released in fresh water are ingested by snails (intermediate host) in which the eggs hatch and develop into cercariae. The infective cercariae are excreted into the water and these cercariae penetrate human skin or are ingested to penetrate the gut. The final habitat of *S. haematobium* is urinary bladder vesicle beds and of *S. mansoni* and *S. japonicum* is the mesenteric beds. Pulmonary schistosomiasis can manifest clinically as an acute form and a chronic form. The acute form, also known as Katayama syndrome, present with fever, chills, weight loss, diarrhea, abdominal pain, myalgia, urticaria, shortness of breath, wheezing and dry cough and is seen in nonimmune patients.[42] Diffuse pulmonary infiltrates are seen radiologically in Katayama syndrome and almost all patients have eosinophilia.[43] Pulmonary nodules and pleural effusions have been reported in acute phase of infection with *Schistosoma mansoni*.[44]

Chest radiography and CT show small ill-defined nodular lesions, reticulonodular lesions or diffuse ground glass opacity. Chronic pulmonary schistosomiasis results from granulomatous reaction to eggs and/or worms embolized from pelvic veins in small pulmonary vessels through inferior vena cava for *S. haematobium*, or from mesenteric veins through portocaval anastomosis in patients with portal hypertension (*S. Mansonii* and *S. japonicum*).

Patients with chronic schistosomiasis present with the features of pulmonary hypertension and cor pulmonale.[45] Diagnosis of chronic schistosomiasis is based on the demonstration of eggs in stool or urine by direct microscopy or rectal/bladder biopsy.

Acute schistosomiasis can be treated with praziquantel 40 mg/kg for three days (for *S. mansoni* or *S. haematobium*) and 60 mg/kg for six days (for *S. japonicum*) with or without steroids.[8,43] Praziquantel can be repeated several weeks later to eradicate the adult flukes. Treatment may cause a reactive pneumonitis to dying eggs or worms. Acute pneumonia can be observed two weeks after treatment, which is thought to be related to lung embolization by detached adult worms in pelvic veins. Artemisinin has been found to be useful in the early stage after exposure, as the drug has been found to act on the juvenile forms of the schistosomes and may reduce the risk of the Katayama syndrome.[46] Chronic schistosomiasis can also be treated with praziquantel in the same dosage. Patients with pulmonary arterial hypertension are treated with specific pulmonary artery hypertension treatment along with antiparasitic medication.

Pulmonary Paragonimiasis

Ninety percent of the cases of paragonimiasis occur in Asia where nearly 20 million people are infected. Paragonimiasis is caused by infection with *Paragonimus* species and manifest as subacute or chronic inflammation of the lung. The main species that cause paragonimiasis in man is *Paragonimus westermani.* Adult worms live in the lungs and the unembryonated eggs of *P. westermani* are excreted in the sputum, or they can be swallowed and passed with stool. The eggs become embryonated in the external environment and miracidia are produced. The miracidia penetrates the soft tissues of the first intermediate host, a snail and go through several developmental stages inside the snail forming free swimming cercariae. Many cercariae then emerge from the snail and invade the second intermediate host, a crustacean such as a crab or crayfish. Cercariae encyst and produce metacercariae, which are the infective stage for the mammalian host. Man gets the infection, when raw or undercooked crabs or crayfishes contaminated with infective metacercariae are ingested. The metacercariae excyst in the duodenum, penetrate through the intestinal wall into the peritoneal cavity, then through the abdominal wall and diaphragm into the lungs. In the lungs they become encapsulated and develop into adults.

Pulmonary manifestations include fever, chest pain, chronic cough with blood tinged sputum or hemoptysis that may mimic tuberculosis. Pleural effusion or pneumothorax may be the first manifestation during intrapleural migration of the juvenile worms.[47,48] Chest radiography or CT may show patchy airspace consolidation due to exudative or hemorrhagic pneumonia that may cavitate. Worm cysts may be seen as solitary or multiple nodules or gas filled cysts with ring shadows and crescent-shaped areas within the cyst that represent worms attached to the wall of the cavity.[49,50]. Diagnosis is confirmed by the detection of eggs in the sputum samples, BAL fluid or lung biopsy specimens. Fine Needle Aspiration Biopsy (FNAB) of pulmonary nodule has been found to be useful in the diagnosis of pulmonary paragonimiasis.[51] Peripheral blood eosinophilia and elevated serum IgE levels are seen in more than 80% of patients with paragonimiasis. Differentiation of paragonimiasis from tuberculosis may be difficult. Paragonimiasis can be treated with praziquantel (75 mg/kg/day for 3 days), bithionol (30–40 mg/kg for 10 days, every alternate day), niclofolan (2 mg/kg as a single dose) or triclabendazole (20 mg/kg in two equal doses).

Pulmonary Ascariasis

Ascaris lumbricoides is the most common intestinal helminthic infection. The fertilized eggs passed in the feces and released in the soil embryonate within two to four weeks and become infectious depending on the environmental conditions (moist, warm and shaded soil). Infection occurs through the contamination of hands or food with soil containing eggs, which is then swallowed. The eggs hatch into larvae in the small intestine. These first stage larvae moult into second stage larvae in the lumen of the small intestine. The second stage larvae penetrate the wall of the intestine and travel via capillaries and lymphatics to the hepatic circulation and to the right side of the heart and then reach the lungs. The second stage larvae moult twice more in the alveoli to produce third and fourth stage larvae. The fourth stage larvae are formed 14 days after ingestion, travel up to the trachea and are then swallowed to reach back the small intestine.

Respiratory symptoms are due to larval pulmonary migration, airway hyper reactivity and bronchospasm. Symptomatic pulmonary disease may range from mild cough to Löffler's Syndrome.[52] Löffler's Syndrome is a self-limiting inflammation of the lungs and is associated with blood and lung eosinophilia. This syndrome can occur as a result of parasitic infestation (especially ascariasis in children) and exposure to various drugs. Patients may present with the general symptoms of malaise, loss of appetite, fever lasting two to three days, headache and myalgia. The respiratory symptoms include chest pain, cough with mucoid sputum, hemoptysis, shortness of breath and wheezing. The respiratory rate may increase and rales can be heard on auscultation. Leukocytosis, particularly eosinophilia is an important laboratory finding. Chest radiographs demonstrate unilateral or bilateral, transient, migratory, or nonsegmental opacities of various sizes. These opacities are often peripherally situated and appear to be pleural based.

A diagnosis of pulmonary disease due to ascariasis can be made in an endemic region in a patient who presents with dyspnea, dry cough, fever and eosinophilia. Sputum may show Charcot-Leyden crystals and the chest radiograph may reveal fleeting pulmonary infiltrates. Due to the occurrence of respiratory symptoms during larval pulmonary migration, stool examination usually does not show *Ascaris* eggs and stool samples may be negative until two to three months after the occurrence of respiratory symptoms, unless the patient had been previously infected. Larvae can sometimes be demonstrated in respiratory or gastric secretions.

Pulmonary disease due to ascariasis usually does not require any treatment, as it is a self-limiting disease. However, the persistence of gastrointestinal ascariasis may result in repeated episodes of respiratory symptoms due to larval migration. In order to eradicate *Ascaris lumbricoides* from the intestine, specific anthelminic treatment is given. Mebendazole and albendazole are equally effective in the treatment of ascariasis.[53] Mebendazole is given in a dose of 100 mg twice a day for three days. It can be also given as a single dose of 500 mg. Albendazole is given as a single dose of 400 mg. The safety of mebendazole and albendazole during pregnancy has not been established. A single dose of pyrantel pamoate (11 mg/kg, maximum dose 1 gram) and piperazine citrate (50 to 75 mg/kg/day for 2 days) are also useful in the treatment. Pediatric dose is same as adult dose. Ivermectin has also been found to be useful.[54]

Pulmonary Ancylostomiasis

Ancylostomiasis or "hookworm disease" is caused by three parasite species, *Ancylostoma duodenale, Necator americanus* and *Ancylostoma ceylanicum*. Man is the only definitive host. The eggs containing segmented ova with four blastomeres are passed out in the feces. A rhabditiform larva develops from each egg in the soil and this larva moults twice and develops into a filariform larva, which is infective to man. The filariform larva penetrates through the intact skin. *N. americanus* larvae can infect man only through the skin whereas *A. duodenale* larvae can enter the human host via the oral route in addition to the entry through the skin.[55] These larvae reach pulmonary circulation through the lymphatics and venules. The larvae then pierce the alveolar walls and ascend the bronchi, trachea, larynx and pharynx and are ultimately swallowed to reach the upper part of small intestine. The interval between the time of skin penetration and laying of eggs by adult worms is about six weeks.

Ancylostoma dermatitis which manifests in form of intense pruritus, erythema and rash (ground itch) occurs at the site of skin penetration. During pulmonary larval migration, patients may present with fever, cough, wheezing and transient pulmonary infiltrates in chest radiographs. This is associated with blood and pulmonary eosinophilia. The other characteristic feature is iron-deficiency anemia due to chronic blood loss. During massive infection from oral ingestion of hookworm larvae, patients can present with nausea, vomiting, cough, dyspnea and eosinophilia. This condition is termed as Wakana disease. Prominent gastrointestinal symptoms in hookworm disease are abdominal pain, nausea, anorexia and diarrhea.

A direct microscopical examination of stool demonstrates the presence of characteristic hookworm eggs. Concentration method may be used when the infection is light. Eosinophilia in the peripheral blood is a prominent finding. A peripheral blood smear examination will reveal microcytic hypochromic anemia. A Polymerase Chain Reaction (PCR) to differentiate between *À. duodenale* and *N. americanus* has been developed.[56] Both mebendazole and albendazole are useful in the treatment of hookworm infestation. Mebendazole is given as 100 mg twice daily for three days and albendazole is given as a single dose of 400 mg. Pyrantel pamoate at a dose of 11mg/kg orally (maximum 1g) as a single dose has also been found to be useful. Ivermectin can also be used in the treatment of hookworm infections. Anemia can be treated with oral ferrous sulfate tablets.

Pulmonary Strongyloidiasis

Strongyloides stercoralis is seen worldwide, but is common in South America, South East Asia, sub-Saharan Africa and the Appalachian region of the United States of America. The parasitic females live in the wall (mucous membrane) of the small intestine of human and lays eggs. The rhabditiform larvae emanating from the eggs pierce the mucous membrane and reach the lumen of the intestine. These larvae are then passed with the feces and eggs are, therefore, not found in the feces. The rhabditiform larvae can metamorphose into filariform larvae in the lumen of the bowel. These filariform larvae can penetrate the intestinal epithelium or perianal skin without leaving the host. This is responsible for autoinfection and for the persistence of infection for 20 to 30 years in persons who have left the endemic areas.[57]

The unique feature of the life cycle of *S. stercoralis* is that it can complete its life cycle either in the human host or in the soil. The rhabditiform larvae that are voided with the feces can undergo two distinct cycles in the soil: Direct (host-soil-host) and indirect cycle. In direct cycle, the rhabditiform larvae directly metamorphose into filariform larvae and can infect human through skin. In indirect cycle, the rhabditiform larvae mature into free-living sexual forms (males and females). A second generation of rhabditiform larvae is then produced and these are subsequently transformed into filariform larvae. The filariform larvae can penetrate directly through the skin, invade the tissues, penetrate into the venous or lymphatic channels and are carried by the blood stream to the heart and then to the lungs. They pierce the pulmonary capillaries and enter the alveoli. These larvae, then, migrate to the bronchi, trachea, larynx and epiglottis and are swallowed back into the intestine. In the duodenum and jejunum, they develop into sexual forms to continue their life cycle.

The cutaneous reaction, as a result of the penetration of the skin by the filariform larvae may be due to immediate hypersensitivity reaction. The cell mediated immunity that develops following primary infection prevents reinfection.[58]. As a result, the larvae and adult worms remain confined to the intestine and the tissue invasion is prevented in immunocompetent individuals. When there is immunosuppression, autoinfection is exaggerated and leads to hyper infection. In this situation, the number of migrating larvae increases tremendously and disseminate into many organs, including lungs, meninges, brain, lymph nodes and kidneys. The parasite can produce hyperinfection syndrome in individuals with deficient cell-mediated immunity as seen in patients with immunosuppressive therapy (especially corticosteroids) and other immune-deficient states (malnutrition, lymphoma, leukemia, etc.). HIV-infected patients are at a higher risk of dissemination and this may occur without the elevations of IgE or eosinophils.[59]

During the migration of filariform larvae through the lungs, bronchopneumonia and hemorrhages in the alveoli can occur. These areas are infiltrated with eosinophils. This is associated with elevated IgE levels and eosinophilia in the blood. As the larvae penetrate the intestinal mucosa, gram-negative bacteria from the gut are carried by the larvae on their cuticle. In addition, small breaks in the mucous membrane as the larvae penetrate the intestine also facilitate the entry of enteric bacteria into the blood stream. The inflammation that follows such invasion of larvae leads to disseminated strongyloidiasis and this is usually fatal. As a result of invasion of bacteria along with larvae, diffuse and patchy bronchopneumonia and pulmonary abscess can occur. In the lung, massive pulmonary bleeding can occur due to alveolar microhemorrhages.

Pulmonary signs and symptoms include cough, shortness of breath, wheezing and hemoptysis.[60] In patients at high risk for strongyloidiasis, acute respiratory distress syndrome and septicemia due to intestinal transmural migration of bacteria can occur. In addition, acute anemia, acute renal failure and systemic inflammatory response syndrome have been reported.[61]. In immunocompetent patients with strongyloidiasis, the parasite load is usually low and the larval output is irregular. As a result, the diagnosis of strongyloidiasis by the examination of a single stool specimen using conventional techniques usually fails to detect larvae in up to 70% of cases. The diagnostic yield can be increased by examination of several stool specimens on consecutive days. In disseminated disease, larvae and adult parasites can be seen in sputum, urine, bronchoalveolar lavage fluid and other body fluids.

Ivermectin, thiabendazole or albendazole can be used for treatment of strongyloidiasis in immunocompetent individuals without complications. Ivermectin is given in a dose of 200 µg/kg orally for one or two days. Thiabendazole is given orally as 25 mg/kg twice a day for two days. Albendazole 400 mg twice a day for five days has been found to be useful in the treatment of strongyloidiasis. In immunocompromised individuals with disseminated strongyloidiasis, the dose of thiabendazole has to be doubled and the duration of treatment may extend up to several weeks. Corticosteroids should not be prescribed to prevent life-threatening hyperinfection syndrome.

Tropical Pulmonary Eosinophilia

Immunologic hyper responsiveness to human filarial parasites, *Wuchereria bancrofti* and *Brugia malayi* results in an occult form of filariasis termed as Tropical Pulmonary Eosinophilia (TPE).[62] The evidences for filarial etiology of TPE are the close epidemiological relationship between filarial infection and TPE, a positive filarial complement-fixation test and a positive immediate reaction to intradermal skin tests with *Dirofilaria immitis* antigens, histopathological demonstration of microfilariae of *Wuchereria bancrofti* in the lungs, liver and lymph nodes of patients, the usefulness of Diethylcarbamazine Citrate (DEC), an antifilarial drug, in the treatment, elevated levels of filarial specific IgG and IgE antibodies and the ultrasonographic demonstration of living adult *Wuchereria bancrofti* in the lymphatic vessels of the spermatic cord of patients with TPE.

The demonstration that basophils from patients with TPE released greater amounts of histamine when cells were challenged with *Brugia* or *Wuchereria* antigens than with *Dirofilaria* antigen suggested that TPE resulted from immunologic hyper responsiveness to human filarial parasites.[63-68] Histopathological examination of lung biopsy specimens has shown acute eosinophilic infiltrations of interstitial, peribronchial and perivascular tissues leading to the formation of eosinophilic abscesses and eosinophilic bronchopneumonia in the acute stage and in untreated cases, fibrosing alveolitis with honey combing.[63]

Bronchoalveolar lavage studies have demonstrated that TPE is characterized by intense eosinophilic inflammatory process in the lower respiratory tract.[69] Electron microscopic examination of lung eosinophils had shown severe degranulation with the loss of both the cores and the peripheral portions of the granules, suggesting that the eosinophils were in an activated state.[68,69] A major IgE-inducing antigen (Bm23-25) of the filarial parasite, *Brugia malayi* has been identified and this antigen has been found to be the homolog of the enzyme, gamma-glutaryl transpeptidase light chain subunit [66,70] and expresses mainly in the infective L3 larvae.[71] In addition, *Brugia malayi* gamma-glutaryl transpeptidase can induce IgG1 and IgE antibody production in patients with TPE.[72] BAL fluid from patients with TPE contains IgE antibodies that recognize *Brugia malayi* antigen, Bm23-25.[66] There is a molecular mimicry between the parasite gamma-glutaryl transpeptidase and the human gamma-glutaryl transpeptidase present on the surface of pulmonary epithelium. Thus, the profound antibody response to filarial infection especially to filarial gamma-glutaryl transpeptidase, observed in the lungs of patients with TPE, plays an important role in the pathogenesis of tropical eosinophilia.

Tropical pulmonary eosinophilia is prevalent in India, Pakistan, Bangladesh, Sri Lanka, Myanmar, Malaysia, Singapore, Indonesia and Vietnam. Tropical pulmonary eosinophilia is a systemic disease involving mainly the lungs, but other organs, such as liver, spleen, lymph nodes, brain, GIT, etc., may also be involved. The disease occurs predominantly in males, with a male to female ratio of 4:1, and is mainly seen in older children and young adults between the ages 15–40 years.[63] The systemic symptoms are fever, weight loss and fatigue. Respiratory symptoms include paroxysmal cough, breathlessness, wheeze and chest pain. The symptoms occur predominantly at night, but can persist during the day. Sputum is usually scanty, viscous and mucoid. The sputum often shows clumps of eosinophils; and rarely Charcot-Leyden crystals. On examination, patients are often breathless. Bilateral scattered rhonchi and rales may be also heard on auscultation.

Leukocytosis with an absolute increase in eosinophils in the peripheral blood is the hallmark of TPE. Absolute eosinophil counts are usually more than 3,000 cells/mm^3 and may range from 5,000 to 80,000.[73] As patients with TPE especially from endemic areas can be simultaneously infected with other helminthic parasites, stool examination may reveal ova or larvae of other helminths (*Ascaris*, *Ancylostoma*, whipworm, and *Strongyloides*) in 20% of patients with TPE. This observation does not deter the physician from making a diagnosis of TPE, if other conditions for diagnosis are fulfilled.

The chest radiological features of TPE include reticulonodular shadows predominantly seen in mid and lower zones and miliary mottling of 1–3 mm in diameter often indistinguishable from miliary tuberculosis. Twenty percent of patients have a normal chest radiograph.[63] Lung function tests reveal mainly a restrictive ventilation defect with superimposed airway obstruction.[74,75] Single breath carbon monoxide transfer factor (TLCO) is reduced in 88% of untreated patients with TPE.[76] The reduction in TLCO is due to reduced pulmonary membrane diffusing capacity (Dm).[77] Most of the patients exhibit mild arterial hypoxemia. Following three weeks treatment with DEC, pulmonary function parameters, including TLCO continued to be significantly lower than the control subjects.[74]

Until a diagnostic test that can differentiate filarial TPE from other TPE-like syndrome due to other helminthic infections is available, the following diagnostic criteria can be used for the diagnosis of TPE:

(a) Appropriate exposure history (mosquito bite) in an endemic area of filariasis,
(b) A history of paroxysmal nocturnal cough and breathlessness,
(c) Chest radiographic evidence of pulmonary infiltrations,
(d) Leukocytosis in blood,
(e) Peripheral blood eosinophils more than 3,000 cells per cu mm,
(f) Elevated serum IgE levels,
(g) Elevated serum antifilarial antibodies (IgG and/or IgE) and
(h) A clinical response to diethylcarbamazine citrate.

The treatment is with oral DEC (6 mg/kg per day) for three weeks.[78] Relapses following treatment occur in approximately 20% of patients followed up for five years.[63] Though most patients show marked symptomatic improvement, there is an incomplete reversal of clinical, hematological, radiological and physiological changes in TPE one month after a three-week course of DEC.[74,79]. Thus, a chronic mild interstitial lung disease has been found to persist in TPE despite treatment.[80]

Pulmonary Dirofilariasis

Pulmonary dirofilariasis is a zoonotic infection caused by filarial nematodes, *Dirofilaria immitis* and *Dirofilaria repens*. Humans are accidental hosts of this parasite, which is transmitted by the mosquito. The parasite, which is a vascular parasite[81] is usually seen in the pulmonary artery where they produce a pulmonary nodule or "coin lesion."[82] Nearly 50% of subjects infected with dirofilariasis are asymptomatic. Clinical symptoms are chest pain, cough, fever, hemoptysis and dyspnea. CT scan may show a well-defined nodule with smooth margin connected to an arterial branch.[83] Rarely cavity formation in the lung has also been reported. A PCR-based diagnosis of *D. repens* in human pulmonary dirofilariasis is available. A definitive histopathological diagnosis of pulmonary dirofilariasis can be made in tissue specimens obtained by wedge biopsy, video-assisted thoracoscopy or rarely by fine needle biopsy. There is no specific treatment for human dirofilariasis.

Pulmonary Visceral Larva Migrans

Certain nematode parasites when enter into an unnatural host (e.g. human) may not be able to complete their life cycle and their progress is arrested in the "unnatural host." If the entry of such parasitic larvae is through skin penetration, it causes cutaneous larva migrans (creeping eruption). If the entry is via oral route, it causes visceral larva migrans. Cutaneous larva migrans is caused by the parasite, *Ancylostoma braziliense*, which is a parasite of dogs and cats. The common parasites that cause Visceral Larva Migrans (VLM) and eosinophilic lung disease in human are a dog ascarid *(Toxocara canis)* and less commonly a cat ascarid (*Toxocara catis*). Adult *Toxocara canis* and *Toxocara catis* live in the intestines of dogs and cats respectively.

Animals acquire infection by the ingestion of eggs of the parasites from contaminated soil. The life cycle is then completed in definitive hosts, dogs and cats and the eggs are passed by the animals in the feces and embryonate in the soil. These embryonated *Toxocara* eggs, when ingested by an intermediate host (e.g. human), hatch into infective larvae in the intestine. The infective larvae penetrate the intestinal wall and are carried by the circulation to many organs, including liver, lungs, muscles, central nervous system and eye. The progress of the larvae is arrested in these sites of the intermediate host by the formation of a granulomatous lesion. In human, the larvae never develop into adult worms. Therefore, infected human never excretes *Toxocara* eggs in the feces. The larvae can get encapsulated within the granuloma where they are either destroyed or persist for many years in a viable state. Larval antigens can cross-react with human A and B blood group antigens.[84]

The main symptoms in patients with VLM are fever, cough, wheezing, seizures, anemia and fatigue. Pulmonary manifestations are reported in 80% of cases and patients may present with severe asthma. Scattered rales and rhonchi are heard on auscultation. Visceral larva migrans is characterized by leukocytosis and eosinophilia. Skiagram chest may reveal focal patchy infiltrates. In some cases, severe eosinophilic pneumonia may lead to respiratory distress.[85] Other clinical features include generalized lymph node enlargement, hepatomegaly and splenomegaly. Visceral larva migrans is usually reported in young children with a history of pica. A history of exposure to puppies or dogs supports the diagnosis of VLM. Serological tests by ELISA method using excretory-secretory proteins obtained from cultured *T. canis* may be useful in the diagnosis. Histopathological examination of lung or liver biopsy specimens may demonstrate granulomas with eosinophils, multinucleated giant cells and fibrosis. Since man is not the definitive host of *Toxocara* species, eggs or larvae cannot be demonstrated in the feces.

Visceral larva migrans is a self-limiting disease and there may be spontaneous resolution. Therefore, mild to moderately symptomatic patients need not require any drug therapy. Patients with severe VLM can be treated with thiabendazole, mebendazole or DEC. Treatment with antihelmintics may exacerbate the inflammatory reactions in the tissues due to the killing of larvae. It is therefore, advisable to combine antihelmintic treatment with corticosteroids. Diethylcarbamazine citrate can be given in a dose of 6 mg/kg/day for 21 days. Mebendazole is prescribed in a dose of 20–25 mg/kg/day for 21 days.[86] Albendazole 10 mg/kg/day for five days has been shown to have a moderate effect compared to thiabendazole.

Pulmonary Trichinellosis

Human trichinellosis is an important food-borne zoonosis. Five species of *Trichinella* (*T. spiralis*, *T. nativa*, *T. nelsoni*, *T. britovi* and *T. pseudospiralis*) can infect human.[87] The most important species that infect human is *Trichinella spiralis*. The parasite has a direct life cycle with complete development is one host (pig, rat or human). However, two hosts are required to complete the life cycle and for the preservation of the species from extinction. Human gets infection from raw and partially cooked pork, when infected pig's muscle containing the larval form of trichinellae is eaten by human. The infective larvae in the muscle are surrounded by a host capsule, which is a modified striated muscle known as "nurse" cell. In the stomach, the "nurse" cell is digested and the free larva is liberated. The larvae develop into adults (males and females) in the duodenum and jejunum. The newborn larvae produced by female parasites pass through the lymphatics or blood vessels to reach the striated muscles.[88] The larvae undergo encystment in the muscle and a host capsule develops around the larvae. Later on, it may get calcified. The life cycle is completed when infected muscle is ingested by a suitable host.

The common symptoms of trichinellosis are muscle pain, periorbital edema, fever and diarrhea.[89] Pulmonary symptoms include dyspnea, cough and pulmonary infiltrates. Dyspnea may be due to the involvement of diaphragm. Leukocytosis , eosinophilia and elevated levels of serum muscle enzymes (creatine phosphokinase, lactate dehydrogenase, aldolase and aminotransferase) are important laboratory findings. An enzyme-linked immunosorbent assay for the detection of anti-*Trichinella* antibodies using excretory-secretory antigens may be useful in the diagnosis. A definitive diagnosis can be made by muscle biopsy (usually deltoid muscle) that may demonstrate larvae of *T. spiralis*.[90]

Symptomatic treatment of trichinellosis includes analgesics and corticosteroids. Specific treatment is with mebendazole 200 to 400 mg three times a day for three days followed by 400 to 500 mg three times a day for 10 days. Albendazole can be given in a dosage of 400 mg per day for 3 days followed by 800 mg per day for 15 days. Trichinellosis can be prevented by consuming properly cooked pork.

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Anaerobic Bacterial Infections of the Lungs and the Pleura

Ashok Shah, Chandramani Panjabi

INTRODUCTION

The role of anaerobes in causing an infective disease process has been appreciated for more than a century, but anaerobic bacterial infections of the respiratory system continue to remain in the subconscious domain of the pulmonologist. Anaerobes as the cause of respiratory infection are infrequently recognized and rarely established. More often than not, these infections are caused by endogenous organisms that predominantly are commensals of the upper respiratory tract. Disruption of the harmonious relationship between the host and the bacteria lead to the various clinicopathologic processes that occur with anaerobic pleuropulmonary infections (Table 63.1).

TABLE 63.1: Clinical categories of anaerobic pleuropulmonary infections

1. Acute pneumonia (consolidation)
   - i. Aspiration pneumonia
   - ii. Community acquired pneumonia
   - iii. Nosocomial pneumonia
2. Chronic anaerobic pneumonitis (pulmonary infiltrates without cavitations)
3. Lung abscess (usually single, greater than 2 cm)
4. Necrotizing pneumonia (bilateral lung infiltrates with multiple cavitations less than 1 cm)
5. Pleural empyema
6. Septic emboli

HISTORICAL NOTE

In 1860, Antonie van Leeuwenhoek, the inventor of the microscope, discovered some "animalcules," which survived in the absence of air.[1] After almost two centuries, Louis Pasteur coined the term "anaerobies" and recognized the phenomenon of anaerobiosis.[2] A few years later, Veillon identified anaerobic cocci in four patients.[3] Anaerobic pleuropulmonary infections were first described in detail a little more than a century ago by Rendu and Rist in 1899.[4] A few years later, Guillemont and coworkers[5] published 13 cases of putrid "empyema". Subsequently, during the next two decades, infections caused by the synergy of fusiform bacilli and spirochaetes were documented.[6-8] These "fusospirochaetal" bacteria were first described by Willoughby Miller, a dentist, in 1883;[9] while ulcerative gingivitis due to these bacilli was reported in detail by Vincent.[10] These microbes, popularly known as "Miller-Vincent" organisms, were chiefly responsible for pulmonary spirochaetosis.

During the late 1920s, elegant work done by Dr David Smith[11] on lung abscess revealed the resemblance of the bacteria seen in the walls of abscesses, on autopsy, to the organisms present in the gingival crevice of healthy individuals. This led to the postulation that lung abscesses commonly occurred due to the aspiration of oral microbial flora. Experimental animal studies[12-14] to prove this hypothesis demonstrated that four anaerobic bacteria, which included (i) an anaerobic spirochaete, (ii) *Fusobacterium nucleatum*, (iii) *Peptostreptococcus* species (iv) Fastidious gram-negative anaerobe (possibly *Bacteroides fragilis*) were collectively responsible for the development of the typical pulmonary abscess. Since no single microorganism was able to cause this disease, this was a classic demonstration of bacterial synergy.

The euphoria caused by the discovery of antibiotics resulted in anaerobes being largely ignored. There were hardly any samples that were not contaminated and cultures for these microbes were rarely performed. Most lung abscesses were labeled as "nonspecific" because no pathogen could routinely be cultured from the sputum.[15] The decade of the 1970s was described by Bartlett[16] as the "renaissance" of anaerobic pleuropulmonary infections. It was during this period that specific sampling methods for anaerobic organisms were evolved. Simultaneously, culture methods too improved and bacteriologic confirmation became easy. Furthermore, the placement of different anaerobic microbes into an organized taxonomic order also helped in generating further interest in this field.

PATHOPHYSIOLOGY

Aspiration

Anaerobic infections of the lungs and their suppurative complications are mainly caused by the aspiration of bacteria that constitute the normal flora of the oral cavity. In the gingival crevice, the anaerobic microbes outnumber the aerobes by a ratio of 1000:1.[17] The concentration of anaerobes here approach geometric limits up to 10^{12}/gram.[17-19] It is well known that edentulous subjects have a lower risk of acquiring anaerobic lung infections. Although aspiration, especially during deep sleep, occurred in 45% of healthy individuals,[20] this phenomenon does not usually cause any disease. Normal bronchopulmonary defenses aid in clearing these aspirates. Any breach in such protective mechanisms facilitates an inflammatory process, thereby leading to disease. The frequency, volume and virulence of the anaerobic organisms in the inoculum aspirated are decisive in determining the pathology.

Aspiration is likely to occur in patients undergoing general anesthesia or having altered consciousness. At one point of time, aspiration was observed in one out of every six patients receiving general anesthesia.[21] The presence of artificial airways impairs glottic closure and makes the patient more vulnerable to aspiration. When aspiration is due to esophageal dysfunction or intestinal obstruction, the gastrointestinal tract is the likely source of the causative bacteria.[22,23] Several other conditions that predispose to clinically significant aspiration are responsible for anaerobic infections (Table 63.2).

Anaerobic Lung Infections and Dental Disorders

Persons with poor dental hygiene are prone to develop anaerobic infections of the respiratory tract. Suppurative periodontitis predisposes to aspiration as it harbors a potentially large quantity of anaerobic bacteria.[24] Any kind of anesthesia in the oropharynx, given for dental treatments, is also associated with a high chance of aspiration. Tooth extraction and scaling lead to a breach in the normal mucosal barrier, thereby further increasing the risk of aspiration.[25] It would be prudent for a pulmonologist to carefully extract a detailed dental history and also to examine the oral cavity for evidence of any inflammatory or suppurative disease while dealing with respiratory infections in order to evaluate for the presence of anaerobes.

TABLE 63.2: Predisposing conditions for anaerobic pleuropulmonary infections

1. Aspiration
    - i. Alcoholism
    - ii. General anesthesia
    - iii. Altered consciousness
        - a. Cerebrovascular accident
        - b. Drug overdose
        - c. Epilepsy
        - d. Smoke inhalation
        - e. Head trauma
    - iv. Dental disorders
        - a. Periodontal disease
            - i. Gingivitis
            - ii. Pyorrhea
        - b. Tooth extraction
    - v. Esophageal dysfunction or intestinal obstruction
2. Local underlying conditions
    - i. Pulmonary infarction
    - ii. Bronchogenic carcinoma
    - iii. Bronchiectasis
    - iv. Foreign body
3. Systemic underlying conditions
    - i. Diabetes mellitus
    - ii. Extrapulmonary malignancy
    - iii. Corticosteroids and other immunosuppresants
    - iv. Preceding antimicrobial therapy

[modified from ref. 57]

Other Predisposing Factors

Anaerobic lung infections can also occur following dissemination from preexisting extrapulmonary infections.[26-28] The classical example of this is Lemierre's syndrome,[26,29] which is almost always accompanied by secondary seeding, most commonly to the lungs. Subsequent to the introduction of effective antibiotics, the natural history of bacterial spread was interrupted and the incidence of such an infection reduced to a great extent. However, in the early 1970s, lung involvement was observed in 20 to 30% of the patients with *Bacteroides* bacteremia.[30,31] This could most probably have been due to penicillin-resistant strains of the genus *Bacteroides*, a phenomenon, which was discovered a few years later.

Necrosis of the lung tissue due to stasis is also associated with anaerobic infections. This commonly occurs in bronchiectasis, pulmonary infarction and postobstructive pneumonitis secondary to bronchogenic carcinoma or a foreign body. The other mechanisms that can cause anaerobic infections in the lungs and the pleural spaces include hematogenous and lymphatic spread and diaphragmatic translocation from subphrenic collections. Infection via the blood stream is noted in patients with septic thrombophlebitis of the jugular or pelvic veins.

NATURAL HISTORY AND CLINICAL CLASSIFICATION

The distinct clinical categories of anaerobic respiratory infections include pneumonitis, lung abscess, necrotizing pneumonia and pleural empyema. These different pathologic entities (Fig. 63.1) are believed to be the manifestation of different stages in the natural history of the infection. By and large, the predisposing event in most anaerobic lung infections is the aspiration of normal upper respiratory tract flora, seen in up to 90% of the patients.[16] The dependent portions of the lungs are the most commonly involved. In the supine position, either the posterior segments of the upper lobes or the superior (apical) segments of the lower lobes are involved. When aspiration occurs in the semirecumbent posture, the basal segments of the lower lobes are chiefly affected. The right lung is twice as commonly affected as the left since the right main bronchus is more aligned with the trachea.[32,33]

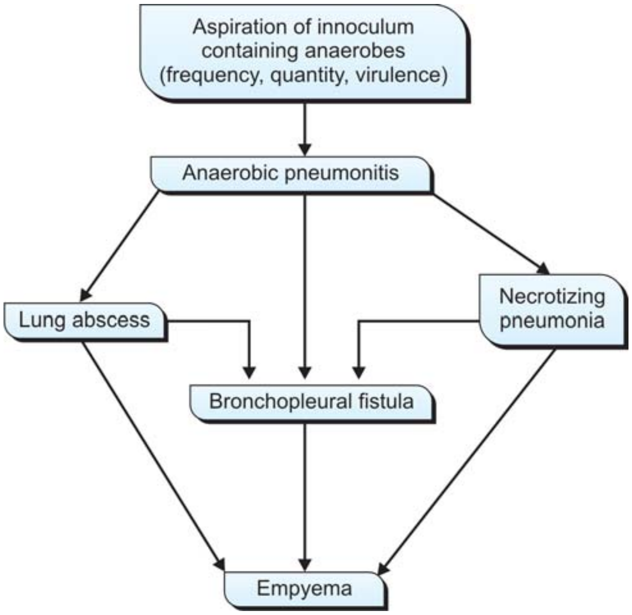

Fig. 63.1: Natural history of anaerobic pleuropulmonary infections

Acute Anaerobic Pneumonia

The earliest manifestation of anaerobic lung disease is pneumonia. The anaerobic etiology may not always be established due to similarities with acute bacterial pneumonias. However, the involvement of dependent segments could provide the initial hint. With appropriate therapy, the pathogenesis is arrested at this stage and the disease does not progress further towards suppuration.

Lung Abscess

Approximately 10 to 14 days later, necrosis and liquefaction in an area of anaerobic pneumonitis leads to the formation of a lung abscess.[34] A thick-walled cavity greater than 1 cm in diameter, often with an air-fluid level, develops within the pneumonic infiltrate.

Necrotizing Pneumonia

Necrotizing pneumonia is characterized by suppurative lung infiltrates with necrotic areas, leading to multiple small cavities (less than 1 cm in diameter); in comparison to a lung abscess, a greater number of pulmonary segments are involved. Such lesions, first described in 1905[35] and labeled as "pulmonary gangrene"[8] were often rapidly spreading and culminated in fatal lung destruction. Even though the incidence of necrotizing pneumonia reduced drastically after the introduction of antibiotics, the clinical response was unsatisfactory and mortality remained high.

Empyema

Empyemas are defined as the collection of pus in the pleural cavity. They result either after an ensuing bronchopulmonary fistula or as a direct extension from subpleural segmental pneumonitis. All the three clinical entities described above can be complicated by an empyema. Spread from infradiaphragmatic and subphrenic collections can also lead to the formation of empyema.

Chronic Anaerobic Pneumonitis

The term chronic anaerobic pneumonitis is used when there is no evidence of either parenchymal necrosis or pleural involvement. Histopathologic examination of such lesions reveals an intra-alveolar or an interstitial infiltrate.[36] Inability to procure an appropriate sample for identifying the causative bacteria renders this entity to be relatively uncommon.

Septic Emboli

Another rarely encountered disease process is the occurrence of septic emboli. Like necrotizing pneumonias, diffuse and discrete infiltrates that appeared due to embolization from anaerobic thrombophlebitis were documented mainly in the first half of the previous century.[37]

ANAEROBES AND UPPER RESPIRATORY SYNDROMES

Lemierre's Syndrome[29,38]

This disease, also known as postanginal sepsis and human necrobacillosis, is a form of thrombophlebitis of the internal jugular vein and is predominantly caused by *Fusobacterium necrophorum*. An acute oropharyngeal infection, leading to a putrid peritonsillar abscess is most often the trigger factor for this potentially destructive disease. Septicemic spread occurs primarily to the lungs and also to bones and joints. A triad of pharyngitis, neck swelling/tenderness and noncavitating lung infiltrates is described.[39]

Ludwig's Angina[40]

This is a periodontal infection arising from the tissues surrounding the lower third molar teeth. Although Ludwig's angina is most commonly caused by *Streptococcus*, polymicrobial infections with anaerobes have been noted in up to 40% of the cases.[41] The key features include marked local swelling over the floor of the mouth, which is usually associated with pain and trismus. Submandibular cellulitis ensues leading to impairment in swallowing. In the cases of glottis obstruction, leading to respiratory distress, tracheotomy may be lifesaving.

Vincent's Angina[42,43]

This is also termed as "trench mouth," heralded by an acute and sudden gingivitis. This progresses to the ulceration of the interdental papillae and necrosis of the gingivae. The most common pathogen is *Prevotella intermedia*. The acute necrotizing ulcerative gingivitis may spread occasionally to cause destruction of the buccal mucosa, teeth and the jaw bones.

INCIDENCE

For reasons more than one, it is not easy to calculate the true incidence of anaerobic lung infections. Sample collection techniques are difficult and appropriate culture methods may not be available in all laboratories. In addition, many patients respond to the initial empiric antibiotics even before specimens are obtained for confirmation.

Lung abscess and empyema are the two most frequently encountered forms of anaerobic pleuropulmonary infections. Prior to 1940s, almost all chronic pulmonary abscesses were either tuberculous or due to anaerobic bacteria. In three different case series, culture of abscess material obtained during surgical drainage or excision of the nontuberculous abscesses yielded anaerobic bacteria in 100% of the patients.[44-46] Landmark studies conducted during the 1970s showed that anaerobes accounted for more than 90% of all the lung abscesses.[47]

During the preantibiotic era, approximately two-thirds of all empyemas were caused by *Streptococcus pneumoniae*, while putrid fluid was aspirated in only 5% to 7% of the patients.[48] However, with the advent of antibiotics, in addition to a marked reduction in the incidence of empyemas, there was a significant alteration in the microbiological profile. During the decades of 1960s and 1970s, anaerobic microorganisms accounted for up to 40% of all patients with empyema.[49-55] A very high yield of 76% in one particular study was attributed to diligent case finding and processing of the samples in dedicated anaerobic research laboratories.[51]

In a prospective study on community and hospital-acquired cases of aspiration pneumonia, the community acquired cases were caused mainly by anaerobic organisms while approximately two-thirds of the hospital-acquired disease were due to aerobic bacteria.[56] Bartlett and Finegold[57] extensively reviewed all available literature on anaerobic pleuropulmonary infections and found that necrotizing pneumonias occurred in approximately a quarter of the patients during the preantibiotic era and in only 13.7% among the cases studied thereafter. Septic emboli were documented in 21% of patients reported prior to circa 1944 and in only 7.6% after effective antibiotics were prescribed. Not surprisingly, there were no cases of septic embolization among 70 cases detailed over a period of 14 years (from 1958 to 1971) at an anaerobic research center in California, USA.

The incidence of anaerobic infections in community acquired pneumonia (CAP) has not been studied in detail. Samples obtained by transtracheal aspiration (TTA) in 89 patients with CAP, implicated anaerobes in one-third of the patients.[58] In another study wherein quantitative cultures were performed on fiber optic bronchoscopy guided protected catheter specimens, anaerobes were recovered from 16 (22%) out of 74 patients.[59] In nosocomial pneumonia, it is not easy to establish anaerobes as the chief cause since patients are already receiving broad spectrum antibiotics before sample collection. When appropriate specimens were processed prior to empiric antibiotic therapy in 159 patients with hospital acquired pneumonia, anaerobes were identified in 56 (35%) of 159 patients.[60]

Although chronic anaerobic pneumonitis was produced in experimental animals,[13] there were hardly any clinical reports. During the last two decades, we have so far documented four patients (three adults and a child) with chronic anaerobic pneumonitis.[61-64] As is evident from the paucity of such a presentation, this chronic clinical category is yet to receive recognition that it deserves.

MICROBIOLOGY

The phenomenon of bacterial synergy, initially described by Smith in the 1920s, was repeatedly demonstrated in many studies on anaerobic lung infections. Way back in 1932,[65] bacteriological cultures performed on the thoracotomy aspirates of 16 patients with lung abscess grew anaerobic streptococci and anaerobic diphtheroids from all patients and *Bacteroides melaninogenicus* from 14 (88%). The other organisms identified included *Fusobacterium* species, *Bacteroides fragilis* and *Sphaerophorus necrophorus*. In subsequent large series[16,57,66] of anaerobic lung infections, the common microorganisms identified were peptostreptococci, *B. melaninogenicus* (now reclassified as *Prevotella melaninogenicus*) and *Fusobacterium nucleatum*. Given their predominance, this triplet is often referred to as the "Big Three" of anaerobic lung infections.[16] It was also noted that approximately one-third to half of the patients had mixed infections with potential pathogenic aerobes or facultative anaerobes as well. Another key pathogen is *B. fragilis* because of its inherent resistance to many of the commonly prescribed broad spectrum antibiotics. This organism was consistently cultured in up to 20% of adults and children with anaerobic lung infections.[16] This assumes clinical importance since *B. fragilis* is not a normal commensal in the oral cavity.

It is also well documented that the same bacteria can be recovered from patients with different clinical expressions, viz. pneumonitis, lung abscess, necrotizing pneumonia and empyema. The clinical course and subsequent development of suppurative complications is not determined by a specific anaerobe but by other non-microbiological factors.

As more anaerobes were identified, the taxonomy of anaerobic bacteria was revised during the last few decades. Many anaerobic streptococci and the genus *Peptococcus* were omitted in the current classification. Almost all clinically relevant species of *Peptococcus*, barring *Peptococcus niger*, were reassigned as *Peptostreptococcus*.[67] Based on lactic acid production, most peptostreptococci were grouped under the genus *Streptococcus*.[68] Many bacteria largely identified as *B. fragilis* were found to be other penicillin-resistant species of *Bacteroides*. Different bacteria grouped as *B. melaninogenicus* were reclassified as either *Prevotella* or *Porphyromonas*. Most of these species produced the enzyme penicillinase. The clinically important organisms that cause pleuropulmonary infections are highlighted in Table 63.3.

TABLE 63.3: Important anaerobic bacteria causing pleuropulmonary infections

Anaerobic gram-negative bacilli
Prevotella
Porphyromonas
Fusobacterium
Bacteroides
Capnocytophaga
Leptotrichia
Campylobacter
Selenomonas
Anaerobic gram-negative cocci
Veillonella
Anaerobic gram-positive bacilli
Eubacterium
Anaerobic gram-positive cocci
Peptostreptococcus
Streptococcus
Clostridium

CLINICAL FEATURES

The clinical spectrum of anaerobic pleuropulmonary infections ranges from an acute pneumonic process to a chronic indolent disease.[69] Based on the duration of symptoms and the disease pathology, the presentation can be divided into acute, subacute and chronic.

In patients with acute anaerobic pneumonitis without any associated suppuration, the clinical findings and the radiologic picture mimics acute pneumococcal pneumonia. When 46 patients with anaerobic pneumonitis were compared with another group of 46 patients with *Streptococcus pneumoniae* pneumonia, the key differentiating features included an absence of rigors, presence of conditions that predisposed to aspiration, and longer mean duration of presenting symptoms in those with anaerobic infections.[69] The common features include a febrile respiratory illness, peripheral leucocytosis and absence of bacteremia. Since the natural history of cavity formation and subsequent tissue necrosis takes about 7 to 14 days, the presentation of lung abscess and empyema is subacute and the median duration of symptoms is around two weeks.

Patients with chronic anaerobic pneumonitis usually present as an indolent disease with a protracted course. The mean duration of illness is usually weeks to months rather than a few days. Recurrent low grade fevers and weight loss are observed. In all of their patients,[61-64] the authors were able to isolate a small number of anaerobic pathogens in the culture, but they were unable to culture any aerobic organism in any patient. It is quite possible that the chronicity is due to selective but paucibacillary presence of anaerobes, unlike in other forms of anaerobic pleuropulmonary infections where there is associated polymicrobial aerobic growth. This prolonged and persistent illness mimics pulmonary tuberculosis, which is very common in our country.

Foul Smell

The association of anaerobes and putrid odor dates way back to 1893, when Veillon[70] observed foul smell in a pure culture of an "anaerobic" organism. Ever since the classical study of Altemeier[71] in 1938, foul smell is considered to be pathognomonic of anaerobic infections. The putridity is believed to be due to volatile short-chain fatty acids, which are the end products of anaerobic metabolism. However, some anaerobic cocci do not produce these volatile fatty acids.

While this characteristic feature is noted in approximately 50% to 60% of the patients with lung abscess, necrotizing pneumonia and empyema, the incidence of putrid sputum is only 5% to 18% in patients with acute anaerobic pneumonitis.[33] The absence of putridness does not exclude the possibility of anaerobic lung infections. None of their reported patients with chronic anaerobic pneumonitis[61-64] had foul smelling sputum.

LABORATORY DIAGNOSIS

Since the anaerobes have an inherent property of inability to survive in the atmosphere, it is not easy to obtain specimens for microbiologic examination. In order to establish the diagnosis, a strong coordination is needed between the clinician and the microbiologist. Appropriate specimens that have been collected stringently in order to avoid contamination should be expeditiously sent in an appropriate transport medium to the laboratory for specific anaerobic cultures.

Sampling Techniques

The collection of specimens for diagnosing anaerobic pleuropulmonary infections is based on the premise that the normal tracheobronchial tree is sterile below the level of the larynx. Expectorated sputum, nasopharyngeal aspirate, endotracheal or tracheotomy tube aspirates and unprotected bronchoscopic aspirates are rendered unsuitable for subjecting to culture methods as these specimens contain a significant amount of commensal anaerobic microbes. Pleural fluid and tissue samples collected during surgical procedures like thoracotomy and thoracoscopy are by and large uncontaminated but difficult to obtain. In order to procure an ideal and valid sample (Table 63.4) that is free of the anaerobic-rich oral flora, various specialized techniques have been described to obtain the specimen directly from the lower respiratory passages and beyond.

Transtracheal Aspiration (TTA)

As the name suggests, this technique involves collection of the specimen directly from the trachea. In doing so, the upper respiratory tract is bypassed thereby avoiding the contamination of the sample. First employed in the 1960s,[72-74] this soon became the procedure of choice in patients with pneumonia.[75] The task of procuring a reliable specimen was made much easier and recovery of anaerobes by this method was consistently demonstrated in many studies.[16,33,57] However, TTA is

TABLE 63.4: Respiratory specimens valid for culture of anaerobes

1. Transtracheal aspirate
2. Percutaneous transthoracic needle aspirate (under imaging guidance)
3. Empyema/pleural fluid
4. Protected fiberoptic bronchoscopic catheter brushing
5. Thoracotomy (open lung biopsy) specimen

[to be collected immediately in an anaerobic transport medium] no longer in vogue as this technique is fraught with complications and samples are rarely obtained prior to initiating empiric antibiotic therapy for "pneumonia."

Percutaneous Transthoracic Needle Aspiration

Transthoracic needle aspiration is another means of obtaining an uncontaminated specimen.[76] The best use of this technique was described from France in 1965[49] where culture of the aspirated material grew anaerobic bacteria in 22 out of 26 patients with lung abscesses. Although there are no large trials with this investigative modality, the advent of modern imaging techniques has resulted in this method being adopted as the procedure of choice in patients suspected to have anaerobic lung infections, including pleural collections. The authors employed this method under image guidance to establish the anaerobic etiology in two of their four documented patients with chronic anaerobic pneumonitis.[62,64]

Bronchoscopic Protected Catheter Brush

The use of bronchoscopic-protected catheter brush for the diagnosis of anaerobic lung infections was also advocated.[77-79] To further improve the bacteriologic yield, local anesthetic agents were restricted and lignocaine preparations without antibacterial additives were preferred.[80,81] The limitation of this procedure is that it may not always be feasible to perform before initiating antibiotic therapy. Moreover, quantitative cultures may not always be readily available.

Specimen Transport and Processing

Given the anaerobic nature of the organisms, it is essential to exercise extra caution while collecting and transporting the specimens. The samples should immediately be transferred into the tubes, which are free from oxygen gas.[82] Once the specimens reach the anaerobic laboratory, recovery of pathogenic bacteria should be ensured by appropriate processing. As expected, the yield of anaerobes was much higher when the specimens were analyzed in dedicated anaerobic research laboratories. When 25 specimens were simultaneously examined in a routine clinical microbiology laboratory and an anaerobic research laboratory, the etiologic bacteria were identified in all 25 specimens by the research laboratory and in only four by the routine laboratory.[57] Furthermore, in the specimens of these four subjects, a total of 14 anaerobes (i.e. 3.5 anaerobes per patient) were grown by the research laboratory while the clinical laboratory recovered only one organism per patient. A negative culture of a potential specimen containing anaerobic organisms can occur due to several factors (Table 63.5).

TABLE 63.5: Causes of failure to culture anaerobes from potential specimens

1. Prolonged air exposure during collection, transport and processing
2. Failure to perform Gram staining so as to obtain the initial clue
3. Failure to utilize satisfactory selective and differential culture media
4. Overdependence on fluid thioglycollate medium
5. Failure to hold anaerobic cultures for a prolonged time

[adapted from ref. 57]

Gram Staining and Culture Methods

Performing Gram's staining of the obtained specimens gives a rapid clue about the class of anaerobic bacteria responsible for the disease. Even staining of expectorated sputum, which is far from ideal sample for diagnosing anaerobic infections, would help in determining whether anaerobes are the causative organisms or not. The microscopic appearances of some of the common anaerobes, as visualized after Gram staining, are quite characteristic (Table 63.6).

Cultures performed on invariably "contaminated" samples containing dense anaerobic flora of the upper respiratory tract are usually meaningless. However, growth of normal oral commensals may be an indication of anaerobic lung infection. The specimens should be inoculated on at least three different culture media to get a definitive growth of anaerobic bacteria. In order to achieve an etiologic diagnosis in as many of the specimens thus obtained, quantitative cultures were applied.[83-85] Newer techniques like gas liquid chromatography have helped in detecting the metabolic end products of anaerobic bacteria.

TABLE 63.6: Appearance of anaerobic bacteria on Gram's stain

P. melaninogenicus:	Pale staining gram-negative coccobacillus
B. fragilis:	Pale, some what pleomorphic gram-negative bacillus
F. nucleatum:	Pale, gram-negative bacillus with pointed ends
Peptostreptococcus:	Small, gram-positive cocci, usually in chains
Veillonella:	Very small, gram-negative cocci in clumps, pairs or short chains

RADIOLOGICAL MANIFESTATIONS

The radiological findings depend on the stages of involvement during the natural history of the disease. Patterns in pneumonia can range from subsegmental infiltrates to bilateral multilobar consolidation. A review of the radiological features in patients with anaerobic pulmonary and pleural infections revealed that approximately 50% of the patients had lung parenchymal involvement while other 30% had pleural empyemas without lung disease, the remaining 20% had combined parenchymal and pleural shadowing.[86] Half of the lung parenchymal abnormalities consisted of consolidation while the other 50% were either lung abscesses or necrotizing pneumonias. A radiologic worsening was noted in all patients during the initial three days and in one-third of the cases, during the first week.

In our four documented patients with chronic anaerobic pneumonitis,[61-64] right lung involvement (Fig. 63.2) was noted in two patients and in the other two the left lung was affected. Radiological progression from pneumonitis to lung abscess after initiation of therapy was noted in 20% to 30% of patients.[69,86] Mediastinal and hilar lymphadenopathy has also been reported in a patient with anaerobic lung abscess.[87] Gas producing organisms can cause a pyopneumothorax.[88]

TREATMENT

During the first half of the previous century, when antibiotics were yet to be discovered, the main therapeutic measures included the postural drainage of lung abscesses and surgical management of empyemas. The main drugs used were arsenicals[89-91] and sulphonamides.[92,93] This was supplemented with adequate rest and proper nutrition.[94]

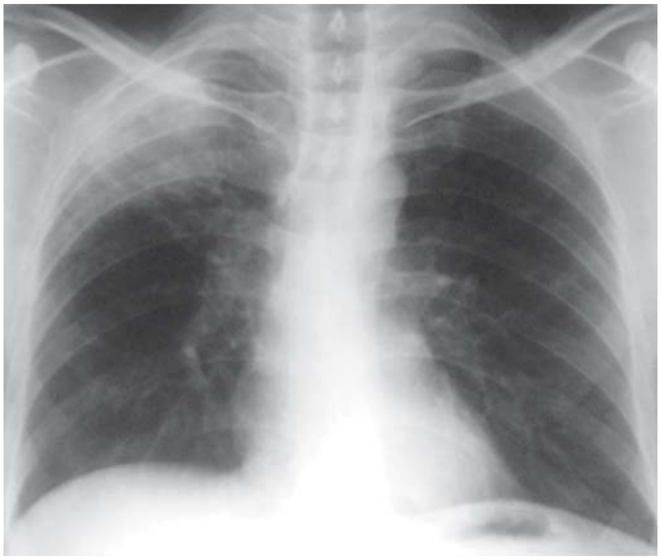

Fig. 63.2: Chest roentgenogram showing nonhomogeneous opacity in the right upper lobe in a patient with chronic anaerobic pneumonitis[64]

Subsequent to the advent of antibiotics, the prognosis improved significantly. During the initial few decades, penicillin G was the treatment of choice for more than half of the cases. Phenoxymethylpenicillin was often used during the follow-up period. Alternative antibiotics used then included lincomycin, chloramphenicol, tetracycline and erythromycin.[95,96] The clinical category of anaerobic lung infections was the deciding factor for usage of combinations, as well as dosage and duration of treatment. Since necrotic lung tissue is relatively avascular, a lower than the required dose would probably result in progressive damage. This could lead to suppurative complications and metastasis to other organs, e.g. cerebral abscess. Insufficient duration of therapy was responsible for a high relapse rate and distant seeding.[97]

Metronidazole too showed good bactericidal activity *in vitro* against anaerobes and initial results were encouraging.[98,99] Other advantages of this drug included 100% oral bioavailability and a substantially lower cost of therapy. After initial promising results, studies with metronidazole were discouraging. Collective data on 28 patients from three studies revealed therapeutic failures in 12 (43%) cases.[100-102] This poor performance was due to the fact that aerobic and microaerophilic streptococci are resistant to metronidazole. In another study[103] spanning six years, clinical success was noted when metronidazole was used in combination with penicillin or amoxicillin.

During the same period, better clinical efficacy of clindamycin in comparison to lincomycin was demonstrated.[104] In 1983, Levison and colleagues,[105] published the first large scale prospective trial wherein clindamycin (1800 mg/day) was compared with penicillin G (6 million units/day). There were no failures with clindamycin, while one in every five patients treated with penicillin did not show a satisfactory response. The mean duration of foul smelling sputum and fever were significantly lower in the clindamycin group. In patients with anaerobic pleuropulmonary infections, these studies led to the endorsement of three different regimes in circa 1984 by the consultants of the "Medical Letter," which include[106] (i) penicillin G, (ii) clindamycin and (iii) metronidazole + penicillin. Subsequently, a randomized controlled trial[107] comparing clindamycin versus penicillin in 37 patients with anaerobic lung infections confirmed the efficacy of clindamycin when a failure rate of 44% with penicillin and only 5.3% with clindamycin was demonstrated. The specimens of nine patients eventually grew penicillin-resistant strains of the genus *Bacteroides*, five of whom had been randomized to the penicillin arm. The authors concluded that clindamycin should be the initial choice for empiric treatment. The authors have documented the occurrence of isolates from a patient with anaerobic lung abscess that were resistant to penicillin and metronidazole.[108]

In recent times, although the efficacy of several new antibiotics has been demonstrated in community-acquired pneumonia, the role of these drugs in bacteriologically confirmed lung abscess and empyema has not been systematically studied. Most of these agents show excellent activity against common aerobic respiratory pathogens including the trio of "atypical" organisms. Amongst the fluoroquinolones, moxifloxacin and gemifloxacin have good *in vitro* activity against anaerobic organisms.[109,110] Although ticarcillin and piperacillin, the semisynthetic penicillins, possess substantial antianaerobic properties,[111,112] up to 30% of beta-lactamase producing anaerobic gram negative bacilli, especially *B. fragilis*, are resistant to this group of drugs.[113] Imipenem, which belongs to the carbapenem group, is highly effective against beta-lactamase, producing *B. fragilis*.[114] The suggested dosages of common antianaerobic drugs are given in Table 63.7. Antibiotics should be continued until symptoms have subsided, any fluid collection has resolved or stabilized and there is appreciable radiological clearing.[115] A minimum duration of two to three weeks is recommended.[116]

Surgery

Surgical drainage is the cornerstone for the management of patients with empyema. However, the frequency of surgery for lung abscess reduced drastically once effective antibiotics became available. In comparison to approximately half of the patients requiring surgical treatment for pulmonary abscess during the preantibiotic era,[117] 40 years later only 10% to 14% patients needed intervention.[118-120] In patients with lung abscess and necrotizing pneumonia without pleural involvement, the indications for surgery include failure of antibiotics and life-threatening hemoptysis. A lobectomy may also be indicated, if an underlying malignancy is suspected. When surgery is contraindicated due to comorbid conditions, percutaneous catheter drainage is helpful in alleviating the symptoms.[121]

TABLE 63.7: Suggested antianaerobic drugs and dosage

Antimicrobial Agents	*Dosages (per day)*
Penicillin G	10 to 20 million units (IV/IM)
Metronidazole	400 mg, 3 times a day (oral)
Clindamycin	600 mg, 3-4 times a day (oral)
Chloramphenicol	500-1000 mg, 4 times a day (oral)
Amoxycillin + clavulanate	500 mg + 125 mg, 3 times a day (oral)
Ticarcillin + clavulanate	3 gm + 100 mg, 3-4 times a day (IV)
Piperacillin + tazobactum	4 gm + 500 mg, 3 times a day (IV)
Imipenem	500 mg, 3-4 times a day (IV)

[Dosages to be adjusted as per the patients' profile]

PROGNOSIS

After the introduction of antibiotics, most patients have had a favorable outcome with the overall mortality rate reducing from 34% to 10% over time.[16] Fatal disease processes like necrotizing pneumonia and septic emboli are rarely seen. A delayed clinical response is noted in subjects with empyema and cavitary disease, especially if the cavity is greater than 6 cm in diameter. Morbidity in such patients does not improve until drainage of fluid is achieved or cavitary closure occurs over time. Other factors responsible for a poor prognosis include a chronic presentation beyond two months, elderly age group, bronchial obstruction, nosocomial aspiration and associated serious comorbidities. In the largest series of 193 patients,[16] mortality directly due to the anaerobic infection was observed in 4% while in another 7%, the disease process triggered a downhill course that eventually culminated in death.

CONCLUSION

The bacterial flora of the oral cavity is predominantly anaerobic. These commensal organisms have the propensity to cause disease in people prone to aspiration. Unfortunately, anaerobes as a key cause of pleuropulmonary infections are largely overlooked. The clinical and radiological features are often mistaken, which increases morbidity. In a patient with poor orodental hygiene and a history suggestive of aspiration along with radiological picture compatible with involvement of the dependent pulmonary segments, pulmonologists must exclude anaerobic lung infections.

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Section

9

ASTHMA

SK Jindal

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Bronchial Asthma—Epidemiology

SK Jindal

INTRODUCTION

Asthma, although known since antiquity, remains a disease of wide heterogeneity and variability. It has been differently understood in different cultures at different times. Some descriptions are available in the ancient Ayurvedic, Greco-Roman, Chinese and Egyptian literature.[1] The word "asthma" is derived from the Greek word, which meant "to pant heavily" or "gasp for breath." In Hindu Vedic medicine, it was known as "Tamaka Swasa."

DEFINITION

There is no uniform agreement on its definition in spite of the fact that the problem is recognized and appreciated by even the lay, all over the world. For a clinician, it is characterized by episodic wheezing, breathlessness and/or cough. Functionally, there is widespread narrowing of the intrapulmonary airways and demonstrable, reversible obstruction. Pathologically, it is a chronic inflammatory disorder of the airways. Description of asthma, proposed by the Global Initiative for Asthma (GINA), is presently the most accepted and understood definition:[2]

"Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with Airway Hyper-Responsive (AHR) that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in early morning. These episodes are usually associated with widespread, but variable airflow obstruction within the lung that is often reversible either spontaneously or with treatment."

The operational definition as above is fairly broad and comprehensive, but lacks precision. This is particularly difficult from an epidemiological point of view for the assessment of burden and comparative analysis.

EPIDEMIOLOGY

There is a marked variability in the global prevalence rates. It is reported to involve from about 1% to over 20% individuals in different populations.[2-4] An overall global asthma burden of about 300 million patients had been previously estimated based on the then prevalence rates.[3,5]

Prevalence rates from India and several other Asian countries have been reported to generally, lie between 2 to 5% in most countries.[4,6-10] The absolute burden is however enormous, considering the density of population in the Asian region, especially in India, China and Bangladesh, which comprise a large chunk in this region. The Indian estimates, based on the average, 2.05% prevalence of current asthma was 21 millions for all age groups, in the total population of 1.028 billion individuals in 2001[9] (See Chapter 34 on The Burden and Clinical Spectrum of Respiratory Diseases).

ECONOMIC BURDEN

There is a huge economic burden of asthma on both the individual and the society.[11-14] The burden is related to the direct costs of management and indirect losses due to school and work absenteeism.[15,16] The costs of "not treating" or mistreating asthma are even higher.[17]

The data available on economic burden in India is rather sparse. An attempt at assessment was made on the basis of prevalence rates available in different studies.[18] The estimated total annual cost of about ₹ 32 billion for patients with chronic asthma with additional costs of about ₹ 5 billion for acute asthma (for the year 2011)[18] is an enormous burden for the health care infrastructure of a developing country.

EPIDEMIOLOGICAL DIFFERENCES

The wide range in prevalence rates of different populations is partly "true" and partly attributable to methodological differences. Most importantly, the definition of asthma employed in different studies is the major determinant. There are epidemiological differences in the diagnosis of "current asthma", "ever-asthma" or presence of airway hyper-responsiveness. The different clinical symptoms and signs used for diagnosis may often overlap and are difficult for interpretation in community studies. For example, wheezing is reported almost twice as often as asthma. Therefore, history of wheezing used for diagnosis of asthma is frequently misleading, especially in case of children. An overlapping diagnosis of chronic bronchitis and Chronic Obstructive Pulmonary Disease (COPD) is also an important mimic of asthma in adults. The sensitivities and specificities of the questionnaires and/or other objective test, used for diagnosis of asthma are also different. One-time single assessment of airway obstruction by the measurement of Peak Expiratory Flow (PEF) or other spirometric indices cannot be used for the diagnosis of asthma and airway reversibility is difficult to perform in the field studies. Validation and standardization of the study methodology are therefore, of great importance for meaningful and comparative assessments.

FACTORS INFLUENCING PREVALENCE OF ASTHMA

True differences in the prevalence of asthma can be attributed to several ethnic, genetic, geographical, occupational and environmental differences. A host of these factors would influence the occurrence of asthma.

The prevalence of asthma is influenced by several risk factors, which can be broadly categorized into the host and the environmental factors that influence the development of asthma (Table 64.1). The development is largely determined by host factors, while the triggering is mostly caused by environmental exposures. Some of the factors from both the host and the environmental groups may also overlap in their roles and cause asthma development, as well as the trigging of symptoms.

TABLE 64.1: Important risk factors that influence the development of asthma

A. Host factors
    1. Age and sex
    2. Socioeconomic status
    3. Racial and ethnic factors
    4. Genetic polymorphisms
    5. Other atopic conditions
    6. Obesity
B. Environmental factors
    1. Aeroallergens
    2. Infections (? Protective role)
    3. Occupational exposures
    4. Environmental pollutants
    5. Outdoor pollution?
    6. Indoor pollution
        - Environmental tobacco smoke/In utero exposure to smoke
        - Solid fuel combustion
    7. Diet: Processed foods
        Breastfeeding (Protective role)

Host Factors

Age and Sex: On an average, asthma occurs with equal frequency in both sexes. There is a male predominance in children, being twice as common in boys as in girls before 14 years of age.[19] The sex difference disappears as the age advances, to a higher incidence in women in adults.

Asthma is more common in children in the 5 to 14 years age groups. Being a chronic disease, the cumulative prevalence of asthma increases as the age advances. The earlier belief that "children often grow out of asthma" is not factually true. Although from about a third to half of the children may become asymptomatic as they grow, the disease cannot be labeled as "eliminated." A large number of these children develop symptoms later in life.

Genetic Factors: There is a strong genetic predisposition of asthma. The presence of a family history of asthma and other allergies in the first degree relatives of patients, indicates the role of genetic factors. Identical twins were found to have a very high relative risk (17.9) of asthma in a study on cumulative incidence of asthma in twins.[20] The evidence was strongly considered in favor of the genetic predisposition.

No single gene defect is identifiable in asthmatic patients. However, multiple genetic polymorphisms associated with clinical asthma and/or BHR have been identified, some of which may actually affect the bronchodilator responsiveness.[21-24] Various other genes are found to modify the treatment response to antiasthma drugs, including the bronchodilators, corticosteroids and leukotriene modifiers.[25-28]

Genetic factors are important determinants of susceptibility to allergic diseases and asthma. Recent studies have highlighted their role in determining the in utero development and early life susceptibility to allergies.[29] This has resulted in better endophenotying, prognostication and prediction of treatment responses.[29] It can be therefore, anticipated that the gene polymorphism may play an important role in future in planning and improving the management of asthma.[27-30]

Other Host Factors: Asthma is known to differ in prevalence in different racial and ethnic populations. Some of these differences could actually be attributed to different genetic polymorphisms. Common environmental exposures may also influence the prevalence differences.

Presence of nasal (allergic rhinitis) and skin (atopic dermatitis) atopies, sinusitis and nasal polyposis is frequently associated with asthma. They possibly share a common genotyping and pathogenesis. Nasal allergy in particular is said to exist with asthma as an essential companion—“one airway–one disease” (Chapter 65).

Presence of obesity is also a recognized risk factor.[31] Obesity is partly genetic and partly environmental in origin. In obesity, asthma is supposedly mediated through the release of leptins.

Environmental Factors

Several environmental exposures, such as aeroallergens, occupational agents, tobacco smoke, outdoor and indoor air pollutants and possibly infectious agents have been implicated in the development of asthma. Some of these agents may also act as “precipitating” or “aggravating” factors (triggers) for clinical symptoms of asthma.

Allergens: The role of allergens in asthma development is not entirely clear. Many air borne pollens, fungal spores, home dust mite, insect debris, cat and dog dander have been implicated as independent risk factors for asthma.[32-35] Early exposure to cat and dog dander has been reported as protective against allergen sensitization in some studies, while others suggest that it increases the risk.[35-37]

Infections: Infections are important triggers of asthma symptoms. Respiratory Syncytial Virus (RSV) and parainfleunza virus infections are known to cause asthma in children.[38] On the other hand, early childhood infections are reported to protect from asthma (Hygiene hypothesis),[39] possibly explaining the lower asthma prevalence in the developing countries, including in India, attributable to higher occurrence of childhood infections. The “hygiene hypothesis” is based on the concept that exposure to airway infections and allergens early in life causes maturation of T-helper 1 (Th 1) lymphocytes over Th-2 lymphocytes, thereby decreasing the risk of allergies.[40] The theory has been further supported by some studies, but not by others.[41,42] The issue remains unresolved. Genetic susceptibility of an individual may also contribute to this development of asthma.

The common organisms, which have been cultured from bronchoalveolar lavage samples are the viruses (adenovirus, parainfluenza, RSV and influenza), mycoplasma and Chlamydia. They may have important role in asthma development, airway inflammation and remodeling.[43] Of various parasites, only hook worm infestations have been shown to reduce the risk.[44]

Occupational Exposures: Exposure to chemical vapors, irritant gases, metal fumes and other exhausts amongst persons engaged in different occupations may cause airway sensitization and increased production of IgE, which commonly manifest as occupational asthma.[45-47] Occupational sensitization is also responsible for both the development and precipitation of asthma.

Occupational asthma occurs mostly in adults, generally after an exposure period of month to years in sensitized individuals.[48,49] (Also see Chapter 111). Both IgE mediated and cell-mediated immunological reactions are involved.[50]

Environmental Pollution and Smoking: Exposure to environmental air pollutants in both outdoor and indoor conditions is an important cause of respiratory morbidity and increased asthma exacerbations.[51] Domestic combustion of solid fuel for cooking and heating is an important cause of indoor air pollution in India as well as in several third-world countries. Combustion exhausts are responsible for increased respiratory infections as well as lung function impairment in children. However, the role of environmental pollutants in the development of asthma remains debatable.[52]

Passive exposure to tobacco smoking, an important source of indoor air pollution Environmental Tobacco Smoke (ETS), is another important cause of increased asthma morbidity amongst both children and adults.[53-55] There is no good evidence to attribute the development of asthma to ETS exposure. However, in utero exposure of the fetus to smoking from a smoker mother is reported to influence the lung development. In utero tobacco smoke exposure is also shown to be responsible for persistent wheezing problems in children in the first year of life.[56]

Diet: Foods are commonly blamed to aggravate asthma in India, but scientific evidence is inadequate.[57] There are some data to suggest the role of processed foods, contributing to the increased incidence of asthma.[58] Breast milk fed infants have been shown to have lower incidence than those fed with formula milk or soy proteins.[59]

Asthma involves a complex interplay of different mechanisms, which result in a common clinical presentation of widespread airway obstruction. There are huge epidemiological and clinical variations in the disease spectrum. Several of these differences are perhaps based on different inflammatory phenotypes, which are now unfolding.[60,61]

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Allergic Rhinitis, Asthma and Comorbidities

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INTRODUCTION

Allergic Rhinitis (AR) and asthma are the most common atopic diseases with an increasing prevalence during the last decades.[1-4] Allergic rhinitis is an IgE-mediated inflammation of the nasal mucosa and IgE-mediated inflammation of the airways can either manifest as AR, asthma or both. However, the vast majority of patients with asthma have rhinitis, and rhinitis is a major independent risk factor for asthma in cross-sectional and longitudinal studies.[5-7] While the temporal relation of allergic rhinitis and asthma diagnoses may be variable, allergic rhinitis often precedes asthma. Moreover, AR is linked to other comorbid conditions like chronic hyperplastic eosinophilic sinusitis, nasal polyposis and serous otitis media.

Over 400 million patients worldwide suffer from AR and 300 million people suffer from asthma. Both AR and asthma are chronic inflammatory diseases of the airways and their inflammatory mechanisms are characterized by an inflammatory infiltrate made up of eosinophils, T cells and mast cells that release several mediators, chemokines and cytokines, local and systemic IgE synthesis, and a systemic link via the bone marrow. Studies have shown that patients with AR exhibit Bronchial Hyperresponsiveness (BHR) and increase in inflammatory cells, and that nasal allergen challenge further increases this hyperreactivity.[8,9] This potential link may be due to cross talk between the upper and lower airway, the direct impact of inflammatory mediators released locally and to the systemic link between the two.

Although cardinal structural differences exist between the nose and the lungs, the relationships between rhinitis and asthma can be viewed under the concept that the two conditions may be the manifestations of one syndrome, the “chronic allergic respiratory syndrome.” Moreover, the impact on costs, frequency of emergency room visits, hospitalization and quality of life is greater if AR is associated with asthma as compared to asthma alone[10,11] and treating AR in patients with asthma, and comorbid AR has shown to reduce hospitalization by 61%.[12]

Inflammation in AR

Upon allergen exposure, sensitized mast cells degranulate within minutes to release preformed and newly synthesized mediators that include histamine, proteases, cysteinyl leukotrienes (CysLTs), prostaglandins and cytokines; some of which induce the characteristic early-phase symptoms of AR, while others orchestrate the late-phase response via the infiltration of inflammatory cells, like eosinophils, basophils and T cells, into the nasal mucosa.[13-14] This infiltration of inflammatory cells can also be orchestrated by T-helper type 2 (Th2) cells within the local microenvironment. The subsequent release of additional mediators from these inflammatory cells, including histamine and CysLTs, sustains the inflammatory characteristic of the late-phase reaction. In chronic ongoing allergen inflammation, mast cells exhibit increased histamine releasability consequent to the enhanced FcεRI expression (increased numbers of IgE receptors) and surface-bound IgE, as well as the enhancement of signal transduction pathways.[14-18] While these processes together induce the phenomenon of priming, mast cells in patients with AR also express increased levels of β1 integrins and activation via the integrin receptors results in an enhanced release of inflammatory mediators even in the presence of lower amounts of allergen.[14-18] This process may, in part, contribute to the phenomenon of nasal hyper-responsiveness.

Link Between Allergic Rhinitis and Asthma

Epidemiology and Trigger Factors

Allergic rhinitis and asthma are closely linked based on a variety of parameters ranging from epidemiologic, immunologic and clinical evidences.[19] Epidemiologically, upto 40% patients with allergic rhinitis have comorbid asthma and up to 80% of patients with asthma experience nasal symptoms. Furthermore, in a study assessing the burden of allergic rhinitis in children, the prevalence of asthma was 3-fold higher in those children who had allergic rhinitis at baseline.[20] The trigger factors of AR, like indoor and outdoor allergens, can also cause asthma.

Inflammation and Pathomechanisms

Both AR and asthma are inflammatory diseases and their inflammatory mechanisms are similar in a way that they are characterized by an inflammatory infiltrate made up of eosinophils, T cells and mast cells that release several mediators, chemokines and cytokines, local and systemic IgE synthesis, and a systemic link via the bone marrow. Typical early- and late-phase responses are also common features to both rhinitis and asthma. Studies have shown that patients with AR exhibit BHR and increased number of inflammatory cells in their bronchial mucosa.[8,9] This increase in bronchial inflammation in response to allergen-induced rhinitis might contribute to the exacerbations of asthma frequently seen in individuals with underlying AR. Experimental studies in patients with Seasonal Allergic Rhinitis (SAR) without asthma have demonstrated an upregulation of adhesion molecule expression, eosinophil infiltration in both the upper and lower airways, after nasal allergen challenge and increased bronchial hyper-reactivity.[21] These results demonstrate that an allergic nasal reaction produces systemic inflammatory changes.

Systemic Inflammation in Allergic Rhinitis

AR is not associated with just localized inflammation of the nasal mucosa but also has a systemic component to it. This may explain in a significant way the mechanisms underlying the rhinitis-asthma link. Thus in patients with AR, allergen exposure results in the activation of immune cells, including Th2 lymphocytes. Some of these Th2 cells migrate to the bone marrow, where they stimulate the bone marrow to produce and recruit inflammatory cells, i.e. basophils, eosinophils and mast cell precursors to the inflamed target tissues. The selective recruitment of inflammatory cells into the lower airways can occur only in those individuals, with at least subclinical inflammation in the lower airways, in whom specific adhesion molecules, such as vascular cell adhesion molecule 1 and chemoattractants, such as TARC, eotaxin, are already upregulated. This parallel relationship is influenced by many interactions between the nose and the lower airways in that the nose plays a major homeostatic role by conditioning inhaled air, but perhaps even more important is the bidirectional interaction that results from the systemic inflammation that is produced after local allergic reactions.

Therapeutic Outcomes of Treating AR in Asthma

Several studies have shown that treating comorbid allergic rhinitis results in a lowered risk of asthma-related resource utilizations and hospitalizations.[12] For patients with asthma, the presence of comorbid allergic rhinitis is associated with higher total annual medical costs as well as increased likelihood of asthma-related hospital admissions and emergency visits.[10,11] Thus, there is a clear evidence that comorbid allergic rhinitis can be an indicator marker for more difficult-to-control asthma or poor asthma outcomes. In a recent international survey on the impact of concomitant AR and asthma on patient health and quality of life, the presence of AR in children with asthma disrupted their lives by limiting their ability to get a good night's sleep, concentrate at work/school or enjoy social activities and that when AR symptoms flared up, asthma symptoms worsened.[22] Corren et al. reported that nasal symptoms of subjects exposed to a "cat room" were more severe if they had concomitant asthma than if they had rhinitis alone.[23] These findings highlight the potential for improving asthma outcomes by treating comorbid AR.

Yet there are individuals who suffer only from rhinitis but not asthma. The precise reason for this is not completely known but can be presumed that these patients might have a milder form of the disease. Therefore, the relationships between rhinitis and asthma can be viewed under the concept that the two conditions are manifestations of one syndrome, the chronic allergic respiratory syndrome, in two parts of the respiratory tract. At the low end of the syndrome's severity spectrum, rhinitis appears to be the sole manifestation, although pathologic abnormalities in the lower airways are already present. At the higher end, rhinitis is worse and the lower airways disease becomes clinically evident. Once manifested, the two conditions track in parallel in the terms of severity.[24]

However, AR is often underdiagnosed and undertreated due to the lack of appreciation of the disease burden and its impact on the quality of life, socially at school and in the workplace and its huge economic burden. Thus, there was clearly a need for a global evidence-based document that would highlight the interactions between the upper and lower airways, including diagnosis, epidemiology, common risk factors, management and prevention. The Allergic Rhinitis and its Impact on Asthma (ARIA) document was first published in 2001 as a state-of-the-art document for the specialist, the general practitioner and other health care professionals.[25]

Allergic Rhinitis and its Impact on Asthma (ARIA)

In 1999, during the ARIA, WHO workshop, an evidence-based document was produced using an extensive review of the literature available up to December 1999. The statements of evidence for the development of ARIA followed WHO rules and were based on those of Shekelle et al.[26]

The ARIA document was intended to be a state-of-the-art review for the specialist as well as for the general practitioner and other health care professionals:

- To update their knowledge of AR.
- To highlight the impact of AR on asthma.
- To provide an evidence-based documented revision on the diagnosis methods.
- To provide an evidence-based revision on the treatments available.
- To propose a stepwise approach to the management of the disease.

The ARIA Classification of Allergic Rhinitis

Allergic rhinitis was previously classified into seasonal, perennial and occupational. Perennial allergic rhinitis is usually caused by indoor allergens such as dust mites, molds, insects (cockroaches) and animal danders. Seasonal allergic rhinitis is related to a wide variety of outdoor allergens such as pollens or molds.

However, from a therapeutic point of view, it is often difficult to differentiate between seasonal and perennial symptoms. Some seasonal allergens cause perennial symptoms, some perennial allergens may cause symptoms only during certain periods of the year and the majority of patients are now polysensitized to seasonal and perennial allergens. Therefore, a new classification to provide a better description of allergic rhinitis has been proposed by the ARIA as "intermittent" or "persistent" rhinitis[25] (Fig. 65.1). The severity of allergic rhinitis on the other hand can be classified as "mild" or "moderate-severe" on the basis of symptoms as well as the quality of life of the patient. Several studies have now validated this classification.[27,28]

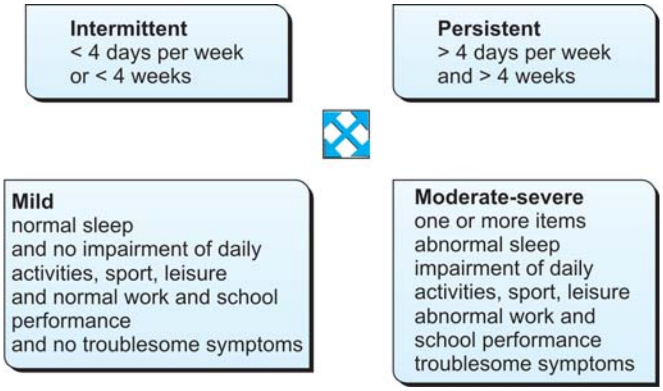

Fig. 65.1: The new ARIA classification

ARIA Update

The pharmacological treatment of AR proposed by ARIA is an evidence-based and stepwise approach depending on the classification of the symptoms and comprises of patient education, allergen avoidance, pharmacotherapy and validated allergen-specific immunotherapy. Nonsedating, second-generation antihistamines are the mainstay in mild-to-moderate intermittent and persistent AR. As a step-up, Intranasal Corticosteroids (INCS) may be added. Intranasal corticosteroids is the first line in moderate-severe persistent AR. However, subsequent research and increasing knowledge have resulted in the ARIA 2008 update which includes new information on existing therapies as well as newer therapies like anti-IgE mAb and antileukotrienes with a new level of evidence for pharmacotherapy and increasing information on the link between the upper and lower airways. Most importantly ARIA emphasizes that successful management of both rhinitis and asthma requires an integrated view of the airways and an integrated approach of treatment.

The ARIA update was commenced in 2004. Several chapters of ARIA were extensively reviewed using the Shekelle evidence-based model and papers were published in peer-reviewed journals: Tertiary prevention of allergy, complementary and alternative medicine, pharmacotherapy and anti-IgE treatment, allergen-specific immunotherapy, links between rhinitis and asthma and mechanisms of rhinitis. There was then a need for a global document that would highlight the interactions between the upper and lower airways, including diagnosis, epidemiology, common risk factors, management and prevention. Moreover, the allergy perspective should also be targeted towards developing countries. Thus, the ARIA 2008 update was published.[29-33]

One important aspect of the ARIA update was to consider the comorbidities of AR and in particular, asthma. Epidemiologic studies have consistently shown that asthma and rhinitis often coexist in the same patients in every region of the world. The vast majority of patients with asthma have rhinitis, but the prevalence of asthma in rhinitis patients still needs to be assessed. Adults and children with asthma and documented concomitant AR experience more asthma-related hospitalizations and physician visits and incur higher asthma drug costs than adults with asthma alone. These patients also experience more frequent absence from work and decreased productivity. However, some studies have not shown such an association.

Many patients with AR have an increased bronchial reactivity to methacholine or histamine, especially during and sometime after the pollen season. Nasal and bronchial inflammation is often related, but remodeling of the nose and bronchi appears to differ.

A large list of treatments was considered in the ARIA 2008 update. Concerning pharmacologic treatments, intranasal corticosteroids are recommended as the first-line therapy in patients with moderate-to-severe disease and are also effective on ocular symptoms, H_1-antihistamines of the second generation are important treatments for all patients and leukotriene receptor antagonists are particularly important for patients with rhinitis and asthma. On the other hand, tertiary prevention of allergy is still a matter of debate since clinical trials do not usually show any efficacy of single allergen avoidance measures. Allergen-specific immunotherapy in patients with AR has a prolonged preventive effect on the development of asthma when stopped. Sublingual allergen-specific immunotherapy has proven to be a safe and effective treatment,[34] but clinical trials need to be standardized. Mechanistic studies have repeatedly demonstrated that Sublingual Swallow Immunotherapy (SLIT) is able to affect the T response by modulating some of the activities of T regulatory cells. Recent studies have shown the dose-dependency of the clinical effects of SLIT and the magnitude of the effect over placebo largely exceeded the 20% suggested threshold, required for defining an immunotherapy as clinically effective and that SLIT has been formally shown the capability of reducing both the direct and indirect costs of the disease. A new World Allergy Organization (WAO) consensus document on SLIT has summarized the state-of–the-art on SLIT with relevant recommendations.[35] Specific immunotherapy, allergen avoidance and pharmacotherapy have come to be the recommended form of treatment for allergic diseases, both in adults and children. An algorithm of the management of AR is provided (Fig. 65.2).

Other Comorbidities of AR

Allergic rhinitis is linked to other comorbid conditions like rhinosinusitis, nasal polyps, sleep disturbances like Obstructive Sleep Apnea (OSA) and otitis media with effusion (Fig. 65.3). As many as 70% of patients with AR reported suffer from nasal and ocular symptoms. Acute sinusitis is found to be more common in patients with AR and Eustachian tube obstruction has been shown to increase in the peak season in patients with seasonal allergic rhinitis. AR interferes with sleep and leads to increased daytime sleepiness. Allergic rhinitis patients reported difficulty falling asleep, nocturnal awakening, early awakening, nonrestorative sleep, lack of sleep and snoring. The treatment of allergic rhinitis is shown to improve coexisting conditions, including conjunctivitis, asthma, rhinosinusitis, otitis media with effusion and sleep disorders.

CONCLUSION

Allergic asthma and rhinitis are manifestations of the atopic syndrome. Epidemiologic, experimental and clinical data underline the importance of this link. Although the diseases commonly occur together, it is still unclear why some allergic patients develop only asthma and others only rhinitis. The reason for the variety in clinical expression of allergic airway disease is not known. Besides a genetic predisposition, environmental factors contribute to the development of the allergic phenotype. Local and systemic inflammatory processes also seem to be involved. However, their exact contribution to the clinical picture of airway allergy still remains to be elucidated. Although it is clear that the condition of the upper airways has an impact on lower airway physiology, the mechanisms underlying this relation are far from being resolved. To date, most data

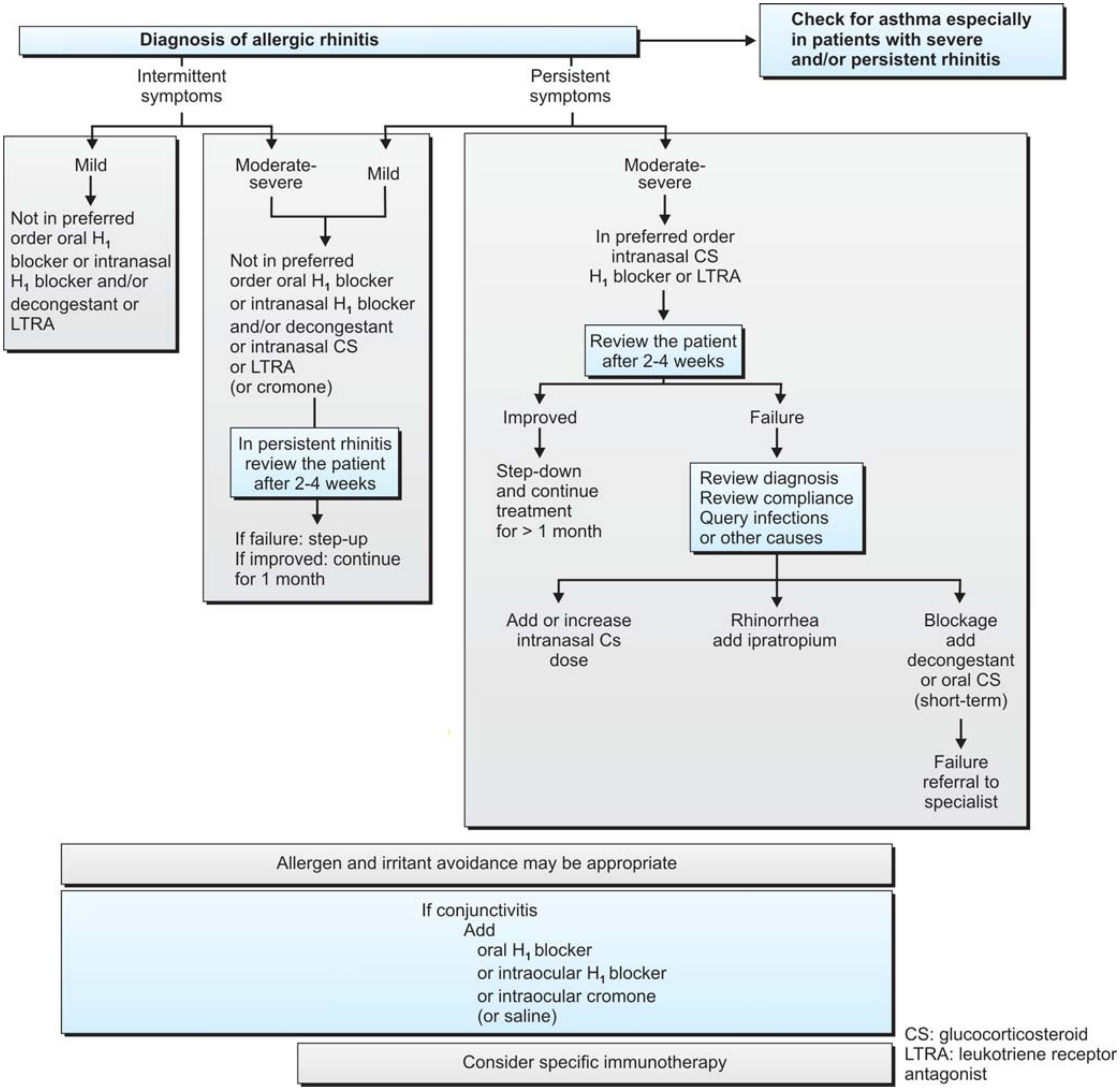
Diagnosis of allergic rhinitis
Check for asthma especially in patients with severe and/or persistent rhinitis
Intermittent symptoms
Persistent symptoms
Mild
Not in preferred order oral H1 blocker or intranasal H1 blocker and/or decongestant or LTRA
Moderate-severe
Mild
Not in preferred order oral H1 blocker or intranasal H1 blocker and/or decongestant or intranasal CS or LTRA (or cromone)
In persistent rhinitis review the patient after 2-4 weeks
If failure: step-up
If improved: continue for 1 month
Moderate-severe
In preferred order intranasal CS H1 blocker or LTRA
Review the patient after 2-4 weeks
Improved
Failure
Step-down and continue treatment for > 1 month
Review diagnosis
Review compliance
Query infections or other causes
Add or increase intranasal Cs dose
Rhinorrhea add ipratropium
Blockage add decongestant or oral CS (short-term)
Failure referral to specialist
Allergen and irritant avoidance may be appropriate
If conjunctivitis
Add
oral H1 blocker
or intraocular H1 blocker
or intraocular cromone
(or saline)
Consider specific immunotherapy
CS: glucocorticosteroid
LTRA: leukotriene receptor antagonist

Fig. 65.2: The algorithm for the treatment of AR recommended by ARIA

point towards a systemic link between upper and lower airways involving bloodstream and bone marrow.

The socioeconomic burden via annual costs of treating asthma and AR—both direct costs (hospitalization, medications) and indirect costs (time lost from work, premature death)—are substantial and represent an even heavier burden in societies with emerging economies. In eight countries in the Asia-Pacific, the annual per-patient direct costs ranged from US $108–1,010, total per-patient costs, including productivity costs, ranged from US $184–1,189.[36]

The recommendations of the ARIA workshop in 1999 are still valid with respect to the ARIA update and in particular, it is recommended that all patients with AR, particularly if it is persistent, should be evaluated for asthma. AR is not only a risk factor for underlying

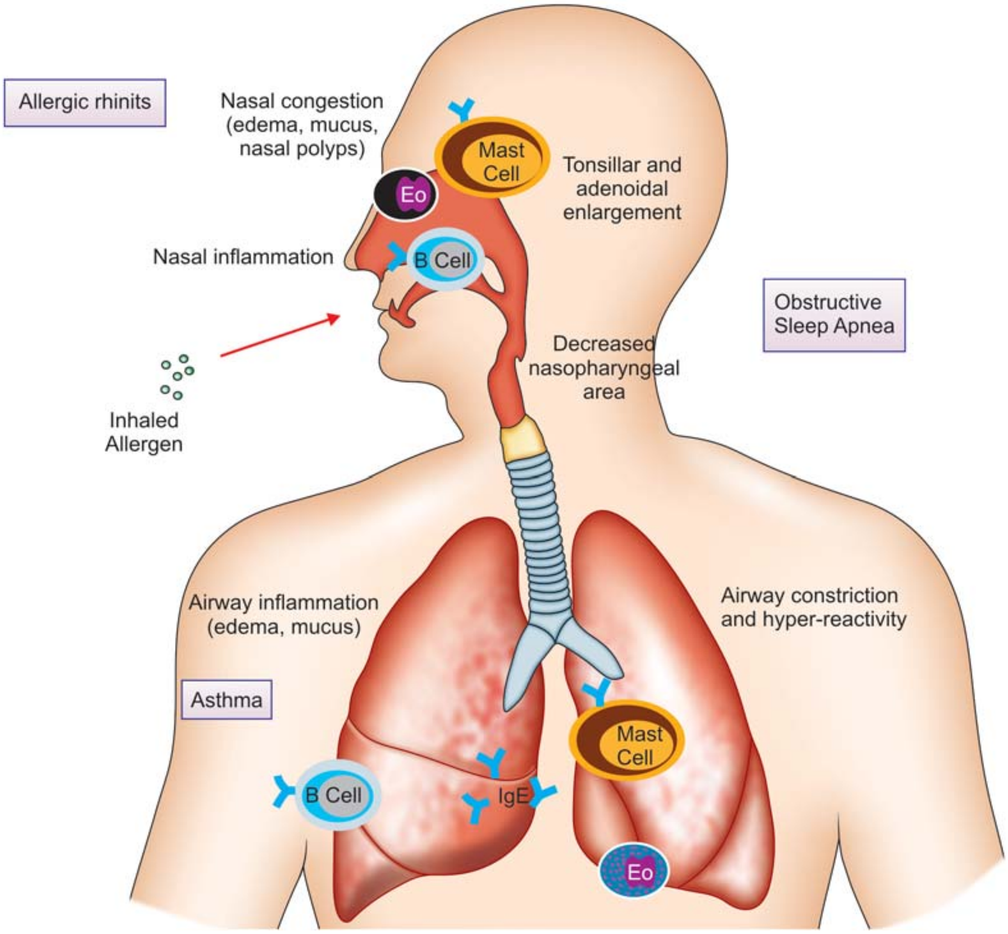
Allergic rhinits
Nasal congestion (edema, mucus, nasal polyps)
Mast Cell
Eo
Tonsillar and adenoidal enlargement
Nasal inflammation
B Cell
Obstructive Sleep Apnea
Decreased nasopharyngeal area
Inhaled Allergen
Airway inflammation (edema, mucus)
Airway constriction and hyper-reactivity
Asthma
Mast Cell
B Cell
IgE
Eo

Fig. 65.3: Chronic allergic respiratory syndrome
[Modified from Stokes JR, Casale T. AR, asthma and OSA- the link. In: Pawankar. Holgate Rosenwasser (Eds.). Allergy Frontiers Epigenetics to Future Perspective.]

asthma, but could be a risk factor for asthma exacerbations. Patients with asthma should likewise be evaluated for rhinitis and a combined strategy should ideally be used to treat the upper and lower airway diseases in the terms of efficacy and safety.

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66

Asthma Diagnosis

Liesel D'silva, Parameswaran Nair

INTRODUCTION

Correct diagnosis of asthma is the first step towards achieving disease control. To establish a diagnosis of asthma, the clinician should determine that episodic symptoms of airflow obstruction or airway hyperresponsiveness are present; airflow obstruction is at least partially reversible; and alternative diagnoses are excluded. The guidelines recommend the use of a detailed medical history, a physical examination and spirometry. Additional pulmonary function studies, bronchoprovocation tests, measures of allergic status, chest radiography and specific blood tests are not routinely necessary but may be useful when considering alternative diagnoses. Over the last 15 years, there has been increasing interest in the noninvasive biomarkers of airway inflammation as an adjunct to the assessment of clinical asthma control.

CLINICAL DIAGNOSIS

Medical History

A detailed medical history of the new patient who is known or thought to have asthma should address the following items (Table 66.1):[1-3]

Physical Examination

Physical examination may reveal findings (Table 66.2) that increase the probability of asthma, but the absence of these findings does not rule out asthma because asthma symptoms are variable. Therefore examination of the respiratory system may be normal during asymptomatic periods.[1]

TESTS FOR DIAGNOSIS AND MONITORING

In 1891, Lord Kelvin (Kelvin L, 1883) emphasized the importance of measurements by stating that "When you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind."

Symptoms are nonspecific and can result from variable airflow limitation, inflammation, moderate or severe chronic airflow limitation or other respiratory and nonrespiratory conditions. There are poor correlations between symptoms and airway function or airway inflammation and between airway function and inflammation. Reliance on symptoms alone could lead to misdiagnosis and under or over treatment. Therefore measurements are critical to understanding and individually treating airway disease such as asthma.[6]

Measurements of Lung Function

Although the diagnosis of asthma is usually based on the presence of characteristic symptoms, patients with asthma frequently have poor recognition of their symptoms. If their asthma is long standing they also have poor perception of symptom severity.[7] Physicians may also be inaccurate in their assessment of symptoms such as dyspnea and wheezing.[8,9] Therefore, measurement of lung function provides an objective confirmation of the

TABLE 66.1: Medical history in asthma

Symptoms that occur or worsen in the presence of precipitating factors	Recurrent cough Wheezing Shortness of breath Chest tightness Sputum production
Pattern of symptoms	Perennial, seasonal or both Continual, episodic or both Onset, duration, frequency (number of days or nights, per week or month) Diurnal variations, especially nocturnal and on awakening in early morning Colds go to the chest or take more than 10 days to clear up Symptoms improve by appropriate asthma treatment
Precipitating and/or aggravating factors	Viral respiratory infections Environmental allergens, indoor (e.g. mold, house-dust mite, cockroach, animal dander, mosquito repellants such as Type I synthetic pyrethroids) and outdoor (e.g. pollens, congress grass) Characteristics of home including age, air conditioning system, wood-burning stove, carpeting, over concrete, presence of molds or mildew, presence of pets with fur, characteristics of rooms where patient spends time (e.g. bedroom and living-room with attention to upholstery) Smoking, environmental tobacco smoke Exercise Occupational chemicals or allergens Environmental change (e.g. moving to new home; going on vacation; and/or alterations in workplace, work processes or materials used) Irritants (e.g. tobacco smoke, strong odors, air pollutants, occupational chemicals, dusts and particulates, vapors, gases and aerosols) Emotions (e.g. fear, anger, frustration, hard crying or laughing) Stress (e.g. fear, anger, frustration) Drugs (e.g. aspirin; and other nonsteroidal anti-inflammatory drugs, beta-blockers including eye drops, others) Food (e.g. black gram), food additives, and preservatives (e.g. sulfites) Changes in weather, exposure to cold air Endocrine factors (e.g. menses, pregnancy, thyroid disease) Comorbid conditions [e.g. sinusitis, rhinitis, nasal polyposis, gastroesophageal reflux disease, obesity, pulmonary tuberculosis*, allergic bronchopulmonary aspergillosis, obstructive sleep apnea, Churg-Strauss syndrome (very rare)]
Development of disease and treatment	Age of onset and diagnosis History of early-life injury to airways (e.g. bronchopulmonary dysplasia, pneumonia, parental smoking) Progression of disease (whether the disease has got better or worse) Present management and response to therapy, including management of exacerbations Frequency of using Short-acting beta2-Agonist (SABA) Need for oral corticosteroids including dose and frequency of use
Family history	History of asthma, allergy, sinusitis, rhinitis, eczema, or nasal polyps in close relatives
Social history	Social factors that interfere with adherence: Substance abuse Social network Level of literacy Ability to afford the medication Employment status
History of exacerbations	Usual prodromal signs and symptoms Rapidity of onset Duration Frequency Severity [need for urgent care, hospitalization, Intensive Care Unit (ICU) admission]

Contd...

Contd...

	Life-threatening exacerbations (e.g. intubation, ICU admission) Number and severity of exacerbations in the past year Usual management (what has worked in the past to treat the exacerbation)
Impact of asthma on patient and family	Episodes of unscheduled care (emergency department visits, urgent care, hospitalization) Number of days missed from school/work Limitation of activity, especially sports and strenuous work History of nocturnal awakening Effect on growth, development, behavior, school or work performance and lifestyle Impact on family routines or activities Economic impact
Assessment of patient's and family's perceptions of disease	Patient's, parent's and spouse's knowledge of asthma and belief in the chronicity of asthma and in the efficacy of treatment Patient's perception and beliefs regarding use and long-term effects of medications especially inhaled corticosteroids Ability of patient, parents or spouse to cope with the disease Level of family support and patient's, parent's or spouse's capacity to recognize severity of an exacerbation Economic resources Sociocultural beliefs

* Presence of additional symptoms of fever, expectoration or chest pain should raise the suspicion of pulmonary tuberculosis. Any patient who presents with cough of more than three weeks duration should have the sputum examined for pulmonary tuberculosis.[4,5]

TABLE 66.2: Physical examination in asthma

System	*Physical examination findings*
Upper respiratory tract	Increased nasal secretion, mucosal swelling, deviated nasal septum, nasal polyp, tenderness over sinuses, ear discharge, oral candidiasis (because of inhaled corticosteroid therapy)
Chest	Wheezing, wheezing during prolonged phase of forced exhalation In severe asthma exacerbations: Wheezing may be absent, cyanosis, drowsiness, difficulty in speaking, tachycardia, hyperinflated chest, use of accessory muscles, intercostal retraction Chronicity of asthma could lead to appearance of hunched shoulders, chest deformity
Skin	Atopic dermatitis, eczema

diagnosis of asthma, measures severity of airflow limitation, its reversibility and variability.

Of the various methods available to assess airflow limitation, spirometry, particularly the measurement of Forced Expiratory Volume in One Second (FEV_1), and Forced Vital Capacity (FVC) and Peak Expiratory Flow (PEF) measurement are widely accepted for use in patients over 5 years of age.[1]

Predicted values of FEV_1, FVC and PEF based on age, sex and height have been obtained from population studies. With the exception of PEF for which the range of predicted values is too large, they are useful to assess whether a given value is abnormal or not. Caucasian prediction equations are most commonly used for the interpretation of the results of routine spirometry in India; however a study[10] was undertaken to assess the interchangeability of Caucasian and north Indian prediction equations while interpreting routine spirometric data. The use of Caucasian prediction equations resulted in poor agreement with Indian equation in most height and age categories among both men and women. One of the reasons suggested was that the lung volumes in Indian subjects are approximately 10% smaller than corresponding values in Caucasians.[11] Therefore one needs to assess the most appropriate prediction equation for use in one's own clinical practice after considering ethnic differences in spirometric values.

Spirometry

Forced Expiratory Volume in 1 second (FEV_1) and FVC are measured during a forced expiratory maneuver using a spirometer. Variable airflow limitation of asthma is recognized objectively by the presence of SABA reversibility of FEV_1, i.e. greater than or equal to 12% and greater than equal to 200 ml from the prebronchodilator value;[12] however many asthma patients may not exhibit this reversibility at each assessment especially if they are on treatment. It is advisable to repeat the test at different visits. As spirometry is effort-dependent, proper instructions on how to perform the forced expiratory maneuver must be given to the patients and the highest of the three recordings selected. Spirometry should be accurately performed on appropriate equipment by trained personnel with monitoring of quality control.[12]

Spirometry with FEV_1 and VC values is an initial requirement and is better than PEF because it is more sensitive and discriminates between obstructive and non-obstructive ventilatory defects. FEV_1/FVC ratio less than 0.75 to 0.80 in adults and less than 0.90 in children suggests airflow limitation.[12]

Normal spirometry does not rule out asthma in a patient with a history of asthma-like symptoms or in a patient taking asthma controller medications.[13] Spirometry is often useful for excluding the possibility of Chronic Obstructive Pulmonary Disease (COPD)[14] and spirometry may reveal that asthma is more poorly controlled (i.e. a low FEV_1) than suggested by the frequency of symptoms and use of a rescue inhaler reported by the patient.[15] A low FEV_1 is also a strong predictor of a subsequent asthma exacerbation particularly in children.[16] FEV_1 can be measured accurately even during acute asthma attacks and helps to determine the need for hospitalization.[12,17]

Some of the common reasons for limited widespread use of spirometry include the lack of availability, a false belief that the test does not reveal additional information; “too time consuming” in a busy clinical practice or difficulty in interpretation of the test. General practitioners should be encouraged to use spirometry in their clinical practice.[18,19]

Peak Expiratory Flow (PEF)

Although spirometry is the preferred method of documenting airflow limitation, PEF monitoring is valuable to confirm the diagnosis of asthma and to monitor the disease particularly in patients who are poor perceivers of symptoms, and to identify occupational causes of asthma symptoms.[20] There are different methods of calculation for within-day variability and between-day variability in PEF, which may be documented in patient diaries.[20,21]

One of the most common methods for calculation of “within-day variability” is the following:

$$\frac{\text{Day's highest PEF value} - \text{Day's lowest PEF value}}{\text{Mean PEF}}$$

A diurnal variability of more than 8% suggests a diagnosis of asthma.

One of the most common methods for calculation of “between-day variability” is the following:

$$\frac{\text{Lowest morning PEF over 1-2 weeks}}{\text{Highest PEF}}$$

This index increases as PEF variation decreases.

Peak expiratory flow measurements are made with peak flow meters, which are relatively inexpensive, portable, plastic instruments that can be used by patients at home. However, PEF measurements are not interchangeable with FEV_1[22,23] and can underestimate the degree of airflow limitation. As the range of predicted values for PEF is too wide when measured with different peak flow meters, PEF measurements should be compared to the patient’s own previous best measurements using his/her own peak flow meter.[24] PEF measurements are effort dependant and careful instruction is required to reliably measure PEF.

Key Recommendations for Clinical Practice

Encourage patients to record and monitor their lung function in a diary for the diagnosis of asthma.
The upper limit of normal for diurnal variability in PEF is 8% and not the traditionally believed cut-point of 15% to 20%.
Normal lung function does not exclude a diagnosis of asthma.
Perform lung function measures accurately, on appropriate (calibrated) equipment, by trained personnel, and monitor quality control.
Enter actual values of lung function in the medical records (not just normal or abnormal).
Use the same peak flow meter on each occasion to compare PEF measurements within the same patient.

Measurements of Airway Responsiveness

When patients have symptoms consistent with asthma, but normal lung function, measurements of airway responsiveness to direct or indirect bronchoprovocation challenges are frequently used to establish a diagnosis of asthma; however bronchoprovocation challenge tests are not readily available in clinical practice. The direct bronchoconstrictors act on the airway smooth muscle receptors to induce bronchoconstriction. The indirect bronchoconstrictors involve an intermediate pathway, such as osmotic or non-osmotic mediator release from inflammatory cells, sensory nerve stimulation, and perhaps others and include exercise and Eucapnic Voluntary Hyperpnea (EVH), hypertonic saline, distilled water, adenosine monophosphate and the newest challenge test which is dry powder mannitol.[25] Direct airway responsiveness has been measured primarily by histamine and methacholine. Histamine and methacholine produce near identical responses on a milligram for milligram or millimole for millimole basis;[26] however histamine is now used infrequently because of a greater prevalence of adverse effects, such as cough, flushing and occasional syncope.[25]

Direct Challenges

Methacholine challenge is a highly sensitive test. Two of the most commonly used methods are the tidal breathing method and the dosimeter method.[27] Doubling concentrations of methacholine up to 16 mg/ml (higher for research purposes) are inhaled at five minute intervals from the start of one inhalation to the start of the next. Single measurements of FEV$_1$ are made at 30 and 90 seconds. The percent reduction in FEV$_1$ is compared with post saline FEV$_1$, and the test is continued until there has been a 20% or more decrease in FEV$_1$ or until the maximum concentration has been administered. The results are expressed as the provocation concentration causing a 20% FEV$_1$ decrease (PC$_{20}$ for the tidal breathing method and PD$_{20}$ for the dosimeter method). A sigmoid log dose-response curve is recorded. The normal range of PC$_{20}$ is greater than or equal to 8 mg/ml,[28] while that for PD$_{20}$ is greater than or equal to 7.8 µmol.[29]

A positive methacholine challenge is consistent with, but not diagnostic of asthma. When a patient has current symptoms, a negative methacholine challenge result excludes asthma with reasonable certainty.[25] Methacholine challenge is of limited value in guiding treatment in patients with isolated cough because a positive methacholine challenge result does not predict response to asthma therapy[30] and a negative methacholine challenge result fails to identify individuals with eosinophilic bronchitis and, does not predict nonresponse to asthma therapy.[31] Serial monitoring of methacholine challenge may serve as a useful guide in asthma therapy,[32] but is valuable as a guide to diagnose occupational asthma.[33]

Indirect Challenges

Indirect airway challenges[34] such as exercise and EVH, hypertonic saline and dry powder mannitol create a hyperosmolar airway milieu, leading to the release of inflammatory cell mediators from mast cells and basophils. Ultrasonic nebulized distilled water is a hypoosmolar stimulus that also causes mediator release but is infrequently used. Adenosine Monophosphate (AMP) results in inflammatory cell mediator release by non-osmotic mechanisms.

In contrast to the direct challenges, the indirect challenges are more specific and thus more valuable for confirming a diagnosis of asthma. Indirect challenges may be preferred for the diagnosis of occupational asthma; however this needs further study.[25] Although the indirect challenges are not sensitive enough to exclude a diagnosis of asthma, the utility of the mannitol challenge test in this area requires further study. Indirect challenge tests are the challenges of choice to evaluate individuals who may have exercise-induced bronchoconstriction and as a guide to monitor asthma treatment. A normal mannitol challenge result in a treated asthmatic patient should be taken as an indication to consider tapering of treatment. On the other hand, a persistent positive mannitol challenge result would indicate that treatment should not be tapered and might even suggest that treatment could be increased.[35]

Normalization of the mannitol challenge result with inhaled corticosteroids has the potential to become a treatment goal.[36]

Key Recommendations for Clinical Practice

Histamine and methacholine challenge tests should be made more available to general practitioners through hospitals or other pulmonary function test laboratories.

It is important to increase the availability of methacholine inhalation tests in general practice because this is where milder disease occurs; patient presents with symptoms but spirometry is normal, which could commonly result in misdiagnosis.

A normal histamine or methacholine challenge test only reflects the current status of the patient.

Normal results do not exclude past asthma which might have been reversed completely by the avoidance of allergen or occupational sensitizer, the clearing of infection or by corticosteroid treatment. In this situation, if current symptoms are present, they are of another cause than asthma.

Noninvasive Markers of Airway Inflammation

Airway inflammation (bronchitis) is an important component of all diseases of the airways of the lungs, including asthma. The inflammation has various causes (inhaled allergens, occupational chemical sensitizers, reduction of corticosteroid treatment, cigarette smoking, air pollution, bacterial or viral infections).[37] These different causes result in different types of inflammation which cause different clinical presentations and respond differently to the treatment. The use of traditional methods to indirectly assess airway inflammation from symptoms, use of reliever medication, peripheral blood eosinophilia and spirometry is problematic and, even among specialists, is frequently inaccurate.[38] Hence its measurement is beneficial, especially in specialist practice where disease is often more severe, complicated and difficult to control.

A number of noninvasive measures (in sputum, blood, urine, exhaled air) have been evaluated in clinical trials, of which only exhaled nitric oxide and quantitative sputum cell counts have reached clinical practice.[39] Use of these markers in practice is supported by published data, the GINA guidelines (since 2008) and Canadian asthma treatment guidelines (since 2007). Therefore, we will focus on these two markers in this chapter.

Although included in recent treatment guidelines, quantitative sputum cell counts and exhaled nitric oxide are available only at a few centers around the world. They are not more widely available because the introduction of new procedures into practice is difficult and physicians cannot appreciate the need for them when they are not available to use. Also, there is a perceived unpleasantness of sputum induction and skepticism related to patient and physician satisfaction with the results of cell counts.

Quantitative Sputum Cell Counts

Spontaneous or induced quantitative sputum cell counts provide the most valid, reliable, reproducible, comprehensive and specific measure of airway inflammation.[40] Sputum induction is safe,[41] has a success rate of more than 80% in adults;[42] however the success rate is somewhat lower in children, and induced sputum may not be possible in children of less than 8 years.[43] Low lung function (FEV_1 less than 1 L) is a relative contraindication.[44]

Two methods have been used to induce sputum with an aerosol of hypertonic saline from an ultrasonic nebulizer. In one, the subject is pretreated with inhaled salbutamol to protect against airway constriction that could be caused by inhalation of hypertonic saline.[45] The concentration of saline and duration of inhalation is either 3% for up to 20 to 21 minutes or 3%, followed by 4%, followed by 5% each for seven minutes. In the other method,[46] 4.5% hypertonic saline is given without pretreatment and inhaled for doubling times from 30 seconds to eight minutes. Sputum plug or whole sputum can be processed with the aid of a mucolytic dithiothreitol.[47] A stained cytospin is examined to obtain a differential inflammatory (eosinophils, neutrophils, macrophages, lymphocytes and epithelial cells, expressed as a percentage based on a manual count of 400 cells) and total inflammatory cell count, cell viability and squamous cell contamination. The induced sputum supernatant can be used to assay molecular markers of inflammation and has contributed significantly to our understanding of the mechanisms of airway disease.[44] Spontaneous or induced sputum may be collected and have generally shown no differences in total or differential cell counts or concentrations of inflammatory mediators.[48] Fifty one to eighty two percentage of spontaneous samples have an adequate cellular viability of more than 40%.[42]

The procedure is not difficult. Sputum can be induced by a pulmonary function technologist. A dedicated hematologically or cytologically trained technologist can process and examine quantitative sputum cell counts. Sputum induction takes about 30 minutes; the results take 1.5 hour to obtain and involve 1 hour of the technologist's time.[39] A questionnaire survey demonstrated that induced sputum cell counts was well accepted by patients and physicians,[49] which further supports the need for their implementation into routine clinical practice, particularly for specialists. Normal values for total and differential cell counts (total cell count of less than 9.7 million cells/g of sputum and proportion of neutrophils less than 64% and eosinophils less than 1.1%) have been well established in healthy subjects.[50]

Sputum cell counts identify different inflammatory subtypes of bronchitis such as eosinophilic (usually normal total cell count, percentage of sputum eosinophils ≥ 1.1%), neutrophilic (total cell count of ≥ 9.7 million cells/g of sputum and proportion of neutrophils ≥ 64%), mixed granulocytic (total cell count ≥ 9.7 million cells/g of sputum and proportion of eosinophils and neutrophils ≥ 1.1% and ≥ 64% respectively) and trivial neutrophilia of unknown significance (an isolated rise in total cell count of ≥ 9.7 million cells/g of sputum or proportion of sputum neutrophils ≥ 64%).[42]

Bronchitis can be heterogeneous during stable (eosinophilic 36%, neutrophilic 14%, mixed granulocytic 6%, trivial neutrophilia 16% , normal cell counts 28%) and exacerbated asthma (eosinophilic 35%, neutrophilic 21%, mixed granulocytic 13%, trivial neutrophilia 16% , normal cell counts 15%).[42] In approximately 50% of the patients, quantitative sputum cell counts can change during successive exacerbations in the same patient.[51]

Eosinophilic bronchitis is usually noninfective. There is strong evidence that sputum eosinophilia (> 3%) is a predictor of clinical improvement with corticosteroid treatment.[52] Monitoring sputum eosinophils benefited patients with moderate to severe asthma by reducing the number of eosinophilic exacerbations and decreasing the severity of all exacerbations without increasing the total inhaled corticosteroid dose.[53] In contrast, neutrophilic bronchitis is usually infective in nature; however the intensity of neutrophilia tends to differ from the trivial neutrophilia of cigarette smoking or pollutants to mild/modest and intense neutrophilia usually associated with viral and bacterial infections respectively.[39,54] When we do not have sputum cell counts to identify the type of bronchitis, it is standard practice to treat presumed infective exacerbations of asthma with both additional antibiotic and corticosteroid treatment. However most infective exacerbations are considered to be viral and will be unresponsive to antibiotic. Also corticosteroid treatment will only be expected to improve eosinophilic and not non eosinophilic exacerbations.[55]

Sputum cell counts should be examined at least twice a year in stable disease and during exacerbations; quantitative cell counts should be repeated after treatment of an exacerbation with additional corticosteroid and/or antibiotic treatment. Determining the inflammatory subtypes of bronchitis with quantitative sputum cell counts will avoid the inappropriate use of antibiotics (and reduce possible antibiotic resistance) or corticosteroids (and reduce their side effects including the potentiation of infection) and eventually lead to better management of asthma, reduce the overall cost of therapy[56] and improve the quality of life of these patients.

Exhaled Nitric Oxide

Nitric oxide is a biological mediator that plays many important physiological and pathological roles. It is synthesized from the amino acid L-arginine by the enzyme Nitric Oxide Synthase (NOS). There are three different isoforms of NOS in the human body, of which the calcium-independent, Cytokine-inducible NOS (iNOS) is the predominant isoform involved in the production of nitric oxide in the airways. Inducible NOS is present in airway epithelial and inflammatory cells of asthma patients and has been implicated in the pathogenesis of asthma. There is an upregulation of iNOS in the airways of asthmatics as part of the inflammatory response. This increased iNOS activity is responsible for an increase in exhaled nitric oxide.[57]

Fractional concentration of exhaled nitric oxide (FeNO) is best measured before spirometric maneuvers at an exhaled rate of 50 ml/second maintained within 10% for more than six seconds and with an oral pressure of 5 cm to 20 cm H_2O to ensure velum closure. The results are expressed as NO concentration in ppb based on the mean of two to three values within 10%.[58]

The exact relationship between fractional concentration of exhaled nitric oxide and the underlying pathology in asthma remains unclear.[59] Although there is an increasing use of FeNO as a surrogate marker for the presence of clinically relevant airway eosinophilia,[60] there is a scope for both false positives and false negatives.[61] FeNO does not reliably identify non eosinophilic bronchitis which is also frequently seen in asthma.

The upper limit of normal of FeNO is widely variable (12.7 to 22.8 ppb in children, 24 to 54 ppb in adults).[62,63] Additionally, FeNO levels are affected by a number of other factors. It is often higher in atopic subjects,[64] higher levels with increasing age in children aged 17 years or less,[65] higher in males and lower in current smokers.[66] Fractional Concentration of Exhaled Nitric Oxide (FeNO) is increased by about 60% during the late allergic response in atopic asthma[67] and is reduced two to four fold by corticosteroids in asthma between three days to eight weeks.[68,69] A dose-response effect is observed with low-dose treatment but no additional benefit is seen above a budesonide dose of 400 mcg/day.[70]

Four studies have shown that a raised FeNO is predictive of loss of asthma control[71-74] but two other studies were less convincing.[75,76] Management strategies based on monitoring FeNO level resulted in lowering of ICS dose[77] and improved Airway Hyperresponsiveness (AHR).[78] However in contrast with the use of sputum cell counts to guide ICS treatment, exhaled nitric oxide was unable to reduce exacerbations in asthma patients.[79] Measurement of FeNO requires expensive equipment and is currently available in a few specialist laboratories. Although cheaper portable FeNO analyzers are now becoming available, there are concerns that absolute values may differ between different analyzers and stability over time needs to be established.[80,81] These factors may have implications in clinical practice.

Although there is some evidence that FeNO is useful in the diagnosis of asthma, in the prediction of asthma exacerbations and tailoring of asthma therapy, yet many ambiguities still remain. The variability of FeNO measurements in populations and within individuals needs to be more clearly defined, and specific cutoff points for FeNO values need to be more firmly established. Further studies are needed to address its exact role in guiding asthma management.

Key Recommendations for Clinical Practice

Noninvasive biomarkers of airway inflammation should be used to identify the bronchitic component of asthma that is otherwise not available to the clinician.

The only clinical comprehensive measurement currently available to assess airway inflammation is quantitative sputum cell counts.

It is imperative to introduce quantitative sputum cell counts in specialist practice to manage moderate to severe asthma.

Identification of eosinophils or neutrophils in the airway does not diagnose asthma. They help to predict the response to anti-inflammatory treatment and guide appropriate treatment.

In contrast to traditional clinical management, the use of induced sputum has been shown to be cost-effective in a specialist setting. FeNO measurements may be used as a surrogate marker for airway eosinophilia, may be used to predict response to corticosteroid therapy, low values may be of use to aid reduction in corticosteroid dose or to determine that ongoing respiratory symptoms are less likely to be due to eosinophilic airway inflammation.

Further studies with FeNO are needed to address outstanding questions about its exact role in guiding asthma management.

Exhaled Breath Condensate

A more recent noninvasive tool to assess airway inflammation is Exhaled Breath Condensate (EBC) measurements. The warm breath of subjects is collected on to cooled tubes so that the moisture condenses and the condensate can be collected. This condensate can then be analyzed for airway pH and various inflammatory markers (e.g. hydrogen peroxide, isoprostanes and cytokines).[20,82] Although the technique is noninvasive, allowing repeated samples to be collected and can be used even with small children, there are several unresolved problems with this methodology.[83] Currently the technique remains a promising research tool, with the potential for monitoring the inflammatory state in the airways and the effect of the novel therapeutic agents; however, more sensitive methods for measuring analytes and standardization of the collection methodology are needed.[20]

Measures of Allergic Status

Physicians commonly encounter patients with symptoms consistent with allergy. It can be difficult to determine which allergen is causing symptoms from the patient's history alone. Allergy tests yield information on sensitization, which is not always equivalent to clinical allergy; thus, interpretation in the context of clinical history is important. The two main allergy tests that are available to assist the physician to make an allergy diagnosis include the allergy skin tests and the measurements of allergen specific IgE (serum s-IgE) in addition to a thorough clinical history. However it is very important for the clinician to understand which allergy diagnostic tests to order, how to interpret the results of these tests and how to use the information obtained from the allergy evaluation to develop an appropriate treatment plan.

Medical History and Physical Examination

A history of allergic symptoms, seasonal variation, rapidity of onset and age of onset will help the clinician to determine if the patient's presentation is likely from an allergic cause. Physical examination findings such as allergic shiners, nasal crease, boggy nasal turbinates and pharyngeal cobblestones may further guide the physician.[84] If you suspect IgE-mediated allergic disease, always request and interpret skin tests and s-IgE tests in context of the clinical history. Positive test results provide objective confirmation of IgE sensitization, which will support a history of symptoms on exposure to a particular allergen. A negative test makes allergy to a suspected allergen unlikely. Avoid indiscriminate use of allergy tests as they may be commonly associated with false-positive results. Skin and serum IgE tests should never be used as a substitute for a careful clinical history.

Allergen skin tests: In clinical practice, the prick or puncture test is the preferred initial technique because it is relatively nontraumatic, elicits reproducible results when placed on specific areas such as arms or back and has better overall predictability. The reliability of prick/puncture tests depends on the skill of the tester, the test instrument, color of the skin, skin reactivity on the day of the test, potency and stability of test reagents. Sensitivity tends to be higher among pollens, certain foods, dust mite and fungi, compared with drugs and chemicals.[84,85] The number of skin tests and the allergens selected for skin testing should be determined from the patient's age, history, environment and living conditions, occupation and activities. A routine use of large number of skin tests without a definite clinical indication is not justified.[84]

Serum s-IgE: Multiple methods have been used to measure serum allergen s-IgE including Radioallergosorbent Test (RAST), Turbo RAST (Agilent Technologies Co, Santa Clara, California), Immulite (Siemens Medical Solutions Diagnostics, Tarrytown, New York), and ImmunoCAP (Phadia, Uppsala, Sweden). ImmunoCAP is the assay that has been most extensively studied.[86]

If the clinical history is positive and the serum s-IgE test result is negative, allergy skin testing should be considered. Serum s-IgE testing is preferred to prick or puncture testing when the patient has severe skin disease, is receiving medications that may suppress skin tests and cannot be removed from them, for uncooperative patients, or if the history suggests a risk of anaphylaxis from the testing.[84]

It is important in serum s-IgE tests and skin tests that results correlate with the history, physical examination findings, and in some cases timing of natural exposure to allergen. Therefore, it is often inappropriate to choose immunotherapy from remote laboratories based on history alone.

DIAGNOSTIC CHALLENGES

Preschool Children

Diagnosis of asthma in children aged 5 years and younger may be difficult because episodic respiratory symptoms such as wheezing and cough are also common in children who do not have asthma, particularly in those younger than 3 years.[87,88] It is further complicated by the difficulty in obtaining lung function in this age group. Alternative causes that can lead to respiratory symptoms of wheeze, cough and breathlessness must be excluded before making an asthma diagnosis. These include recurrent respiratory infections, allergic rhinitis, sinusitis, tuberculosis, foreign body in trachea or bronchus, vocal cord dysfunction, enlarged lymph nodes or tumor that may compress the large airways, recurrent aspiration due to dysfunction of swallowing reflex or gastroesophageal reflux and congenital problems such as tracheomalacia, tracheal stenosis, bronchostenosis, cystic fibrosis, bronchopulmonary dysplasia, congenital malformation of intrathoracic airways, primary ciliary dyskinesia syndrome, immune deficiency and congenital heart disease.[89]

Nevertheless, a diagnosis of asthma in young children can often be made based on symptom patterns, family history (first degree relatives, especially the mother) and physical findings. The presence of atopy (atopic dermatitis, food allergy, and/or allergic rhinitis) increases the likelihood that a wheezing child will have asthma.

It is important to avoid under diagnosing asthma, and thereby missing the opportunity to treat a child, by using such labels as “wheezy bronchitis,” “recurrent pneumonia,” or “reactive airway disease”.

Symptoms

Wheeze, cough, breathlessness and nocturnal symptoms/awakenings may indicate a diagnosis of asthma.

i. *Wheeze:* Not all wheezing indicates asthma. The ERS Task Group[90] has described two wheezing phenotypes (episodic wheeze and multiple trigger wheeze), whereas the US cohort study[91] has identified three wheezing phenotypes (transient wheeze, persistent wheeze, late-onset wheeze). The “episodic wheez” is the wheeze that occurs during discrete time periods, often in association with a common cold, with absence of wheeze between episodes. A “multiple trigger wheez” occurs as episodic exacerbations but also with symptoms including cough and wheeze occurring between these episodes, during sleep or with triggers such as activity, laughing, or crying. In “transient wheeze,” symptoms begin and end before the age of 3 years; in “persistent wheeze,” symptoms begin before the age of 3 years and continue beyond the age of 6 years; and in “late-onset wheeze,” symptoms begin after the age of 3 years. The clinical usefulness of these phenotypes remains a subject of much debate. Asthma occurs much more rarely in the episodic wheeze and transient wheeze phenotypes compared to the other phenotypes.

   Based on data from the Tucson (USA) Respiratory Study,[92] the Asthma Predictive Index (API) is recommended to predict the development of asthma in children with four or more wheezing episodes in a year.[93] A child with a positive API has a 4 to 10 fold greater chance of developing asthma between the ages of 6 and 13, while 95% of children with a negative API remained free of asthma.[93] The applicability and validation of the API in clinical practice is awaited.[89]

   Since many young children may wheeze with viral infections (respiratory syncytial virus and rhinovirus), it is challenging to differentiate whether the presence of wheeze with infections is truly an initial or recurrent clinical presentation of childhood asthma.[94]

ii. *Cough:* Cough due to asthma is recurrent and/or persistent, and is usually accompanied by some wheezing and breathing difficulties. Nocturnal cough or cough occurring with exercise, laughing or crying in the absence of an apparent respiratory infection, strongly supports a diagnosis of asthma.

iii. *Breathlessness:* Very often, parents describe this symptom as difficult breathing, heavy breathing or shortness of breath. Breathlessness that occurs during exercise, laughing and crying and is recurrent increases the likelihood of asthma.

Tests for Diagnosis and Monitoring

There is no test that will diagnose asthma with certainty in young children, but the following may be useful in making a diagnosis:[89]

i. *Therapeutic trial:* A marked clinical improvement in daytime and nocturnal symptoms and frequency of exacerbations during a trial of treatment with short-acting bronchodilators and inhaled glucocorticosteroids for at least 8 to 12 weeks and deterioration when it is stopped supports a diagnosis of asthma. A therapeutic trial may need to be repeated more than once to confirm the diagnosis of asthma.

ii. *Tests for atopy:* Sensitization to allergens can be assessed using either skin testing or antigen-specific IgE antibody. Skin prick testing is less reliable for confirming atopy in infants.

iii. *Chest radiograph:* If there is doubt about the diagnosis of asthma in a wheezing child, a plain chest radiograph may help to exclude infection (e.g. tuberculosis), congenital malformations of the airway such as congenital lobar emphysema or other diagnoses.

iv. *Other tests:* Lung function testing, bronchial challenge tests and other physiological tests do not have a major role in the diagnosis of asthma in children of 5 years and younger because children in this age group do not perform reproducible expiratory maneuvers. Such tests are only possible in specialized centers, and are undertaken mainly for research purposes.

v. *Exhaled nitric oxide:* High exhaled nitric oxide levels have been used to differentiate preschool wheezers with a high and low risk of developing asthma from preschool coughers.[95] However there is still no evidence to show whether exhaled nitric oxide levels can be used to differentiate persistent wheezers who are likely to develop asthma from other wheezy phenotypes.[89]

Older Children and Adults

In most cases, a careful history and physical examination together with the demonstration of reversible and variable airflow limitation by spirometry will confirm the diagnosis of asthma. Other causes of airway obstruction leading to wheeze should be considered both in the initial diagnosis and if the patient does not respond to initial therapy. These conditions may coexist with asthma or complicate the diagnosis and management of asthma. Common diagnostic challenges include the following:

Cough-Variant Asthma (CVA)

CVA is a distinct subset of asthma in which the main respiratory symptom is chronic cough associated with bronchial hyperresponsiveness and airway eosinophilia.[96] It can be encountered in both children and adults. In some patients, the cough may be associated with wheezing, chest tightness and various degrees of airflow obstruction, whereas in others cough could be the only presenting symptom with normal pulmonary function.[97] Higher sensitivities of cough reflex could explain the predominance in females.[98] In both adults and children, CVA may be a precursor of typical asthma; adults developed typical asthma after a period ranging from 1.5 to 9 years.[96] The predictors of progression to typical asthma include increased airway hyperresponsiveness,[99] eosinophilic airway inflammation,[100] blood eosinophilia,[101] longer duration of coughing,[102] age of onset[103] and no use of inhaled corticosteroids.[101,104] Typical asthma developed in 7.4% of patients taking inhaled corticosteroids and in 35.7% patients not taking inhaled corticosteroids.[101] Monitoring of PEF or bronchoprovocation may be helpful. Diagnosis is confirmed by a positive response to asthma medications.[96]

Vocal Cord Dysfunction (VCD)

Vocal cord dysfunction can mimic asthma, but it is a distinct disorder that is caused by abnormal adduction of the vocal cords during inspiration causing extrathoracic airway obstruction resulting in episodic dyspnea and wheeze.[105-106] In addition to severe asthma, VCD frequently occurs in mild-to-moderate asthma (72%).[106] Although physicians commonly refer patients with "classic" symptoms of stridor or hoarseness for VCD testing, a recent study[106] reports the lack of classic VCD symptoms among asthmatics. In fact, patients with both VCD and asthma present with nonspecific symptoms such as dyspnea, cough and wheeze, highlighting the need for a high index of suspicion for VCD in patients with asthma. The high prevalence of GERD (56.8%) raises the question of the role of acid reflux in the pathogenesis of VCD in asthmatics.[106]

Diagnosing vocal cord dysfunction requires a high index of suspicion. There is variable flattening of the inspiratory flow loop on spirometry; however a normal flow-volume loop should not influence the decision to perform a laryngoscopy.[107] Access to specialized Videolaryngostroboscopy (VLS) testing is required to definitively document VCD. The laryngeal movements during the entire procedure are digitally recorded. In order to be diagnosed as VCD, the patient must demonstrate abnormal constriction during the respiratory cycle and also normal complete abduction during some portion of the examination;[106] however false-negative tests can occur because VCD is paroxysmal.[105,108] Therefore, provocation with exercise or noxious stimuli is important to increase the likelihood of capturing an episode of VCD during VLS testing.[106]

It is yet unknown whether diagnosis and treatment of VCD has any impact on asthma control. Future prospective studies are needed to establish the impact of the diagnosis and treatment of VCD on asthma control.[106]

Gastroesophageal Reflux Disease (GERD)

Although 80% of asthmatic patients with positive pH probes have typical GERD symptoms such as heartburn,[109] approximately 40% have asymptomatic or silent GERD.[110]

GERD may induce asthma symptoms either by direct bronchospasm and increased airway hyperresponsiveness[111] or indirectly via microaspiration- induced airway inflammation.[112] Asthma patients have hyperinflated chests. Descent of the diaphragm in hyperinflated lungs increases the pressure gradient between the abdomen and chest and may cause the Lower Esophageal Sphincter (LES) to herniate into the chest where its barrier function is impaired.[113,114] Asthma medications such as beta 2-agonists and methylxanthine bronchodilators may decrease LES tone and may promote acid reflux.[113]

The use of pH probe findings is considered the most sensitive diagnostic test for GERD; however it does not reliably identify a subgroup of asthmatic patients who is likely to benefit from GERD treatment.[106]

Other Differential Diagnosis

Other differential diagnostic possibilities for asthma include congestive heart failure, pulmonary embolism, mechanical obstruction of the airways (benign and malignant tumors), pulmonary infiltration with eosinophilia, cough secondary to drugs [e.g. Angiotensin Converting Enzyme (ACE) inhibitors].[1]

Elderly

The diagnosis of asthma in the elderly is based mainly on clinical history and demonstration of reversible airflow obstruction with pulmonary function testing, but there are unique diagnostic challenges in older patients.

Medical History

Shortness of breath, chest tightness, usually dry cough, recurrent wheezing, nocturnal symptoms, worsening of disease at night, precipitation of symptoms following exposure to cold air, exercise or allergens support a diagnosis of asthma in the elderly.[115]

Pulmonary Function Testing

Many older patients will have difficulty in performing PFT. Performing PFT has been shown to be feasible in up to 88% of outpatients aged 65 and older.[116] Older adults may find it difficult to perform effective PFT because of the following reasons:[115]

- Inability to perform efficient forced expiration.
- Unable to follow instructions from the PFT technician because of cognitive impairment, sensory deficits (e.g. deafness, cataract) and/or impaired coordination (e.g. stroke).
- Poor post bronchodilator reversibility with beta 2-agonists.
- Fatigue and associated co-morbidities (e.g. cardiovascular disease).
- Mouth or dental problems (e.g. ulcers, dentures), which may affect the ability to hold onto the mouthpiece.

Difficulties Faced by a Clinician During Interpretation of PFT Reports

An obstructive pattern alone on spirometry in the absence of symptoms may reflect age-related pulmonary change such as decreased vital capacity, increased residual volume and functional residual capacity and not necessarily asthma.[117]

The predicted values of FEV_1 and FVC in normal elderly patients are based on data that is extrapolated from younger patients and therefore, tend to over predict values.[118] There is an accelerated decline in FEV_1 and FVC with advancing age, which is more rapid in men than women.[117] The clinician should consider these factors while making a diagnosis of asthma.

Age-dependent changes in pulmonary function and fixed obstruction (unchanged FEV_1 and FEV_1/FVC values pre- and postbronchodilator administration), which develops subsequent to airway remodeling makes it difficult for clinicians to differentiate between long-standing asthma and COPD.[119] Although bronchodilator reversibility will aid in distinguishing between asthma and COPD, a low Diffusion Capacity of Carbon Monoxide (DLCO) may tilt the diagnosis toward COPD and not asthma.[115] Beta-adrenergic dysfunction may be implicated in older patients.[120] Therefore, with the absence of a detectable change in the reversibility of airflow obstruction with SABAs, the test may be repeated with an anticholinergic agent. In some individuals, PFT does not demonstrate post bronchodilator reversibility, but an improvement is seen after systemic corticosteroid. The explanation of this phenomenon is based on the anti-inflammatory effect of corticosteroids. A two week trial of oral corticosteroid should be considered before repeating spirometry to detect an improvement in airflow obstruction which will aid in diagnosing asthma in difficult cases.[121] Nonetheless, asthma and COPD can both coexist in the same patient.[122]

Alternative Assessments

i. *Peak flow rates:* The use of peak flow variability to diagnose asthma in the elderly patients is not recommended because peak flow declines with age and peak flow variability becomes less reliable.[123] It is useful in detecting poorly controlled asthma, but it may not be fully reliable even in these circumstances.
ii. *Relaxed vital capacity:* Since older patients find it difficult to perform efficient forced expiratory maneuvers, a suitable alternative test is relaxed VC because it will be more discriminatory in older patients. The ratio of FEV:relaxed VC may be used to determine whether obstructive airway disease is present; however assessment of relaxed VC is more time consuming and requires technical expertise to perform the test correctly.[115]
iii. *Airway resistance:* As measurement of airway resistance or impedance using impulse oscillometry[124] and plethysmography[125] do not rely on maximal expiratory efforts, these methods have been proposed as a measure of airflow obstruction in older patients. Impulse oscillometry was successfully used to assess and quantify the airway obstruction in patients with dementia.[124] Further clinical studies need to address the validity and feasibility of these methods to assess airflow obstruction in the elderly.

Occupational Asthma

It is first necessary to establish a diagnosis of asthma in a patient and then identify Occupational Asthma (OA). A thorough medical history and objective work-related testing usually provides a reliable diagnosis of occupational asthma. A detailed history for suspected OA include chronological work history, job duties, exposures at work, onset and timing of symptoms, use of protective devices, presence of respiratory disease in coworkers, medication use and past lung function.[126]

The 2008 ACCP guidelines[127] recommend that the physician needs to address the following questions related to the onset and timing of the symptoms:

- Whether there were changes in work processes preceding the onset of symptoms
- Whether there was unusual exposure to sensitizers at work within 24 hours before the onset of symptoms
- Whether there is a temporal relationship of symptoms to periods while at and away from work (e.g. weekends, holidays)
- Whether symptoms of allergic rhinitis and /or conjunctivitis get worse with work

It would be very helpful to have up-to-date Material Safety Data Sheet (MSDS) in place for every chemical or material that may pose an occupational hazard for patients. MSDS contains information that will help to identify the suspect agent in the workplace.[128]

Objective Testing

i. *Peak expiratory flow rates:* Current guidelines[127] recommend that Peak Expiratory Flow Rates (PEFR) should be recorded at the workplace for a minimum period of four weeks including at least one week away from work. These PEFR readings should be performed in triplicate at least four times a day (e.g. preshift, midshift, postshift and bedtime, with similar times on days off work). Careful patient instruction is required because PEFRs are effort dependent. A typical pattern of OA is for patients to have better peak flow rates when they return to work after a weekend (e.g. on a Monday) or after holidays and get worse as the week progresses. Peak expiratory flow assessment has a sensitivity of 64 and 77% specificity.[129]
ii. *Airway hyper-responsiveness:* A methacholine or histamine challenge test should be performed at the end of a work week. The patient should remain away from work for at least 10 to 14 days, following which the challenge test should be repeated. A worsening of PC20 at work versus off work (greater than or equal to 4 fold change) further supports a diagnosis of OA.[127] A methacholine challenge test can revert to normal when a patient is away from occupational exposure.[130]
iii. *Specific inhalation challenge:* Specific Inhalation Challenge (SIC) exposes a worker to a specific suspect OA sensitizer in a controlled setting to demonstrate a direct relationship between exposure to the test agent and an asthmatic response. SIC may be associated with significant risk and should be performed in a specialized center under close supervision. This test is performed at limited centers in the world.[126]
iv. *Immunologic testing:* A negative skin test to a validated occupational protein allergen can reliably exclude occupational asthma.[127,131] Low Molecular Weight (LMW) sensitizers (e.g. metals, organic chemicals) may be associated with specific IgE antibody but limited *in vitro* tests are available for specific IgE to LMW agents and commercial tests have not been validated. Although these tests are not very sensitive, when positive they can support a diagnosis of OA.[132]

v. *Workplace challenge:* Workplace challenge testing is used when a specific agent cannot be identified as a potential cause for sensitizer induced OA or SIC is not available. The patient's spirometry is monitored at the workplace suspected to cause sensitizer induced OA.[133] For the purpose of comparison, the workplace challenge testing should be preceded by a control spirometry performed away from work.

vi. *Induced sputum cell counts:* Induced sputum analysis may assist in diagnosis of OA even before the development of respiratory symptoms and pulmonary function changes.[134] Although majority of subjects with OA show an eosinophilic airway inflammation after exposure to occupational agents during SIC,[135,136] neutrophilic inflammation has also been reported following exposure to isocyanates[137] and metal working fluid.[138] If there is an isolated increase in sputum eosinophil count of at least 2% without functional changes, the physician should pursue further investigation by increasing the duration of exposure to the suspected occupational agent.[139]

vii. *Exhaled nitric oxide:* There have been few studies examining work related changes of exhaled nitric oxide. Some studies have reported a higher exhaled nitric oxide in patients with OA[140,141] while others do not report a clear relationship.[142]

viii. *Exhaled breath condensate:* Exhaled breath condensate (EBC) collection is a noninvasive and repeatable tool to assess oxidative stress, acidification and inflammation in the airways.[143] The EBC concentration of hydrogen peroxide was increased in asymptomatic welders.[144] EBC pH was lower in welders exposed to cadmium, chromium, iron, lead, and nickel, than those exposed to aluminum and iron at the workplace. EBC analysis may be useful in occupational studies on a group level and in individuals who serve as their own controls. Based on methodological limitations, lack of standardization and difficulties in the interpretation of the data, EBC collection and analysis are primarily research tools and not yet suitable for implementation into clinical practice.[145]

Differential Diagnosis

Other conditions that may mimic occupational asthma include vocal cord dysfunction, upper respiratory tract infection, hypersensitivity pneumonitis, rhinosinusitis, byssinosis, popcorn worker's disease, flock worker's disease, eosinophilic bronchitis and psychogenic factors.[126]

Asthma and COPD

Guideline-recommended definitions for asthma and COPD are useful but limited because they do not fully depict the spectrum of obstructive airway disease that we see in clinical practice. There is a need to revaluate the concept of asthma and COPD as separate conditions. The various components of airway disease include symptoms, variable airflow limitation (asthma), chronic airflow limitation (COPD), airway hyper-responsiveness and airway inflammation. They can exist in various combinations, and bronchitis or airway inflammation is the central component. When considered in this way, asthma and COPD are physiological components of airway disease and bronchitis is the inflammatory component.[146] An asthma patient may or may not have eosinophilic bronchitis, COPD can occur in a nonsmoker. A smoker with COPD may have an eosinophilic bronchitis. A neutrophilic bronchitis can occur in asthma or COPD. Hence the diseases are not mutually exclusive and can overlap (overlap syndrome). Combinations commonly occur and can vary from one patient to another.

Why is the Overlap Syndrome Important?

With increasing age, there is a greater increase in the proportion of patients (55%) with the overlap syndrome and fewer (19%) older patients have the classical phenotypes of emphysema alone or chronic bronchitis alone.[147]

Patients with the overlap syndrome are excluded from randomized controlled clinical trials and therefore, data on the efficacy of treatment may not be relevant in this population.[148] Studies on the efficacy of inhaled corticosteroids in asthma excluded smokers with asthma despite the fact that up to 32% of asthma patients are smokers.[149] As a result extrapolation of efficacy results for corticosteroids in nonsmokers to smokers with asthma is flawed and we know that smokers with asthma have a relative corticosteroid resistance.[150] Overlap syndrome of asthma and COPD need to be included in drug evaluation programs.

Clinicians are often confused as to how to differentiate between asthma and COPD and use extended nonuniform diagnostic labels for obstructive airway disease (e.g. asthma with chronic bronchitis, asthmatic bronchitis).[151] Recognition of the overlap syndrome may help identify shared risk factors such as increasing age and smoking,[152] bronchial hyper-responsiveness[153] and exacerbations,[154] which will help to understand and modify the accelerated decline in lung function that leads to COPD.

Clinical Recognition of the Overlap Syndrome

The clinical recognition of both asthma and COPD requires assessment of symptoms and physiological function abnormalities.[148] Patients with asthma, COPD and overlap syndrome can all present with symptoms; however there is a difference in the physiological function abnormalities. Patients with the overlap syndrome have incomplete reversible airflow obstruction [$FEV_1/FVC < 70\%$, $FEV_1\%$ Pred (post bronchodilator) < 80%] but also have increased bronchial hyperresponsiveness (PD_{15} of hypertonic saline that induces a 15% fall in FEV_1 is less than 12 ml).

Patient groups that have features of both asthma and COPD include smokers with asthma, asthma patients who develop COPD and nonsmokers who develop COPD.[148] Long-standing asthma patients who develop COPD tend to be older (44 years), more often males and have a long duration of disease (25 years).[155,156] Sixteen percent of patients with asthma developed COPD after 21 to 33 years of follow-up.[157] In a recent study[148] only 16% and 21% patients could be reported definitely as asthma and COPD respectively. Majority (65%) of the patients had the overlap syndrome of asthma and COPD. The rate of atopy was intermediate (64%) in the overlap syndrome. Airway complications resembled COPD rather than asthma.

Inflammatory Features of the Overlap Syndrome

The pattern of airway inflammation associated with both asthma and COPD is heterogeneous but is more likely to resemble COPD rather than asthma with increased sputum neutrophils. Smokers with asthma are less likely to have eosinophilic inflammation[158] and more likely to have airway neutrophilia.[159] In our retrospective survey of 2,443 patients with airway disease,[42] 9% had asthma with COPD. In stable disease, eosinophilic bronchitis was more frequently seen (35%) whereas neutrophilic inflammation was more common during exacerbations (33%). Induced sputum biomarkers such as IL-12, IL-13 and IFN-gamma were predominant in patients with both asthma and COPD, whereas IL-9, IL-17, monocyte chemotactic protein 1, and Regulated Upon Activation, Normal T Cell Expressed And Secreted (RANTES) were dominant in those with asthma without chronic airflow obstruction.[160]

Airway Remodeling in Overlap Syndrome

Subjects with severe asthma and chronic persistent obstruction have increased airway smooth muscle (15.65%) versus that (8.96%) seen in patients without chronic airflow obstruction; however airway measurements on high-resolution computed tomographic scans revealed no differences between the groups.[160]

The overlap syndrome of asthma and COPD is supported by the Dutch Hypothesis,[161] which states that the different types of airway diseases should not be considered as separate conditions but as one disease entity with different components. The presence of different components (asthma, COPD) is influenced by host and environmental factors. We need to evaluate the components of the disease in order to individualize and optimize treatment to achieve the best effect with the least side effects and cost to the patient.

CONCLUSION

The clinical diagnosis of asthma is usually based on an accurate medical history, supported by physical examination and demonstration of variable airflow obstruction. This would involve demonstration of bronchodilator reversibility in patients with baseline airflow obstruction or bronchial hyperresponsiveness in patients without baseline airflow obstruction. An alternative would be demonstration of natural variability in airflow obstruction using home peak flow recording. Although this is less sensitive than demonstration of bronchial hyperresponsiveness to diagnose asthma, new statistical methods to analyze peak flow recording such as autocorrelation and coefficient of variation of measurements[162] may prove increasingly useful. Objective assessment of airway inflammation especially quantitative sputum cell counts need to be implemented into specialist practice to identify the bronchitis component of asthma. They do not help to diagnose asthma. A referral to a specialist centre that has expertise to perform bronchial provocation tests, evaluation of allergy and measurement of airway Inflammometry is appropriate in patients with uncertain diagnosis, particularly, those who do not seem to improve with conventional treatment for asthma.

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67

Airway Inflammation and Remodeling

Ruby Pawankar, Shu Hashimoto, Bassam Mahboub

INTRODUCTION

Both Allergic Rhinitis (AR) and asthma may factually be considered as one single disease, based on the unifying concept of "One airway – One disease." Allergic rhinitis is a chronic inflammation of the nose, characterized by symptoms of sneezing, rhinorrhea, nasal itching and nasal obstruction. Asthma is a chronic, inflammatory condition of the lower airways characterized by largely reversible airflow obstruction, airway hyperresponsiveness, and episodic respiratory symptoms, including wheezing, productive cough, and sensations of breathlessness and chest tightness.[1]

Clinically, AR is an Immunoglobulin E (IgE)-mediated, T helper cell 2-type (Th2-type) inflammatory disease whereas asthma may be divided into allergic and non-allergic asthma, distinguished by the presence or absence of IgE antibodies to common environmental allergens. About 80% of childhood and 50% of adult asthma is allergic (i.e. IgE associated). In the latter, the triggers are not well known, but are probably microbes or microbial components. However, both forms of asthma are characterized by Th2-type inflammation, stimulation of inflammatory cells, like mast cells, causing eosinophilia, leukocytosis, and enhanced B-cell IgE production, leading to airway hyperresponsiveness and tissue remodeling. The determinants for an individual to develop an asthmatic phenotype require both exposure to appropriate stimuli and a genetic predisposition.[2,3]

Airway remodeling involves structural changes in the airway wall characterized by epithelial alterations (epithelial shedding or denudation as a result of toxic proteins released especially by eosinophils), goblet cell metaplasia (their numbers increase first), bronchial mucus gland enlargement (excess production of mucus), subepithelial fibrosis and extracellular matrix deposition, increased smooth muscle mass and increased vascularization.[2] Chronic inflammation causes tissue injury, which is partly repaired between inflammatory exacerbations. Airway remodeling is associated with poorly-reversible or nonreversible airway narrowing, more severe airflow limitation and airway hyperresponsiveness and may be involved in component of adult severe asthma.[4] These changes involve both large and small airways, but the individual variation is large. Airway secretions also contribute to the airflow limitation in asthma, and increase in amount and viscosity of the secretions plays a crucial role especially in acute, life-threatening exacerbations.[5] However, based on current knowledge the characteristic structural changes seen in remodeling is not a feature of AR.

Although much more is known in terms of the inflammatory mechanisms underlying AR and asthma, there is still a gap in our understanding of the cellular and molecular pathways involved in remodeling. Both inflammation and remodeling occur in the tracheobronchial tree of patients with asthma. Persistent, eosinophilic inflammation seems to be a prerequisite for the development of remodeling.[6] Increased vascularity and expression of Vascular Endothelial Growth Factor (VEGF) are features of the asthmatic airway, but little is known about their contribution to airway remodeling. Siddiqui et al.[7] showed that vascular remodeling is a feature of asthma, and is inversely correlated with postbronchodilator Forced Expiratory Volume in One Second (FEV_1) indicating a role in airflow obstruction.

Until recently, airway remodeling was considered to be a secondary phenomenon, developing later in the disease process as a consequence of persistent inflammation. The presence of airway inflammation and remodeling in children[8] with asthma indicates that the process of remodeling begins early in the disease process of asthma and synchronously with ongoing and repeated airway inflammation rather than as a consequence of airway inflammation. Structural changes of the airways are already present and maximal in severely asthmatic school children,[9] indicating the changes begin early in life between the ages of 1 and 3 years; and in good association with tissue eosinophilia and reticular basement membrane thickening.[10] This gives a window of opportunity for early intervention that can possibly modify the natural history of asthma.[11]

CHRONIC INFLAMMATION IN AR AND ASTHMA (FIGS 67.1 AND 67.2)

The Inflammatory Response

The upper and lower airways have a similar mucosal structure, and exhibit similar inflammatory reactions to irritants and allergens. Increasing evidence indicates that there is marked similarity in the degree of cell infiltration or cytokine expression during allergic inflammation between the nasal mucosa and bronchial mucosa.[12,13] However, there are minimal structural changes of the nasal mucosa in AR unlike that in asthma.

In allergic asthma and AR, inhaled allergens penetrate the mucociliary lining and enter the airway epithelium either via the tight junctions that surround the apical zone of epithelial cells or by direct uptake by the cells per se. Allergens are presented to T-cells that then react by forming a pool of Th2 (IL-4, IL-5 and IL-13 secreting T-cells) that drive the production of IgE via interaction with B-cells. Subsequently, the IgE binds to the high affinity IgE receptor on mast cells, and cross-linking of allergen specific IgE on the surface of mast cells by allergens causes the activation of mast cells and the release of mediators such as histamine and leukotrienes. They increase vascular permeability and initiate a cascade of recruitment of more inflammatory cells and further release of proinflammatory mediators.

Effector Cells of Inflammation

Mast Cells and Basophils

Mast cells are critical in mediating the early phase of inflammatory response in AR and asthma. However, more recently it is known that mast cells are not only effector cells of the immediate phase response, but also play a role in on-going allergic inflammation. They store and produce Th2-type cytokines, chemokines, induce IgE synthesis in B cells,[14,15] express the $CysLT_1$ receptor,[16]

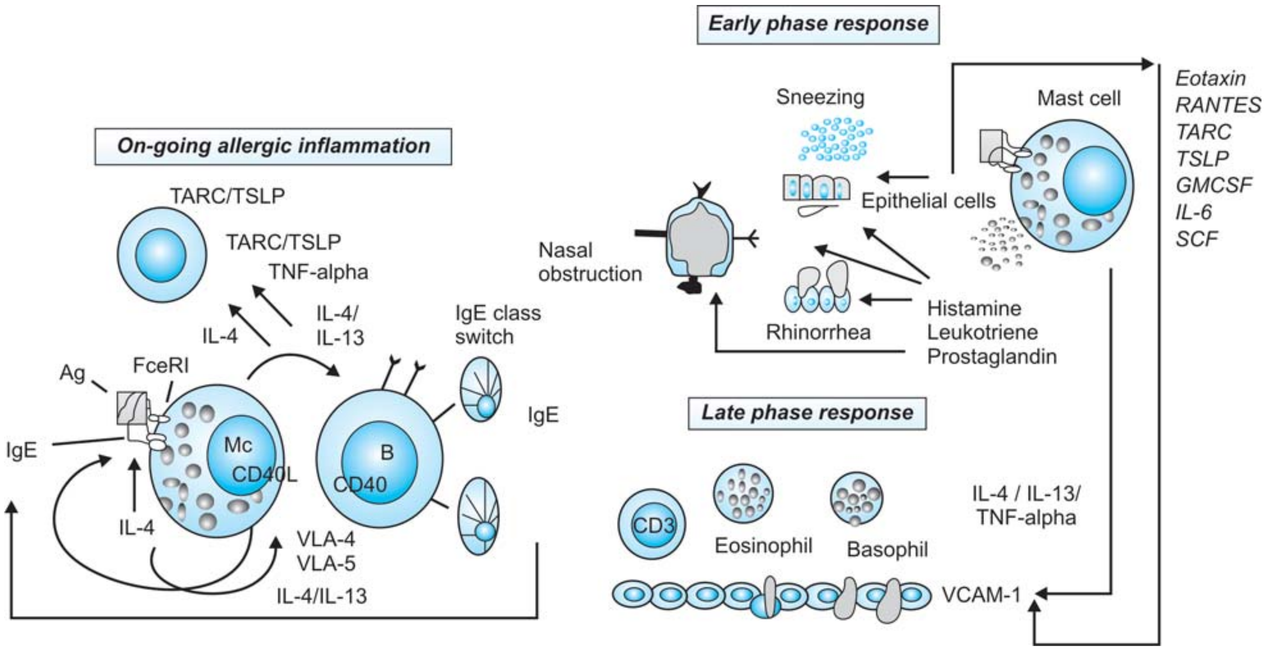
Early phase response
Sneezing
Mast cell
Eotaxin
RANTES
TARC
TSLP
GMCSF
IL-6
SCF
On-going allergic inflammation
TARC/TSLP
Epithelial cells
TARC/TSLP
TNF-alpha
Nasal
obstruction
IL-4
IL-4/
IL-13
IgE class
switch
Histamine
Leukotriene
Prostaglandin
Rhinorrhea
Ag
FceRI
Mc
CD40L
B
CD40
IgE
IgE
Late phase response
IL-4
IL-4 / IL-13/
TNF-alpha
CD3
Eosinophil
Basophil
VLA-4
VLA-5
IL-4/IL-13
VCAM-1

Fig. 67.1: Inflammatory mechanisms in allergic rhinitis [Modified from Pawankar et al. Allergic Rhinitis pathomechanisms. Ed Kurup et al]

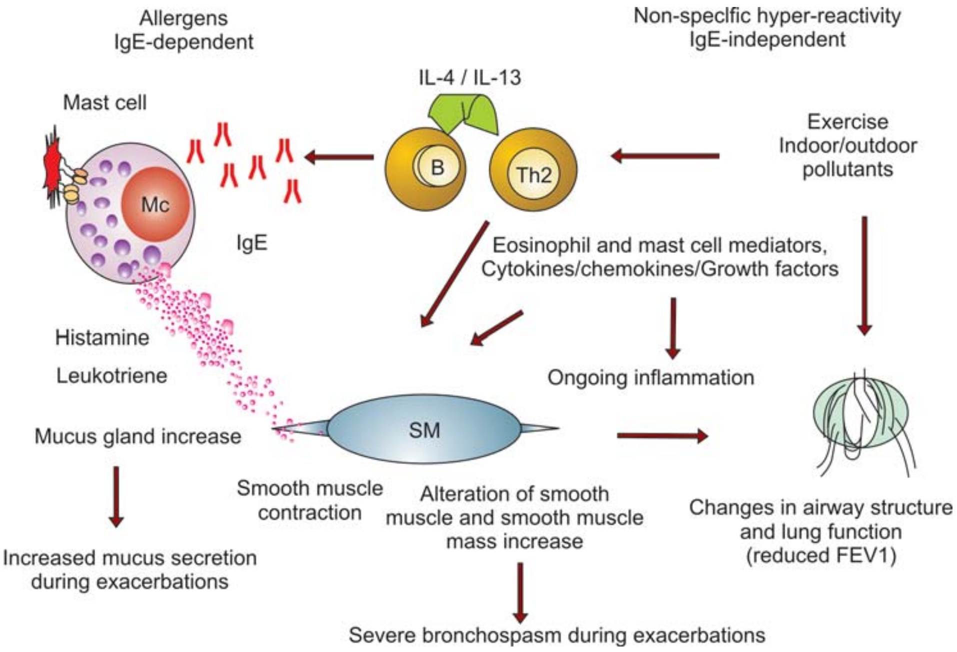
Allergens
IgE-dependent
Non-speclfic hyper-reactivity
IgE-independent
IL-4 / IL-13
Mast cell
Mc
B
Th2
Exercise
Indoor/outdoor
pollutants
IgE
Eosinophil and mast cell mediators,
Cytokines/chemokines/Growth factors
Histamine
Leukotriene
Ongoing inflammation
Mucus gland increase
SM
Smooth muscle
contraction
Alteration of smooth
muscle and smooth muscle
mass increase
Changes in airway structure
and lung function
(reduced FEV1)
Increased mucus secretion
during exacerbations
Severe bronchospasm during exacerbations

Fig. 67.2: Pathophysiology of asthma

GR receptor,[17] and SAF-2,[18] and upregulate the production of cytokines/chemokines in epithelial cells and fibroblasts.[19]

Accumulation of mast cells into the nasal and bronchial epithelium, a feature of AR and atopic asthma is also reported in idiopathic rhinitis.[20] Regulated Upon Activation, Normal T-Cell Expressed and Secreted (RANTES) and TGF-β are implicated in the intraepithelial migration of mast cells.[19,21] Increase in mast cells and basophils occur within one hour of Nasal Allergen Challenge (NAC).[22] Patients with AR with or without asthma have similar number of intraepithelial mast cells,[23] and Segmental Bronchial Challenge (SBC) induces an increase in basophils and eosinophils predominate in nasal and Bronchoalveolar Lavage (BAL).[24-27]

Airway mast cells stimulated via the FcεRI are an important source of Th2 cytokines, proinflammatory cytokines like TNF-α (preformed in mast cells) and chemokines like Thymus And Activation-Regulated Chemokine (TARC), as well as the IL-7 like cytokine Thymic Stromal Lymphopoietin (TSLP).[28,29] FcεRI-mediated TSLP production from mast cells is further enhanced in an autocrine manner by IL-4.[30] Moreover, mast cells can interact with structural cells, like epithelial cells to enhance the production of cytokines and chemokines from epithelial cells. TNF-α in concert with IL-4 and IL-13 enhances the production of TARC, TSLP and eotaxin from epithelial cells.[19] These result in increased infiltration of Th2 cells, eosinophils and differentiation of dendritic cells. Moreover, tryptase and chymase from mast cells can upregulate RANTES and GMCSF production from epithelial cells.[19] TNF-α also promotes antigen and Th17 cell-dependent neutrophilia after allergenic stimulation and induces dendritic cell migration.[31,32] Murine mast cells have been shown to induce CD4$^+$T-cell migration *in vitro*, but down-regulate FcεRI expression in T regulatory (T reg) cells, while activated T reg cells suppress mast cell FcεRI expression.

Mast cells can induce IgE synthesis in B-cells and local IgE synthesis has been demonstrated in the nasal mucosa of patients with AR.[33,34] IL-4 and IgE upregulate *FcεR*I expression in mast cells suggesting a crucial role for the mast cell-IgE-IgE receptor cascade in on-going inflammation in AR and asthma.[34] A role for mast cells in antigen presentation is also suggested.[35]

While classically, mast cell activation occurs following the allergen crosslinking of *FcεR*I-bound, allergen-specific IgE, they may also be activated through multiple other mechanisms, like via the complement receptors, FcγRI and via TLRs even in the absence of FcεRI stimulation.[36-40]

Basophils are increased in the nasal secretions and BAL of patients with AR and asthma. Like mast cells, basophils can also initiate allergic inflammation through the binding of allergen-specific IgE antibodies to the FcεR1 on basophil cell surface.[41] Basophils also drive Th2 cell differentiation of activated naive CD4$^+$T cells via production of IL-4 and direct cell-cell contact.[42] Basophils in AR and atopic asthmatics also express high levels of the *FcεR*I.[43] Downregulation of *FcεR*I in basophils and mast cells comprises one of the target mechanisms of the efficacy of anti-IgE monoclonal antibody (Omalizumab).

Eosinophils

Eosinophils increase in both the early and late phase of AR[44] and correlate with nasal flow, IL-4, IL-5, IL-8 and IFN-γ, spirometric values, methacholine test positivity, percentage of predicted FEV_1 and Bronchial Hyperreactivity (BHR).[45-54] Eosinophils are increased in symptomatic ectopics and increase in nasal, as well as bronchial epithelium and lamina propria after NAC.[22,55-57] Eosinophils are a major source of Migration Inhibitory Factor (MIF)[58] and Nerve Growth Factor (NGF),[59] express 5-LO, FLAP and LTC_4S, and $CysLT_1$ and $CysLT_2$ receptors,[60] are involved in the loss of epithelial integrity[61] and are also seen in the esophageal mucosa of symptomatic patients with respiratory allergy.[62]

Interleukin-5 has a key role modulating eosinophil differentiation and survival. Targeting IL-5 as a therapeutic strategy for allergic asthma with anti-IL-5 therapy has demonstrated marked reduction of peripheral blood eosinophils, but only partial abrogation of the pulmonary eosinophilic response and with minimal impact on clinical outcomes.[63,64] More recently, in selected patients with refractory, eosinophilic asthma anti-IL-5 monoclonal antibody (mepolizumab) reduced both peripheral blood and sputum eosinophil levels, asthma exacerbations, and resulted in a reduction in oral corticosteroid dose.[65,66]

Eosinophil chemoattractants include eotaxin, Macrophage/Monocyte Chemotactic Protein-4 (MCP4), RANTES, and cysteinyl leukotrienes (cysLTs) among others.[67,68] They act on distinct cell surface receptors [e.g. CC chemokine receptor 3 (CCR3) and $cysLT_1$] present on the eosinophil, but not exclusively so. Challenge with leukotriene E_4 (LTE_4) or leukotriene D_4 (LTD_4) results in increased nasal secretion and nasal obstruction in AR and greatly increased numbers of eosinophils in the bronchial wall.[67,68] $CysLT_1$ receptor is expressed on a variety of nasal and bronchial inflammatory cells, including eosinophils, neutrophils, mast cells, macrophages, B lymphocytes and plasma cells.[69] These numbers of inflammatory cells expressing the $cysLT_1$ receptor are also increased in AR and asthma and there is a further, significant increase among patients experiencing a severe exacerbation of asthma leading to hospitalization.[70]

Activated eosinophils release highly toxic granules, the evolutionary function of which has probably been killing the potentially dangerous invader. Especially in asthma, eosinophil derivatives damage the surface epithelial cells, loosening their attachments and resulting in the shedding of cells into the airway lumen, where they admix with eosinophils, neutrophils and mucus.

T Lymphocytes

In PAR patients, $CD3^+$, $CD25^+$ (activated) and $CD45RA^+$ (naïve) T-lymphocytes are increased in the nasal mucosa. In PAR, Memory T-cells and in idiopathic rhinitis, CD8+ T-cells correlate with mucosal mast cells.[71] While CD86 is expressed on CD19; CD1a, CD14 and CD3 T-cells in PAR; CD80, CD28 and CD152 are expressed after NAC.[72] Moreover, CCR4+ CD4 cells are increased in AR.[73] Besides, Th2 cytokines and chemokines, T-cells in AR express IL-16,[74] CXCR1[75] and CX(3)CR(1).[76] Mucosal δγ T-cells in PAR and asthma are increased, induce IgE synthesis in B-cells and induce proliferation of αβ T-cells.[77] $CD23^+$ B-cells increase in PAR, but do not correlate with the mucosal Th2 cells.[73]

Although conventionally, both AR and allergic asthma have been considered to be due to a disruption in the normal Th1/Th2 balance, more recently, there is new evidence on the emerging roles of Th17 cells, which are a distinct subpopulation of CD4+ T-cells that produce IL-17A, IL-17F, IL-22, TNF-α, and IL-21.[78] Th17 cells were found in the nasal mucosa of AR patients[79] and in bronchial biopsies of asthmatics.[80] IL-17 induces the release of proinflammatory cytokines/chemokines from a variety of cell types,[79] is linked to the development of airway neutrophilia, and its presence in the asthmatic airway, correlates with increased severity of disease. T reg cells play roles in the determination of self tolerance and the regulation of immune responses. Th17 and T reg cells have opposing actions, and T reg cells secrete IL-10 and TGF-β and are increased in patients after immunotherapy.

Neutrophils

Although neutrophils are predominantly increased in nonallergic infective rhinitis and chronic rhinosinusitis, the increased expression of activation markers on neutrophils and Myeloperoxidase (MPO) levels in AR and increase in neutrophils in BAL after NAC suggests roles for neutrophils in AR.[25,81] In acute, severe exacerbations of asthma, there are increased eosinophils and neutrophils within the airway, and the increase in neutrophils is proportionately greater.[82] Inhaled corticosteroids reduce airway eosinophils, but increase airway neutrophils and neutrophil chemoattractant IL-8, with loss of asthma control.[83]

Epithelial Cells

Conventionally, epithelial cells placed at the interface between the external environment and the host have been considered to play a role as a defense barrier against environmental agents. However, over the past several years, the roles of epithelial cells as effector cells has become more evident, directly via the action of inflammatory mediators, as well as via cell-cell interaction with immune cells. Moreover, its pivotal position in orchestrating airway remodeling and fibroblast proliferation is also crucial.[84]

Airway epithelial cells are an important source of a variety of inflammatory mediators, including multifunctional cytokines and chemokines like IL-1, IL-6, IL-8, TNF-α, GMCSF, RANTES, Eotaxin and TARC, leading to their crucial role in the migration and activation of immune cells like eosinophils, basophils and Th2 cells.[85,86] More recently, TSLP derived from epithelial cells is increased in the nasal mucosa of AR patients and in the asthmatic airway.[87] TSLP can activate dendritic cells, promote Th2 responses and activate mast cells.[30] Epithelial cells also express costimulatory molecules like CD86 and HLA-DR, CD86 and the FcεRI can present antigen to T-cells.[88,89] Particulate matter like DEP can induce the release of proinflammatory mediators and enhance the expression of costimulatory molecules on epithelial cells.

Minimal Persistent Inflammation

Even when symptoms are absent in chronic inflammatory diseases like AR and asthma, a minimal level of persistent inflammation may persist and, to prevent unexpected exacerbations, the treatment strategy may need to include its management. Immunotherapy and antihistamines reduce persistent inflammation by decreasing ICAM-1 expression in epithelial cells and eosinophil cationic protein in patients with mite-induced AR.

REMODELING IN ASTHMA (FIG. 67.3)

Remodeling is defined as a change in structure that is inappropriate to maintain the normal airway function.[90,91] Some features of remodeling are evident, even in newly diagnosed or mild asthmatics and is characterized by epithelial fragility and reticular basement membrane thickening. With increasing severity of asthma, the changes are more pronounced and clear: Increase of airway smooth muscle mass, vascularity, numbers of fibroblasts, and interstitial collagen, as well as mucus gland hypertrophy.[92] These changes appear to be the greatest in the larger, more proximal airways. Thickening of the reticular basement membrane occurs early in asthma, even before diagnosis, and is detected

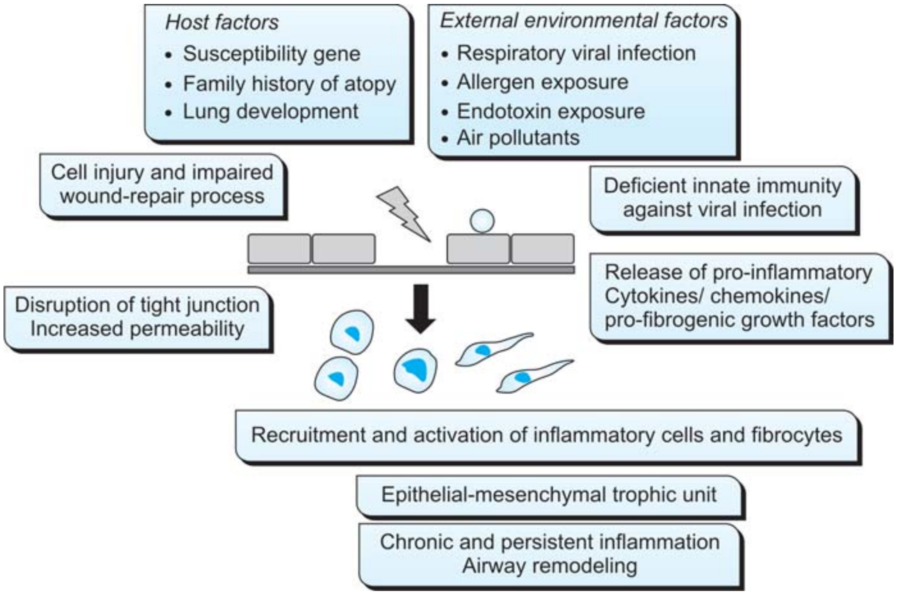
Host factors
• Susceptibility gene
• Family history of atopy
• Lung development
External environmental factors
• Respiratory viral infection
• Allergen exposure
• Endotoxin exposure
• Air pollutants
Cell injury and impaired wound-repair process
Deficient innate immunity against viral infection
Disruption of tight junction Increased permeability
Release of pro-inflammatory Cytokines/ chemokines/ pro-fibrogenic growth factors
Recruitment and activation of inflammatory cells and fibrocytes
Epithelial-mesenchymal trophic unit
Chronic and persistent inflammation Airway remodeling

Fig. 67.3: Airway inflammation and remodelling in asthma [Modified from Hashimoto et al ACII. 2002]

in children with mild asthma.[93] In school children between the ages of 6 and 16 with severe asthma there is already maximally thickening, but with no relation to the age or symptom duration.[9] These changes appear in preschool wheezy children by the age of 29 months.[7] Bourdon et al.[94] showed recently, that reticular basement thickness is a hallmark of severe asthma, but not of mild asthma or Chronic Obstructive Pulmonary Disease (COPD).

Airway smooth muscle surrounds the airways as two opposing helices, i.e. a geodesic pattern and as muscle shortens, it constricts and also tends to shorten the airway against an elastic load. Airway smooth muscle mass is increased in the asthmatic airway.[95] Airway smooth muscle cells can secrete mediators that may promote mast cell chemotaxis, proliferation and survival, while cell-cell interaction between airway smooth muscle cells and mast cells enhances activated complement-induced mast cell degranulation.[96-98] Human lung mast cells migrate towards Th2 cytokine-stimulated airway smooth muscle cells from asthmatics, while supernatants obtained from airway smooth muscle cell cultures of non-asthmatics inhibit this chemotaxis.[99] Large numbers of mast cells have been found located within the bronchial smooth muscle of asthmatics and mast cell mediators, such as tryptase and cytokines can modulate airway smooth muscle cell function. Mast cells also express MMP-9 and contribute to multiple features of chronic asthma tissue remodeling.[19]

Bronchial epithelial cell experiments have demonstrated a role for TLR signaling in the activation of epidermal growth factor receptor, suggesting a role for TLRs in potentiating remodeling.[100] In the asthmatic airway, there are increased numbers of subepithelial myofibroblasts, and allergen challenge in people with asthma leads to the increased accumulation of myofibroblasts in the airway mucosa.[84,101]

Histamine can induce the transition from fibroblasts to myofibroblasts (as measured by α–smooth muscle actin expression), and induce connective tissue growth factor expression in fibroblasts, suggesting the ability to participate in the process of remodeling.[101,102] Fibroblastic infiltration of the lung may be secondary to the recruitment of circulating bone marrow-derived progenitors of fibrocytes to the airway and to the proliferation and expansion of resident fibroblasts, or possibly, epithelial cells may undergo phenotypic change to effector fibroblasts through a process termed Epithelial-Mesenchymal Transition (EMT).

Airway epithelial cells derived from asthmatics demonstrated increased susceptibility to TGFβ-induced EMT than those derived from normal subjects.[103] In addition to the stimulation of epithelial cells and ECM synthesis, TGFβ can elicit other responses in bronchial fibroblasts, including stimulating their proliferation and synthesis of a range of growth factors. It also has effects on the asthma susceptibility gene, a disintegrin and metalloprotease 33 (ADAM33), which has been implicated as an asthma remodeling gene.

Measuring airway function (e.g. FEV_1) can give indirect information on the long-term airway inflammation and structural changes, but cannot detect the early inflammatory processes. Such inflammatory changes can exist even in patients with normal lung function, but with symptoms indicative of asthma.[104] On the other hand, symptomatic infants, who have reversible airflow obstruction may not have bronchial mucosal eosinophilia or remodeling.[8]

How Early Can Remodeling Start?

Airway biopsy studies in children suggest that pathological changes, such as epithelial loss, basement membrane thickening and angiogenesis occur early in the asthmatic airway. In children with difficult asthma (mean age of 13, age range of 6–16) recruited to investigate whether the thickening of reticular basement membrane could occur in the childhood asthma[9] have shown that the thickening of reticular basement membrane was seen in the airway. Barbato A et al. had examined the biopsy specimens of airway in nine children with asthma (age of 4–12 years), six children with atopy without asthma (age of 4–12 years), and in eight control children without asthma or atopy to elucidate whether airway inflammation and remodeling could occur even in mild childhood asthma.[92] It was nicely demonstrated that airway eosinophilia and basement membrane thickness were present in children with mild asthma, and even in children with atopy without asthma. This indicates the following:

- Airway inflammation shown by airway eosinophilia occurs even in mild as well as in difficult asthma
- Airway inflammation occurs in the airway before developing episodic wheezing, although asthma symptom is difficult to establish in children
- The presence of both airway inflammation and remodeling indicates that remodeling process begins early in the disease process of asthma and occurs synchronously in ongoing and repeated airway inflammation rather than as a subsequent event of airway inflammation.

Update on Therapy for Airway Remodeling

Current advances in our understanding of the treatment for airway remodeling highlight that though the remodeled asthmatic airway cannot be fully reversed, targeting therapy towards reducing the risk of developing airway remodeling is crucial. Myofibroblasts are key cells that play a crucial role in the process of remodeling via the synthesis of collagen. Therefore, targeting myofibroblasts can be useful. Recently, it was reported that the combination of Inhaled Corticosteroids (ICS) with Long-acting beta2-Agonists (LABA) reduced the allergen-induced increase in airway myofibroblasts as well as airway eosinophilia as compared with inhaled corticosteroids alone, indicating that the combination of ICS with LABA is superior for reducing airway inflammation and the risk of developing airway remodeling.[105] For difficult-to-control asthma or severe corticosteroid-refractory asthma, an immunomodulator like the anti-IgE mAb (Omalizumab) is recommended. Bronchial thermoplasty is another novel and potentially effective therapy with growing evidence on its clinical effectiveness. However, more evidence is needed on the long-term benefits of thermoplasty.[106]

SUMMARY

The development of AR and asthma requires an interaction between the environment, immune system and genetic susceptibility. While pollen-induced rhinitis is the most characteristic IgE-mediated allergic disease; in perennial allergic rhinitis the allergic triggers are more continuous and lead to an on-going inflammation. Several cells and mediators orchestrate and maintain this inflammation. Although histamine is still one of the major mediators of the allergic reaction, many other mediators produced by different cell types are involved. Thus, the intricate interaction amongst these mediators, cytokines, chemokines, neuropeptides, adhesion molecules and various cells in the form of a complex network leads to the development of specific symptoms and the nonspecific hyperreactivity of allergic rhinitis.

Asthma is characterized by variable degrees of chronic inflammation and structural alterations in the airways, which include epithelial denudation, goblet cell metaplasia, subepithelial thickening, increased airway smooth muscle mass, bronchial gland enlargement, angiogenesis, and alterations in extracellular matrix components, involving large and small airways. Chronic inflammation is thought to initiate and perpetuate cycles of tissue injury and repair in asthma, although remodeling may also occur in parallel with inflammation. While AR and asthma share several similarities in the inflammatory cell and mediator profiles and responses, remodeling as seen in asthma is not characteristic of AR. In asthma, the relationships of airway inflammation, remodeling and lung function are becoming better understood. A variety of inflammatory cells and structural cells play a role in orchestrating the inflammation and structural changes in asthma. Increased airway responsiveness is a surrogate marker of inflammation and may reflect the development of structural changes in the airways. Such persistent increased bronchial responsiveness indicates remodeling, which is partly resistant to therapy.

Moreover, with the increasing evidence on the links between allergic rhinitis and asthma from epidemiological, immunological and clinical studies, early intervention and downregulation of inflammation are the keys to better control of both AR and asthma. New modes of immunomodulatory therapies are under trials or at different stages of development for both AR and asthma. Anti-IgE and anti-Tumor Necrosis Factor (TNF) alpha therapies hold more promising outcomes, but their effect on halting airway remodeling in severe asthma is not known. Given the similarity that exists between the patterns of inflammation in asthma and allergic rhinitis and the impact of AR on asthma, treatment should focus to have a global approach to treat both the upper and lower airways for better outcomes.

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68

Control and Management of Stable Asthma

Sidney S Braman, David Lee

INTRODUCTION

Treatment protocols for the management of stable asthma have undergone considerable change over the past 50 years. During the mid 20th century, an effort was made to improve the currently available bronchodilator medications. Selective, inhaled short-acting adrenoceptor agonists became available in 1969. They offered fewer cardiostimulatory effects than were experienced with commonly used drugs like racemic epinephrine and isoproterenol. Beta-agonist agents with more potency and a longer duration of action were produced, at times with disastrous results that lead to epidemics of asthma mortality.[1] Ephedrine, a drug used for centuries as a Chinese herbal remedy, Ma Huang, was eliminated in some countries as an asthma treatment because of the potential for cardiovascular and CNS stimulatory effects and the use as a recreational drug. Anhydrous theophylline, another bronchodilator, was the mainstay of asthma treatment, although it was fraught with side effects and drug-drug interactions that lead to significant toxicity and mortality. While its use has declined in the recent years, theophylline still plays a role in asthma care as a third or fourth-line agent and when less expensive alternatives are required. In the past years, agents were used to reduce the "anxiety" of asthma, such as phenobarbital and hydroxyzine, but this practice is no longer advised. The end of the 20th century introduced a dramatic new approach to asthma care as the disease became recognized as a chronic inflammatory disease of the airways. In susceptible individuals, it was inflammation that caused the recurring symptoms.

While sudden, unexpected asthma symptoms can be relieved with "rescue" inhaled bronchodilator treatment, the long-term goal of asthma treatment is directed at reducing and possibly eliminating airway inflammation. Medications labeled "controller therapy" are used for this purpose. In 1974, inhaled glucocorticoids became available to treat asthma and since that time, they have become the mainstay of controller therapy for persistent asthma symptoms. It is also recognized that proinflammatory mediators called leukotrienes are important in the pathogenesis of asthma. Agents that are capable of inhibiting the synthesis or action of leukotrienes were introduced in the 1990s as controller treatment for asthma.

With new insights into the pathogenesis of asthma, and advent of newer and safer medications to control the disease, there is reason for optimism in the management of asthma. A global strategy through international asthma guidelines has provided a roadmap for asthma care, including the goals of treatment and evidence-based protocols to lead clinicians to successful outcomes for their patients.[2-5]

THE GOALS OF ASTHMA TREATMENT

There are both short- and long-term therapeutic objectives for every asthmatic patient (Table 68.1). The short-term objectives are to control immediate symptoms and respond to falling lung function measurements (peak flow rates, spirometry). Long-term objectives are those directed at disease prevention, since there are now well-proven strategies to avoid serious exacerbations of acute bronchospasm that may lead to emergency care,

TABLE 68.1: Goals of asthma treatment

1. Limit symptoms of dyspnea, wheeze, chest tightness and cough; day and night
2. Provide normal daily activity level; no absenteeism from work or school
3. Maintain normal or near-normal lung function
4. Reduce or eliminate asthma exacerbations; avoid emergency visits and hospitalizations
5. Minimize the use of rescue medication and use lowest dose and fewest medications possible
6. Avoid side effects of medications

hospitalization and asthma mortality. In order to meet these therapeutic objectives, four components of asthma care should be addressed (Table 68.2). First, measures should be taken to avoid exposure to respiratory allergens and irritants, or other "triggers" of asthma that can cause the worsening of symptoms (Fig. 68.1). This includes the avoidance of outdoor and indoor allergens and irritants that can be found in the household or work environment and treatment of asthma comorbidities such as gastroesophageal reflux. Second, the optimal management of asthma depends on a careful assessment of the patient's symptoms, including the use of objective measures of asthma control with questionnaires and physiological testing. Third, the treatment of asthma with bronchodilator and anti-inflammatory medications is tailored to the patient's needs in a step-up and step-down manner. This approach begins with a staging system that is based on the patient's symptoms and objective measures of lung function and relies on an assessment of the control of asthma symptoms for ongoing care. Fourth, patient education can be a powerful tool in asthma control. Family members can be helpful, especially with children and elderly adults. Active participation by a patient in monitoring lung function, avoiding provocative agents, and making decisions regarding therapy provide asthma management skills that give that patient the confidence to control his or her own disease.

TABLE 68.2: Essential components of successful asthma care

Avoidance: Eliminate asthma "triggers", such as allergen exposure and home/workplace irritants

Monitoring: Use of self-assessment questionnaires, peak flow measures, spirometry

Treatment: Anti-inflammatory therapy is the foundation of successful treatment for persistent asthma; short-acting bronchodilators for rescue from sudden symptoms

Patient education: Provide the necessary tools for self-management, including an action plan for exacerbation of symptoms

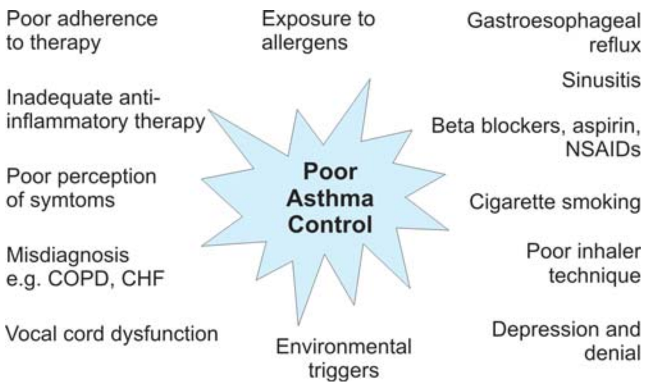


Fig. 68.1: Causes of poor control of asthma

ESSENTIAL COMPONENTS OF ASTHMA CARE

Avoidance

In the developing regions of the world (Africa, Central and South America, Asia, and the Pacific), asthma prevalence has been rising sharply with increasing urbanization and westernization.[6] The reasons for this increased prevalence remain largely unknown, but it has been noted to be associated with a parallel rise in atopic sensitization and increase in other allergic conditions (e.g. eczema and rhinitis). While there is unquestionably a genetic component to asthma, it is possible that changing patterns of environmental influences, such as exposure to microorganisms, pollutants, indoor and outdoor allergens, exert a strong influence on the development of the disease in susceptible individuals.

Allergens and occupational factors are considered to be the most important triggers of asthma. For successful long-term management of asthma, these triggers must be identified and the prevention of exposures should be the first line of defense.[7,8] National and International guidelines for the diagnosis and management of asthma recommend controlling allergen and irritant triggers contributing to asthma severity.[2,3]

Several epidemiological studies have shown a correlation between allergen exposure and the risk of developing asthma.[9-11] For example, there is a dose response relationship between levels of house-dust mite allergen found in the beds of infants of atopic parents at the age of two to three months and asthma at school age.[12] Symptoms and need for medication correlate with the level of household exposure of known allergens in susceptible individuals.[11,13] Improvement in asthma symptoms occurs when allergen exposure is reduced.[14-17]

The important allergens for children and adults appear to be those that are inhaled. Important indoor allergens include a number of domestic factors: House dust mites; cockroach allergen; fungi (Alternaria, Aspergillus, Cladosporium and Candida); and warm-blooded animals (cats, dogs and rodents). Rodents are problematic as they excrete urine, feces, saliva and dander that can be highly allergenic. Removal of a pet from the home of a sensitized patient is encouraged, but it may require several months before allergen levels decrease.[18] These antigens have also been identified in locations where there are no pets residing, including homes, schools, day care centers and work environments. Controlled trials of animal dander avoidance have been reported to be successful in schools and homes without an animal.[19] House dust has been shown to be composed of several organic and inorganic compounds, including insects and insect feces, mold spores, mammalian danders, pollen grains, fibers, mites and mite feces. In poor and inner city locations, mouse and rat allergen exposure and sensitization are common in children who have asthma.[20] Rodent exposure is also common in underdeveloped regions of the world and must be considered in asthma control in these populations.

Single-intervention efforts to improve environmental allergen control in the home are not likely to improve asthma control. For example, a study using allergen-impermeable mattress covers failed to show significant differences between intervention and control populations.[21] Single-interventions are likely to be unhelpful because most of the patients are sensitized to more than one allergen. Multiple-intervention environmental control studies have been conducted in high-risk urban asthmatic children with comprehensive allergen reduction methods. They have demonstrated positive outcomes.[16,22,23] Studies that have shown effective interventions include construction remediation, aimed at moisture sources within the homes of those with documented mold problem,[23] and home visits by community health workers who promote dust mite and cockroach control. Home visits have stressed behavior changes, such as smoking cessation, and offer an individualized approach to address pressing concerns, including asthma-related questions and social issues (e.g. housing, income). Multiple visits are required to encourage the completion of asthma action plans and deliver resources to reduce exposures. These have included allergy control pillow and mattress encasements, low-emission vacuums, commercial-quality doormats, cleaning kits, roach bait and rodent traps. Such multiple intervention programs have advocated for improved housing conditions and provided much needed education and social support. Overall, targeted home-based environmental interventions can improve health and reduce health care costs for poorly controlled asthmatics that live in resource poor communities.[24] A list of effective measures of environmental control is listed in Table 68.3.

TABLE 68.3: Avoiding asthma triggers: Effective environmental control

- Stop smoking and avoid exposure to second-hand smoke.
- Use insecticides to eliminate cockroaches from the house (if the patient can stay away for some time).
- Shake mattresses, pillows, bedspreads and blankets and expose them to the sun as often as possible.
- Remove carpets from the bedroom; minimize number of stuffed toys for children and wash them weekly.
- Avoid piling up books, toys, clothes, shoes and other items that accumulate dust in the bedroom.
- When cleaning the house: Sprinkle the floor with water before sweeping to avoid raising dust; clean furniture with a damp cloth.
- Wash the sheets and blankets on the patient's bed weekly in hot water.

  A temperature of >130°F is necessary for killing house-dust mites (but will not remove the allergen). Cold water and detergent/bleach wash is also acceptable.
- If available, encase pillow and mattress with allergen-impermeable cover.
- If possible, avoid exposure to gas stoves and appliances that are not vented to the outside, fumes from wood-burning appliances or fireplaces, sprays or strong odors.

Outdoor allergens include pollens (mainly from trees, weeds and grasses), fungi, molds and yeasts, but these agents carry less risk for asthma.[25] Grass and ragweed pollens have been especially associated with seasonal asthma symptoms.[26,27] Food allergens while an important cause of anaphylaxis, are not common precipitants of asthma symptoms.

Both outdoor and indoor pollutants contribute to worsening asthma symptoms.[28-32] They may directly trigger bronchoconstriction and act indirectly to worsen asthma by increasing bronchial hyperresponsiveness. This would further enhance responses to inhaled aeroallergens, as well as other provoking agents. The two main outdoor pollutants are industrial smog (sulfur dioxide particulate complex) and photochemical smog (ozone and nitrogen oxides). Whether long-term exposure is injurious or not, presently remains unclear. It is advisable to recommend to asthmatic patients to avoid, to the extent possible, exertion or exercise outside, when levels of air pollution are high.

Indoor pollutants include cooking and heating fuel exhausts, as well as insulating products, paints and varnishes. Modern construction techniques have been suspected of causing greater indoor air pollution. In energy-efficient buildings, there is 50% less turnover of fresh air. Formaldehyde and volatile organic compounds, such as isocyanates have been implicated as potential risk factors for the onset of asthma and wheezing.[30-32] Clinicians should advise patients to be aware of the potential irritating effects of newly installed furnishings and finishes, which can arise from new linoleum flooring, synthetic carpeting, particleboard, wall coverings, furniture and fresh paint.

The use of poorly vented gas stoves and appliances results in increased indoor levels of NO_2 and has been associated with increased respiratory symptoms.[33,34] Installing non-polluting, more effective heating in the homes of children with asthma does not significantly improve lung function, but can reduce symptoms of asthma, days off school, health care utilization, and visits to a pharmacist.[35] Also, fumes from wood-burning appliances or fireplaces, commonly used for heating and cooking in poor, underserved regions of the world, can precipitate symptoms in persons who have asthma.[36] Sprays and strong odors, particularly perfumes, can also irritate the lungs and precipitate asthma symptoms.

In asthmatics, active smoking is a cause of worsening symptoms and the deterioration of lung function and also reduces the efficacy of inhaled and systemic corticosteroids in treating asthma.[37,38] Long-term passive cigarette smoke exposure has been linked to new-onset asthma in children and adults, as well as worsening asthma symptoms, decreased lung function, and greater use of health services in those with preexisting asthma.[39] Children are more likely to be affected when the mother smokes rather than others in the household.[40] Tobacco smoke exposure in adults with asthma may be more likely to occur in the work environment.[41]

Estimates of the prevalence of occupational asthma vary.[42,43] It has been reported that 2 to 15% of all cases of adult-onset asthma arise from workplace exposure. Taking an occupational history can be very rewarding and can lead to primary prevention and avoidance of the offending environment. Patients should be questioned about exposure to animals, shellfish, fish and arthropods. They may cause asthma in farmers, grain handlers, and laboratory and poultry workers. Exposure to wood, plants and vegetables can cause asthma in woodworkers, carpenters, grain handlers, bakers and tobacco workers. Exposure to enzymes and pharmaceuticals should be questioned in pharmaceutical workers, pharmacists and detergent industry workers. Solderers, spray painters, electronics workers, and chemical and polyurethane manufacturers are another susceptible group. And, electroplaters, hard metalworkers, polishers, and solderers may have asthma caused by metals and metal salts such as aluminium, chromium, cobalt, nickel and platinum fumes.

Monitoring Asthma: Use Objective Measures of Asthma

Pulmonary Function Tests

Objective measurements of pulmonary function are important in patients with asthma to confirm the diagnosis and to assess disease activity from time to time. While there is a poor correlation between the airway inflammation and lung function,[44,45] measurements of the physiological consequences of asthma are extremely important in the control and management of asthma. Physiological testing can demonstrate the major diagnostic features of asthma: (1) airflow obstruction, (2) reversibility of airflow obstruction, and (3) bronchial hyper-responsiveness, and therefore can be useful in confirming the diagnosis. The following four tests of pulmonary function are extremely useful for establishing the diagnosis of asthma and/or for following the clinical course of the patient once the diagnosis has been made: (1) Spirometry; (2) Peak Expiratory Flow (PEF) measurements; (3) Pulse oximetry and/or arterial blood gas analysis; and (4) Bronchoprovocation testing.

Physiologic tests are also important tools to assess the disease activity of asthma. The perception of asthma symptoms by the patient is often poor, especially in the elderly or if the patient has had long-standing asthma.[46-49] Also, the physician's findings on physical examination may either overestimate or underestimate the severity of the airflow obstruction. Although the measurements of lung function do not correlate that well with patient-reported symptoms, they do add an objective measure to the assessment of how well the disease is controlled and have been proven to be important tools in the management and control of asthma.[50,51]

i. *Spirometry* is useful for the diagnosis of asthma and for following clinical outcomes.[52] Airflow obstruction, a classic feature of asthma, can be demonstrated on spirometry using the timed vital capacity maneuver. The test provides a quantitative assessment of asthma and can be used in children who are five years of age and older, The Forced Vital Capacity (FVC), which is the total amount of volume exhaled and the FEV_1, which is the volume exhaled in the first second of expiration are measured. The patient's results are compared with reference values based on age, height, sex and race.[53] A reduced FEV_1 and ratio of FEV_1/FVC show the presence of airflow obstruction.

A brisk improvement in spirometry (post-bronchodilator FEV_1 increases more than 12% and 200 mL), 10–20 minutes after the inhalation of a short-acting beta agonist can demonstrate the second cardinal feature of asthma reversibility.[53,54] Some patients with asthma never meet the reversibility criteria after repetitive testing with a short-acting bronchodilator. In such patients, after vigorous treatment, the FEV_1 may show significant improvement on a subsequent clinic visit and this would strongly support a diagnosis of asthma. A single post-bronchodilator test, therefore can not be used to exclude the diagnosis of asthma.

Regular monitoring of pulmonary function is important for asthma patients. It is helpful after treatment has been initiated to document improvement and also during the periods of worsening symptoms to offer an objective assessment of airflow obstruction. Spirometry has been advised atleast every one or two years to monitor lung function.[2] Physicians have a poor ability to assess the degree of airflow and patients too often can not perceive the severity of their disease.[50,51,55,56] One study reported that one-third of the children who had moderate-to-severe asthma based on symptoms, were reclassified to a more severe asthma category when pulmonary function was considered.[57] This is especially important in patients with poor lung function, as a low FEV_1 is associated with an increased risk of severe asthma exacerbations.[58,59] On the other hand, another study showed that a majority of children who had mild-to-moderate asthma classified by symptoms had normal FEV_1.[60] The assessment of reversibility to an inhaled short acting bronchodilator correlates with the degree of airway inflammation and can also offer an assessment of future risk.[61] A pronounced increase in FEV_1 after a bronchodilator is a strong marker of subsequent risk of death from asthma. In one study, compared with subjects with 15 to 24% reversibility in FEV_1, asthmatics with 25 to 49% and those with more than 50% reversibility had a 2.7 and 7.0 higher risk of death from asthma, respectively.[62] In addition, those patients who have the greatest degree of reversibility in response to a short-acting bronchodilator may be at the greatest risk of developing fixed airflow obstruction and have the greatest loss of future lung function.[63]

ii. *PEF: Short-term home monitoring* with the PEF meter can be useful in diagnosing asthma and identifying environmental triggers of asthma and can detect early signs of deterioration when symptoms change. Long-term monitoring is useful for those with severe brittle asthma and for those who have a poor perception of asthma symptoms. Spirometry, however, is the preferred method for measuring lung function to classify asthma severity as peak flow measures may underestimate airflow obstruction, particularly with more severe disease.[64,65] Peak flow measurements ideally should be done 10–20 minutes after inhaling a β-agonist. A zone system has been developed[3] for patient ease as follows: Green is 80 to 100% of the personal best peak flow measurement and shows good control; yellow is 50 to 80% of the personal best and signals caution that asthma is not under sufficient control; and red is less than 50% of personal best and signifies danger and the need for immediate physician intervention.

A diurnal variation in PEF of 20% is the diagnostic of asthma. The magnitude of peak flow variability is in general proportional to the severity of the disease. A high degree of variability signals unstable asthma that demands increased medication.

iii. *Oximetry/ blood gas analysis:* Virtually all asthmatic patients have hypoxemia during an acute exacerbation; the more severe the attack, the lower the arterial oxygen tension. Oximetry or arterial blood gas analysis is helpful during a severe attack and would not be generally done in the routine management of stable asthma.

iv. *Inhalation challenge testing* is useful in some patients when the diagnosis of asthma is not secure.[66] This occurs when the patient has normal peak flow rates and spirometry findings, yet typical asthma symptoms are present. Increasing concentrations of an agonist, such as methacholine are inhaled and if the FEV_1 drops 20% below baseline at any standard dose, the test result is positive, supporting the diagnosis of asthma. A negative test rules out asthma.

Measures of Inflammation

The presence and quantification of various inflammatory cells and mediators in sputum and body fluids have been used to reflect the activity of inflammation in asthma. These biomarkers of disease activity, such as sputum eosinophil counts, have mainly been used for clinical investigation. Elevated levels of Nitric Oxide (NO) have been detected in the exhaled air of asthmatic subjects. Exhaled NO is well established as a marker of eosinophilic inflammation. A standardized method of measurement must be carefully followed to prevent spurious results.[67] It has been shown to be a fairly effective screening tool with a sensitivity of 88% when there are levels of 20 parts per billion or greater in patients with asthma symptoms. Unfortunately, exhaled NO levels do not correlate with disease severity, but serial measurements may aid in monitoring disease activity. It has shown promise, for example, in identifying pending exacerbations of asthma. The availability of a low cost handheld analyzer may lead to future use in resource poor regions, although the scope for both false positives and false negatives remains significant.[68]

Treatment of Stable Asthma

Asthma Pharmacotherapy

i. *Beta 2-adrenoceptor agonists*: Selective inhaled β 2-adrenoceptor agonists are the main bronchodilating agents for the treatment of asthma, through their rapid and potent effects in relaxing airway smooth muscle. Their classification is according to the duration of action: Short and long acting. They produce bronchodilation by direct stimulation of the airway smooth muscle leading to relaxation via the activation of the adenylate cyclase pathway. Inhaled agents are preferred and they can be delivered by metered-dose inhaler, dry-powder capsules, and compressor-driven nebulizers. Corticosteroids upregulate the expression of β 2-adrenoreceptors by increasing the transcription of the gene.

   Short-Acting Beta-Agonists (SABAs), such as salbutamol, are widely used due to their acute (4–6 hour) bronchodilator effects and for the ability to protect against various challenges such as cold air, exercise and allergen. They are generally well tolerated, even with frequent use. They should be used as guide for symptom control. Anti-inflammatory treatment should be given when the use of SABAs become excessive (> 2x/week).

   Long-acting Beta-agonists (LABAs), mainly salmeterol and formoterol, provide bronchodilation and improve bronchial responsiveness for up to 12 hours. Like SABAs they also inhibit the acute early allergic response, but in addition, they inhibit the late phase response and airway hyperresponsiveness lasting up to 34 hours after allergen challenge.[69] The use of LABAs as monotherapy should be avoided in the stable asthmatic. Conclusions from a large randomized study[70] showed that LABA monotherapy may increase asthma-related deaths and hospitalizations, especially in certain ethnic groups. A large meta-analysis showed that the concomitant use of inhaled steroids appears to modify this effect.[71] Side effects are generally uncommon with inhaled LABA therapy (Table 68.4).

ii. *Inhaled corticosteroids (ICS):* Since their introduction in the early 1970s, ICS have become the mainstay of treatment in persistent asthma. This is because of its proven efficacy, above any other class of asthma therapy and also its lower potential for systemic side effects compared to oral glucocorticosteroids. It exerts its anti-inflammatory activity via the glucocorticoid receptor complex that regulates the gene transcription of proteins that inhibit proinflammatory cytokines. ICS have highly lipophilic compounds that have much higher binding affinity compared to hydrocortisone and also a highly efficient first-pass hepatic metabolism, resulting in lower systemic absorption. Clinically, they improve airway inflammation, hyperresponsiveness, airflow obstruction and symptoms in asthmatics. In the stable persistent asthmatic with persistent symptoms, adherence to ICS treatment is of paramount importance as it has been associated with the decreased risk of near fatal and fatal asthma (Fig. 68.2).[72]

   Establishing the dose-response relationship characteristics of ICS have been challenging as there is a relatively flat dose-response relationship and characteristics do vary between patients. The impetus for discovering the lowest effective dose in any patient is to minimize the potential systemic side effects especially when used over many years. In adults with mild to moderate asthma, most of the therapeutic benefit of budesonide is achieved at 200–400 mcg/day and its maximum effect at 1,000 mcg/day.[73] Equipotent daily therapeutic doses of beclomethasone are estimated to be between 200 and 500 mcg; doses higher that 1,000 mcg are discouraged because of the risk of absorption leading to systemic side effects. Dose response curves of fluticasone have been seen to plateau at lower doses (100–200 mcg).[74] Side effects of ICS are both local and systemic (Table 68.4). They are generally well tolerated, especially at lower doses.

iii. *Theophylline*: The xanthines, particularly theophylline, are the most widely prescribed oral therapy for the maintenance of stable asthma worldwide. In the 1980s, the introduction of the slow release preparation that provided more steady plasma levels was a large cause of its widespread use. The weak bronchodilator effect of theophylline on the airways can be

TABLE 68.4: Pharmacological agents for stable asthma

Pharmacological agent	*Potential adverse effects*	*Therapeutic considerations*
Corticosteroids (Glucocorticoids)	Cough, dysphonia, oral candidiasis	The use of chamber devices and mouth washing after inhalation decreases local side effects
Inhaled: Beclomethasone dipropionate, Budesonide, Flunisolide, Fluticasone propionate, Triamcinolone acetonide	In high doses, systemic effects may occur. Although studies are not conclusive, and clinical significance of these effects has not been established since it has been studied for long periods (e.g. adrenal suppression, osteoporosis, growth suppression, and skin thinning and easy bruising)	The risk-benefit ratio of uncontrolled asthma to the limited risks of inhaled corticosteroids should be considered.
Systemic: Methylprednisolone, Prednisolone, Prednisone	Short-term use: reversible hyperglycemia, increased appetite, fluid retention, psychological alterations, hypertension, gastric ulcer, and rarely aseptic necrosis of femur. Long-term use: adrenal axis suppression, growth retardation, dermal thinning, hypertension, diabetes, Cushing's syndrome, cataracts, muscle weakness	Use at lowest effective dose. For long-term use, alternate-day am dosing may produce less adverse effects.
Cromolyn Sodium and Nedocromil	15 to 20% of patients complain of an altered or unpleasant taste from nedocromil.	Therapeutic response to cromolyn and nedocromil often requires a 4 to 6 week trial to determine response clinically. Safety is the main advantage of these agents.
Long-Acting Beta2-Agonists	Tachycardia, muscle tremor, hypokalemia, prolongation of QT interval in overdose.	Not for monotherapy or clinical asthma exacerbations.
Inhaled: Salmeterol Formoterol	Tolerance may occur within 1 week of chronic therapy	Clinical significance of potentially developing tachphylaxis is uncertain
Oral: Albuterol, sustained-release		Inhaled long-acting beta2-agonists are preferred because they have fewer adverse reactions than oral agents.
Methylxanthines Theophylline, sustained-release tablets and capsules	Dose-related acute toxicities: tachycardia, nausea and vomiting, arrhythmias, headache, seizures, hematemesis, hyperglycemia, and hypokalemia.	Routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, individual differences in metabolic clearance and drug-drug interactions as well
Leukotriene Modifiers Zafirlukast, Montelukast Pranlukast	Well tolerated overall. One reported case of reversible hepatitis and hyperbilirubinemia; high concentrations may develop in patients with underlying hepatic disease	Administration with meals decreases bioavailability
Zafirlukast	Limited case reports of reversible hepatitis	Zafirlukast can inhibit the metabolism of terfenadine, warfarin, and theophylline.

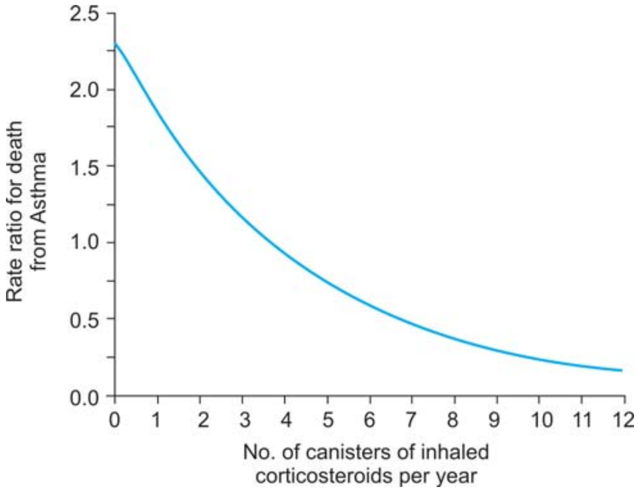


Fig. 68.2: Relation between death due to asthma and use of corticosteroids per year. Suissa S et al. Fitted Rate Ratio for Death from Asthma as a Function of the Number of Canisters of Inhaled Corticosteroids Used during the Year before the Index Date. NEJM. 2000; 343:332-6.

demonstrated *in vitro* on human airway tissues and it may result from inhibition of phosphodiesterases especially type III and IV.[75] Inhibition of these phosphodiesterases also appears to have anti-inflammatory effects and also inhibits the late response to allergen challenge.[76] The guidelines recommend that theophylline may be considered for use as add-on therapy in patients, not well-controlled on low-dose ICS, but recommend LABAs as more effective with fewer adverse events.[77] For the patient with uncontrolled asthma, low-dose inhaled budenoside with theophylline compared to high-dose inhaled budesonide produced similar benefits[78] and this may be achieved at theophylline concentrations below the recommended therapeutic range of 5–15 mg/dl.

Despite its attractiveness, side effects and their frequency is the main limitation to its use (Table 68.4). This is especially pronounced in the elderly where polypharmacy and potential drug-to-drug interaction are becoming more frequent. Theophylline has a rather narrow therapeutic window and unwanted effects are usually seen at plasma levels above 20 mg/dl. To avoid untoward effects it is advisable to monitor blood theophylline levels.

iv. *Leukotriene pathway modifiers:* Substantial evidence exists for involvement of the cysteinyl leukotrienes in the pathophysiology of asthma. They exert a number of important pharmacological actions that contribute to airflow obstruction in asthma: Airway smooth-muscle contraction, edema formation and mucus secretion. Numerous studies have shown that leukotriene modifiers have protective effects against bronchoprovocative challenges and they ease bronchial obstruction in asthma patients.

The antileukotrienes may be used as first line therapy when anti-inflammatory therapy is needed, but they are generally less effective than ICS. They also have less effect compared to LABA as add on therapy to ICS.[79] They may however have special role in the aspirin-sensitive asthmatic.[80] If one is chosen, a therapeutic trial of 4–6 weeks should be allowed to determine its effectiveness. There is currently no evidence that supports its use beyond this time if there is no symptomatic improvement. The leukotriene modifiers may have an additive effect to ICS and inhaled β-2 agonist in the severe asthmatic when step-up care is needed.[81,82]

Anti-leukotrienes are generally well-tolerated. In a safety study, over 3,000 patients, 4.5% developed reversible elevations of transaminases with zileuton after a few months of therapy.[83] Reports of Churg-Strauss syndrome after the initiation of Zafirlukast and Montelukast have also emerged, but it is likely that this has occurred as a result of systemic steroid withdrawal.

v. *Oral corticosteroids:* Systemic administration of corticosteroids are generally reserved for patients with severe asthma, or as trial of therapy to attempt to optimize lung function in patients with a component of fixed airflow obstruction despite conventional asthma therapies. Corticosteroids, such as prednisolone and methylprednisolone are rapidly absorbed across the gastrointestinal tract and have very high bioavailability. High doses (0.5–1.0 mg/kg/day) are recommended by most consensus documents for the treatment of severe exacerbations of asthma and should be avoided in the routine treatment of chronic stable asthma even at lower doses.

A summary of the therapeutic agents used for chronic stable asthma is listed in Table 68.4.

Biologic Therapies

Immunoglobulin E (IgE) is recognized as a key component of atopic asthma pathophysiology. Omalizumab is an IgE monoclonal antibody, which binds free IgE and decreases circulating IgE. It therefore, decreases allergen-driven cell degranulation and reduces the release of preformed proinflammatory mediators and newly synthesized cytokines.[84] This agent is used in difficult to control asthmatics who are not responding to conventional therapy. Interleukin (IL)-5 plays an important role in regulating the production, differentiation, recruitment, activation and survival of eosinophils. Neutralizing IL-5 with an antibody was regarded as a promising therapeutic strategy, however it does not appear to add significant clinical benefit in patients with asthma.[85]

Allergen Immunotherapy

Allergen-specific immunotherapy is the practice of administering gradual quantities of an allergen extract to a patient to ameliorate symptoms from subsequent exposures. Clinical evidence suggests that inhaled immunotherapy is effective to treat seasonal or perennial allergic rhinitis and asthma. It has also been shown to reduce the development of asthma in children with seasonal rhinoconjunctivitis.[86] Subcutaneous administration has generally been used and it is highly effective when the optimal does of high quality vaccine is administered. An important limitation of this route is the risk of potential side effects, which include systemic allergic reactions, occasional anaphylaxis and, even, fatalities.[87] As a result, safer approaches, such as sublingual immunotherapy, have been used to induce tolerance to inhaled antigens.[88] Allergen immunotherapy should always be combined with appropriate allergen avoidance strategies. The mechanisms of immunotherapy are based on a restored balance between Th2 and Th0/Th1 cells, inducing a reduction of inflammation in the target organ. Clinical indications and relative contraindications offered by the WHO, 1998 position paper[89]are shown in Table 68.5.

TABLE 68.5: Allergen Immunotherapy*

Allergen immunotherapy is indicated in the following circumstances:
- IgE-mediated disease (symptoms on exposure to relevant allergen supported by a positive SPT/RAST to that allergen)
- Inability to avoid allergen
- Inadequacy of drug treatment
- Limited spectrum of allergies
- Patients who understand risks and limitations of treatment.

Relative Contraindications:
- Coexistent uncontrolled asthma (within the UK, presence of asthma is considered a relative contraindication).
- Patients taking beta blockers
- Patients with other medical/immunological disease
- Small children (less than five years)
- Pregnancy (maintenance injections may be continued during pregnancy)
- Patients unable to comply with the immunotherapy protocol.

* Bousquet J, Lockey RF, Malling HJ. WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Allergy. 1998; 53 (Suppl 44):1-42.

Antifungal Therapy

Airborne exposure to fungi is a common phenomenon worldwide. Fungal sensitization is uncommon, but in some asthmatics it can greatly affect the course of their disease.[90] There are three main recognized syndromes related to fungal sensitization and asthma: Allergic Bronchopulmonary Aspergillosis (ABPA), Allergic Bronchopulmonary Mycosis (ABPM) and trichophyton asthma. While anti-fungal therapy can not eliminate the exposure to fungal elements, it can be effective in these syndromes. Itraconazole is effective adjunct therapy in the treatment of stable ABPA together with oral corticosteroids and in asthmatics with SAFS it can improve quality of life measures and lung function.[91,92]

Diet and Asthma

Epidemiological data has long supported the notion that differences in diet may lead to different predisposition to allergic disorders. This association to the course and the control of the asthmatic patient, however is a much different concept. The International Study of Asthma and Allergies in Childhood (ISAAC), asthma prevalence was lowest in those countries with the highest dietary fat intake and those with a Mediterranean diet.[93] Numerous studies have since examined the relationship between dietary nutrients, fruits and vegetables for possible associations with asthma. While nutrients, such as vitamins A,C, E, various fatty acids, and increase in fresh food and vegetables appear promising, evidence from prospective and randomized trials are lacking.[94] Maternal nutrition on the fetus during pregnancy may have a role in subsequent childhood asthma, but data on this subject remains scarce. Intervention studies promoting the avoidance of cow's milk and eggs during pregnancy have failed to protect the infants from asthma.[95] General advice for patients with stable asthma, however needs to be based on the individual and their atopic history as there are no consensus recommendations currently. Eating a balanced diet in natural foods and vegetables seem to be intuitive and would probably yield benefits in other disease areas.

Patient Education

Asthma management plans have become popular, especially with high-risk patients. They are designed to give patients the skills for routine management, their disease and how to recognize and control the exacerbations of symptoms (Table 68.6). Evidence is now abundant that asthma self-management education is effective in improving outcomes of chronic asthma.[96-100] Benefits from self-management education include reduction in symptoms, less limitation of activity, improvement in the quality of life and perceived control of asthma, and improved medication adherence.[101-107] Also, death from asthma can be reduced. The use of a peak flowmeter, a written action plan and oral glucocorticoids prior to a severe attack can impact mortality.

A written action plan should include instructions for daily management, including what medications to use and how to avoid specific triggers relevant to the patient, and for recognizing and handling worsening asthma. Patients should know how to recognize the signs and symptoms of worsening asthma and how peak-flow measurements can be used to recognize an attack. It should also include what medications to take in response to these signs, what symptoms and peak-flow measurements indicate the need for urgent medical attention and the logistics of obtaining the required urgent medical care. Written action plans are particularly recommended for patients who have moderate or severe persistent asthma, who have difficulty perceiving the signs of worsening asthma and for those with a history of severe exacerbations or poorly controlled asthma.

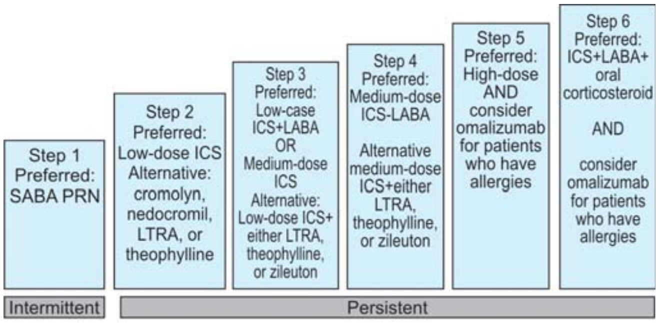
TABLE 68.6: Essential elements of asthma self-banagement program

- **Develop active partnership with patient and family**
  - – Provide an open two-way communication
  - – Establish realistic goals of successful therapy
  - – Discuss treatment preferences
  - – Explore barriers to successful treatment.
- **Offer basic knowledge of asthma causes and how to avoid triggers**
  - – Identify potential environmental allergens
  - – Discuss occupational triggers
  - – Avoid outside exposure on high pollution days.
- **Give pharmacy-based education**
  - – Difference between controller and rescue medications
  - – Role of each medication prescribed
    - proper inhaler technique
    - MDI (with holding chamber or spacer)
    - dry powder inhalers.
- **Provide patient with action plan for**
  - – Daily control
  - – Recognition and management of acute exacerbations of symptoms
  - – Where and when to seek help.
- **Explain how to measure asthma control**
  - – Peak flowmeter use
  - – Home diary or asthma control tests.
- **Offer when available computer and Internet programs for asthma care**

TREATMENT PROTOCOLS FOR ASTHMA

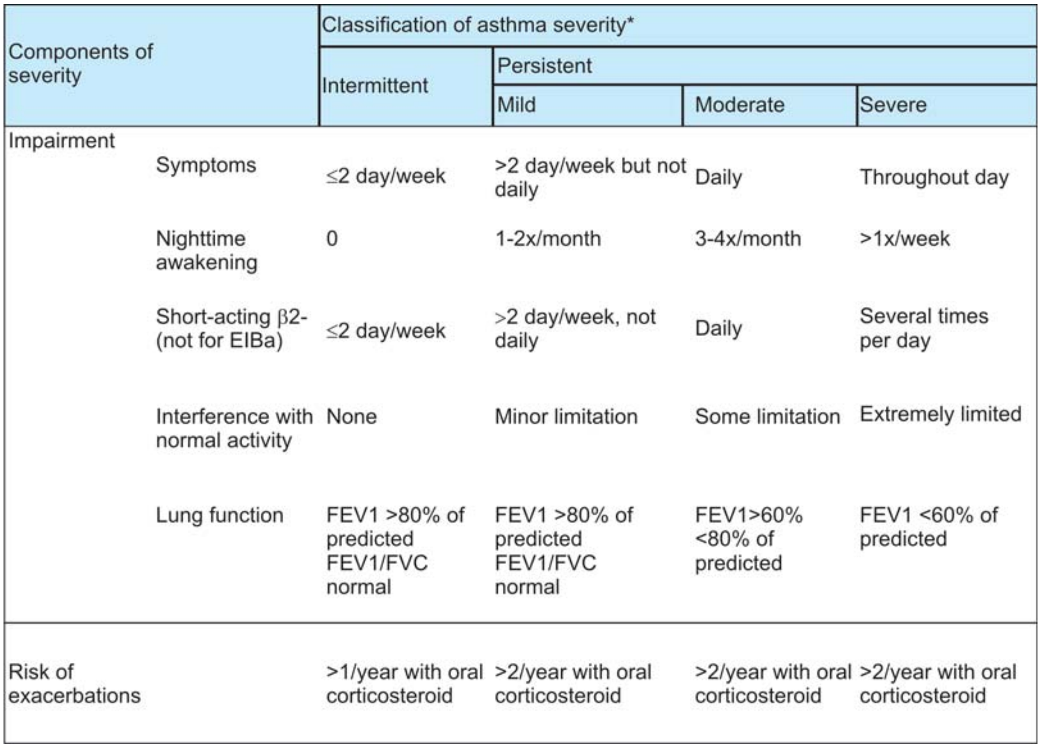
Asthma is an episodic disease and the clinical presentation and natural history is highly variable from patient to patient and for any individual patient. Some patients have persistent symptoms and exacerbations from time to time. Others show long periods of remission, with sudden worsening with exposure to asthma triggers (Fig. 68.1). Treatment protocols are based on this variability and use a step-care pharmacological approach based on the intensity of the asthma over time[2,3] (Fig. 68.3). As symptoms and lung function worsen, step-up or add-on therapy is given. As symptoms improve, therapy can be "stepped down."

It has been challenging to clinicians to quantify the degree of asthma for any given patient and to make decisions based on that assessment regarding treatment. Lung function was often used as the primary endpoint, but because of the poor correlation between lung function and patient symptoms and outcomes, a composite of measures has been suggested by international asthma guidelines. Initially, they were based on a scale of disease severity.[2,3] Asthma severity can be considered the intrinsic intensity of the disease. It is advocated for use when a patient is not receiving long-term control therapy. The components of current impairment include daily symptoms, night-time awakenings, need of quick relief


Step 1
Preferred:
SABA PRN
Step 2
Preferred:
Low-dose ICS
Alternative:
cromolyn,
nedocromil,
LTRA, or
theophylline
Step 3
Preferred:
Low-case
ICS+LABA
OR
Medium-dose
ICS
Alternative:
Low-dose ICS+
either LTRA,
theophylline,
or zileuton
Step 4
Preferred:
Medium-dose
ICS-LABA
Alternative
medium-dose
ICS+either
LTRA,
theophylline,
or zileuton
Step 5
Preferred:
High-dose
AND
consider
omalizumab
for patients
who have
allergies
Step 6
Preferred:
ICS+LABA+
oral
corticosteroid
AND
consider
omalizumab
for patients
who have
allergies
Intermittent
Persistent

SABA = short-acting beta$_2$-agonist; ICS = inhaled corticosteroid; LTRA = leukotriene receptor antagonist; LABA = long-acting beta$_2$-agonist.

Fig. 68.3: Guidelines for the diagnosis and management of asthma



Components of severity		Classification of asthma severity*			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 day/week	>2 day/week but not daily	Daily	Throughout day
	Nighttime awakening	0	1-2x/month	3-4x/month	>1x/week
	Short-acting β2- (not for EIBa)	≤2 day/week	>2 day/week, not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	FEV1 >80% of predicted FEV1/FVC normal	FEV1 >80% of predicted FEV1/FVC normal	FEV1>60% <80% of predicted	FEV1 <60% of predicted
Risk of exacerbations		>1/year with oral corticosteroid	>2/year with oral corticosteroid	>2/year with oral corticosteroid	>2/year with oral corticosteroid

Fig. 68.4: Classification of asthma severity adults not on controller therapy

** Adapted from NAEPP, NHLBI, NIH. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. August 2007*

rescue therapy, work/school days missed, interference with normal daily activities and lung function, measured by spirometry (Fig. 68.4).

When symptoms are more than two times per week, nocturnal symptoms are more than twice per month or FEV_1 is less than 80% of predicted, regular treatment with anti-inflammatory therapy (low-dose inhaled corticosteroids preferred) is recommended and the patient is considered to have "persistent" asthma. The response to therapy, that is how the manifestations of asthma have been reduced or removed, is the degree of asthma control achieved. Asthma control has two components: The level of clinical asthma control (symptoms and quality of life) and the risk of future adverse events (exacerbations of asthma, loss of lung function, side effects of the therapy). At each visit, the patient should be assessed for the level of asthma control, adherence to the recommended treatment and for potential side effects of the drugs used. A simplified scheme to identify patients who are controlled, partly controlled and poorly controlled has been developed (Table 68.7).[2,3] Several composite control questionnaires have been developed to help the clinician assess asthma control.[108-112] Step-up therapy is advised for patients not well controlled according to guideline recommendations. There are no hard and fast rules on stepping down asthma care, but atleast three months of stability is recommended until a reduction in medication is tried. The lowest dose of medication to maintain stability is offered. At each step, reliever medication with a SABA is used for breakthrough symptoms, but increased use implies poor control and need for step-up therapy.

Significant reductions in the rate of severe exacerbations and improvements in the quality of life can be achieved by aiming at achieving guideline-defined asthma control and by adjusting therapy to achieve it. At the end of one year, with the use of an inhaled corticosteroid and LABA, 30% of the patients can achieve total control (i.e. the absence of any sign or symptom of asthma), and 60% had achieved well-controlled asthma.[113] For those who do not reach adequate control, step-up care is given according to the guidelines. Helpful general guidelines for the use of asthma medications are given in Table 68.8.

TABLE 68.7: Classification of Asthma Control youths >12 years and adults*

Characteristics of impairment	*Controlled (All of the Following)*	*Not well controlled (Any measure present in any week)*	*Very poorly controlled*
Daytime symptoms	None (d ≤ 2/week)	> 2 times/week	Throughout day
Interference with normal activities	None	Any	Extremely limited
Nocturnal symptoms/awakening	< 2 times/month	1-3 times/week	> 4 times/week
Need for short-acting beta agonist (rescue treatment)	None(d ≤ 2/week)	> 2 times/week	Several times a day
Lung function (PEFR or FEV_1)	> 80% predicted or personal best	60-80% predicted or personal best	< 60 predicted or personal best
Validated Questionnaire (e.g. ACT score)	> 20	16-19	15 or less

* Adapted from NAEPP, NHLBI, NIH. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007.[3]

TABLE 68.8: Principles of Asthma Treatment

1. Use rescue medication (SABA) for symptoms of dyspnea, wheezing and chest tightness at any stage
2. Begin anti-inflammatory medication (inhaled ICS preferred) when symptoms occur two or more times a week
3. Do not use LABA bronchodilators continuously as solo treatment
4. Adding LABA to ICS is preferred approach when step-up therapy is needed
5. Medium or high dose ICS may be necessary to control persistent symptoms, but risk more systemic absorption
6. Sustained-released theophylline is a bronchodilator with weak anti-inflammatory properties and frequent side effects
7. The use of a spacer device is recommended when MDI cannisters are used to reduce oropharyngeal deposition and reduce systemic absorption; consider the use of single or multi-dose Dry Powder Inhalers (DPIs). They are easier to use correctly that MDIs
8. Systemic corticosteroids have many side effects. They may be necessary for severe asthma; oral use is preferred over intramuscular or intravenous delivery

SABA: short-acting beta agonist; **LABA:** long-acting beta agonist; **ICS:** inhaled corticosteroid; **MDI:** metered dose inhaler

ASTHMA CONTROL IN DEVELOPING COUNTRIES

More than 500 million patients live in developing countries or in deprived populations. They have received insufficient attention from the health care community, government officials, media, patients and families.[114] While the value of asthma disease management interventions has been well documented, they are expensive and difficult to implement, especially in developing countries where the infrastructure for the diagnosis and management of chronic diseases, such as asthma, is either not available or is viewed as low priority on the public-health agenda. In addition, surveillance systems and diagnostic services are often poorly developed, and the true burden of diseases, such as asthma and occupational lung disease is largely unknown. It is evident that asthma is mostly under-diagnosed and under-treated (particularly in children), causing a high morbidity and a significant mortality.

The World Health Organization (WHO) has given priority to the prevention and control of chronic diseases, such as asthma, with special emphasis on developing countries.[115] Models have been developed like the WHO-Practical Approach to Lung Health (PAL).[116] This is an initiative for low and middle-income countries that is focused on improving the management of patients with respiratory symptoms in the primary care setting and, improving the efficiency of the delivery of respiratory services within a district health care system, with a focus on coordination and integration of respiratory case management. The program uses standardized clinical practice guidelines that have been developed to suit the local needs. Key components are: (1) providing guidance, technical support and assistance with funding; (2) assuring access to essential diagnostics and drugs; and (3) education for health care workers in these activities.

Using a PAL educational outreach program for the integrated case management of chronic respiratory diseases has been used in poor, underdeveloped regions such as in South Africa.[117,118] Combining educational outreach delivered to nurse practitioners by health department trainers, and integrated case management has provided a promising model for disease prevention and improved care for respiratory diseases such as asthma. With local adaptations of international asthma guidelines, success with asthma control in resource poor areas have been also reported from Latin America.[119,120] Important suggestions for asthma control of patients in low and middle-income countries are suggested by the World Health Organization in the "Practical Approach to Lung Disease Handbook."[121]

In the majority of developing countries, diagnostic tests like spirometry that are required for the diagnosis and assessment of severity of asthma are not readily available, resulting in incorrect assessment and under-diagnosis of asthma. Most asthmatics who live in developing countries and in deprived areas often have limited access to essential drugs as they are either not available or not affordable.[122] The Asthma Drug Facility has been proposed by the International Union to address this issue and make good quality essential asthma drugs available to all patients who live in low- and middle-income countries.[123] Steps have been taken by the Union to ensure a transparent, straightforward and efficient approach.

Similarly in India, the Government of India and WHO (India) had developed asthma-management guidelines for use at the primary levels of health care. The guidelines advocate a simple algorithmic approach based on the local conditions and feasibility.[124]

CONCLUSION

The approach to the patient with asthma has undergone a great transition in recent years. Successful outcomes can be expected for most patients. International guidelines have underscored the importance of controlling the underlying inflammation that drives the manifestations of the disease. A step-up approach has been advocated, beginning with a short-acting beta agonist for infrequent symptoms. For persistent symptoms, inhaled corticosteroids are recommended as first-line therapy. Monitoring with objective measures of disease activity, including pulmonary function and symptom questionnaires, have been advised and patient education programs can lead to self-reliance, better adherence to therapy and improved outcomes. The challenges in asthma control faced by underdeveloped countries can be overcome with educational outreach programs adapted to local needs and resources.

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Management of Severe Asthma

Liesel D'Silva, Parameswaran Nair

INTRODUCTION

There is no universally accepted definition of difficult or chronic severe asthma. Using the consensus definition of American Thoracic Society (ATS), severe asthma has been defined as persistent symptoms, airflow limitation and treatment resistance.[1] A patient who requires prolonged treatment with oral corticosteroids for $\geq$ 50% of the year and/or high dose inhaled corticosteroids along with two or more minor criteria (use of daily long-acting bronchodilators, daily or near daily use of rescue medication, persistent airflow obstruction, one or more emergency visits per year, three or more courses of oral corticosteroids per year, rapid clinical deterioration if the corticosteroid dose is reduced by $\leq$ 25% or history of near fatal asthma) is diagnosed with severe asthma.

As the phenotype of severe asthma is less common (up to 10%) than other forms of asthma and there are no validated animal models of severe asthma, multicenter networks have been initiated to characterize severe asthma phenotypes.

The "European Network for Understanding Mechanisms of Severe Asthma" (ENFUMOSA)[2] is the first, large, multicenter European program designed to understand the mechanisms involved in chronic severe asthma. This, along with US based networks such as the Severe Asthma Research Program (SARP) (chartered by the US National Heart, Lung, and Blood Institute)[3] and The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR)[4] have suggested that severe asthma might be a distinct disease or a different form of asthma rather than only an increase in asthma symptoms.

Severe asthma includes the phenotypes controlled by, and those resistant to, currently available high-intensity therapy. More importantly, proper treatment of severe asthma can shift the disease to be controllable (Fig. 69.1).[5]

Although, difficult asthma may account for only 5 to 10% of adult asthma,[6,7] chronic severe asthma contributes to 40 to 50% of health care costs[8] owing to unscheduled doctors' visits, frequent hospital admissions and drug consumption.

DEVELOPMENT OF SEVERE ASTHMA

Development of severe asthma is rather complicated. In addition to macrophages, mast cell, eosinophil and Th2 lymphocyte-associated inflammation, neutrophilic

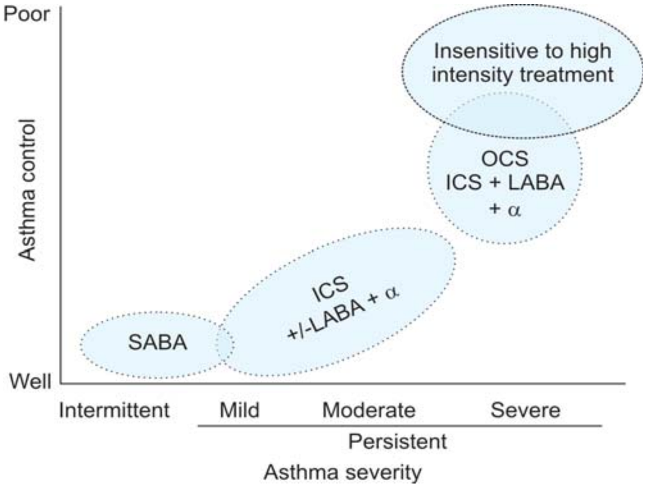


Fig. 69.1: Asthma severity and asthma control. The x-axis shows asthma severity and y-axis shows the level of asthma control. Severe asthma includes high-intensity treatment dependent patients and high-intensity treatment resistant patients

α: others; ICS: Inhaled corticosteroids; LABA: Long acting β2 agonists; OCS: Oral corticosteroids; SABA: Short-acting β2 agonists inflammation and airway remodeling are seen in severe refractory asthma. Risk factors such as genetics, and environmental conditions, such as infection, pollution, smoking, diet and global warming, might contribute to the development of severe refractory asthma.[5]

PHENOTYPES IN SEVERE ASTHMA

Chronic severe asthma is a heterogeneous condition that has different clinical, etiological, physiological and pathophysiological features making phenotyping an important aspect of this disease. Phenotyping of severe asthma is important because it will improve our understanding of the underlying mechanisms, natural history, prognosis and current and future therapeutic interventions for this subset of patients. *In vitro* studies showed that theophylline improved corticosteroid sensitivity only in the HDAC-defect group[9] and formoterol/salmeterol improved corticosteroid sensitivity only in the severe asthma with defective Glucocorticoid Receptor (GR) nuclear translocation.[5,10] Therefore, in future, identification of molecular or pathological abnormality will be most important for identifying an effective treatment. This approach will help to individualize appropriate therapy and avoid the overuse of corticosteroids in patients who have corticosteroid resistant disease and will help to develop novel phenotype-specific therapies.

Clinical Phenotypes

A cluster analysis in difficult asthma patients identified four clusters.[11] The first cluster described a subgroup of early onset of atopic asthma, with the evidence of airway dysfunction, symptoms and eosinophilic airway inflammation. This cohort was associated with significantly greater number of previous hospital visits and asthma exacerbations requiring oral corticosteroids and had a higher rate of failed clinic appointments compared with the other refractory clusters. The second cluster included obese patients with a female preponderance, evidence of asthma symptoms, and an absence of eosinophilic airway inflammation. The third cluster was a subgroup with refractory eosinophilic disease, with recurrent exacerbations, but relatively few symptoms. The other severe-specific cluster was a subgroup with early onset of atopic disease with virtually no eosinophilic inflammation but with symptoms. Molecular typing using gene arrays has the potential to detect asthma phenotypes.[12]

In clinical practice, severe asthma phenotypes are characterized by a variable combination of:

- Frequent severe asthma exacerbations
- Irreversible airway obstruction
- Systemic steroid dependent asthma.

Frequent Severe Asthma Exacerbations

The cause of frequent exacerbations in severe asthma could be related to the underlying susceptibility to respond abnormally to viral respiratory infections, allergens, occupational agents, environmental pollutants and discontinuation of corticosteroid therapy. Increased airway responsiveness,[13] air trapping and early airway closure[14] and blunted perception of dyspnea[15] are some of the factors responsible for the abnormal response. Risk factors that favor the exacerbation prone phenotype include psychological disorders and nasal polyposis,[16] low baseline FEV_1, early age at onset, allergic status, aspirin sensitivity[17] and airway eosinophilic inflammation.[18]

Irreversible Airway Obstruction

Some severe asthma patients display irreversible airflow limitation associated with significant health problems and a rapid decline in lung function and are therefore likely to have a poorer prognosis.[19] It is difficult to distinguish the airway obstruction in these patients from the smoking related chronic airflow limitation seen in patients with Chronic Obstructive Pulmonary Disease (COPD). However, several of these patients do retain some degree of bronchodilator reversibility to β2-agonists.[19] The reasons why these patients suffer from an accelerated decline in lung function are unclear. This feature has been associated with late onset of the disease, severe airway hyperresponsiveness to methacholine,[20] intense granulocytic inflammation of the airways particularly refractory eosinophilic and neutrophilic inflammation,[21,22] and chronic or recurrent infection with pathogens, such as *Chlamydia pneumoniae* that can lead to ongoing inflammation and subsequent structural changes in the airway wall.[23]

Systemic Steroid-Dependent Asthma

Many patients with severe asthma show a reduced response to inhaled and oral corticosteroids and require high doses of prednisone (>30 mg) to control their asthma symptoms but deteriorate as soon as the dose of corticosteroid is tapered. The relatively corticosteroid-insensitive asthmatic patient, also labeled the Corticosteroid-Dependent (CSD) patient, is part of a spectrum of patients that ends with the extreme Corticosteroid-Resistant (CSR) asthma.

There are different molecular mechanisms to explain corticosteroid resistance in asthma.[24] Corticosteroids act through a cytosolic GR that is activated by ligand binding and translocates to the nucleus. Once in the nucleus it can bind to DNA and in combination with coactivator proteins, switch on the expression of anti-inflammatory genes such as MKP-1. Alternatively, activated GR can recruit corepressor proteins that can suppress the activity of proinflammatory transcription factors such as NF-κB and AP-1. These activation steps may be attenuated in severe asthma because of oxidative stress or cigarette smoking, viral infection, allergen challenge or chronic inflammation. High levels of IL-2 and IL-4 can repress GR ligand binding, Mitogen-Activated Protein Kinases (MAPKs) activation can reduce GR nuclear translocation and Phosphoinositide 3-Kinase (PI3K) activation can reduce GR corepressor activity.

Genetics could also have role in corticosteroid resistance in asthma. Reduction in Histone Deacetylase (HDAC) activity, particularly HDAC2, has been observed in severe asthma, leading to some degree of steroid nonresponsiveness.[25] Mutation of the Corticotropin-Releasing Hormone Receptor-1 (CRHR-1) is also associated with corticosteroid resistance.[26] Unlike familial corticosteroid resistance where there are mutations in GR, CSR patients have normal cortisol levels and are not Addisonian.[27]

Obesity and Asthma

There is an increasing body of evidence suggesting that obese asthma is a new phenotype of asthma[28] because it may be characterized by greater severity,[29] increased utilization of health care resources, decreased asthma control[30] and impaired response to glucocorticosteroids.[31,32]

Cross-sectional and prospective studies show variable association between asthma and obesity, ranging from no effect up to an odds of three or more.[28,33] Most of the studies have examined Body Mass Index (BMI), but it is still not clear whether other measures, such as body fat distribution would add more value than BMI.[28] There is conflicting data on whether there is an association between obesity and airflow obstruction or AHR in asthma.[34,35] It is plausible that obesity associated systemic inflammation can enhance airway inflammation in asthma. Animal studies show that high serum leptin (adipokine) enhances airway inflammation,[36,37] whereas high serum adiponectin (anti-inflammatory adipokine) concentration attenuates allergen-induced airway inflammation;[38] however more recent data suggest that there is no involvement of systemic adipokines between obesity and asthma.[39,40,41] Contrary to studies that have reported obese asthmatics to have eosinophilic inflammation less commonly,[42] there was no association between BMI and airway inflammation in a cross-sectional study.[43] The mechanism for the obesity-asthma association is unknown. The proposed theory that oxidative stress due to obesity may cause airway inflammation and lead to asthma is not supported by a study that showed a lack of association between plasma F2-isoprostane levels and asthma and obesity.[44] There is growing evidence to suggest a genetic basis for obesity and asthma.[45,46]

Although, epidemiologic and animal evidence demonstrate a strong link between obesity and asthma, there are no clinical studies in obese asthma clearly demonstrating the effect of obesity on airflow obstruction, AHR and airway inflammation. Therefore, it is still debatable whether obese asthma is a unique phenotype of asthma. Further prospective studies in which both obesity and asthma are well characterized are needed to better understand the underlying mechanisms. Randomized controlled trials are needed to determine the best therapeutic options for obese asthma.

The Key Aspects of Severe Asthma Phenotypes

Differences in Severe Asthma between Children and Adults

It is more difficult to study severe asthma in children than in adults, there is a greater variability in the outcomes. Atopic features, such as eczema and allergic rhinitis may be common features of severe asthma in children.[47] Severe asthma in children is more likely in males, whereas severe asthma in adulthood is more common in women.[48]

Duration of Asthma

Adult asthmatic patients whose asthma onset was in adulthood had a similar decline in lung function as those with childhood onset, despite the shorter overall duration of disease. Late onset asthma is associated with less atopy by skin test, lower IgE levels and fewer symptoms with allergen exposures.[47,48] These data suggest that the development of severe asthma may not require an atopic predisposition. Adult-onset asthma is a significant risk factor for chronic airway obstruction (odds ratio 3.3).[20]

Persistent Abnormalities of Lung Function

There is a large subset of patients with severe asthma who manifest chronic airflow obstruction. However, the specific cut-off point for postbronchodilator FEV_1 was less than 75% predicted in one study[20] and less than 50% predicted in another study.[49] Patients with chronic airflow limitation were older and had longer duration of disease. They also had elevated residual lung volumes because of chronic air trapping but normal diffusion capacity (not suggestive of emphysema). Bronchial wall thickening is seen on high resolution computed tomography scans in chronic airway obstruction.[49]

Fraction of Exhaled Nitric Oxide

The data on Fraction of Exhaled Nitric Oxide (FeNO) are variable and inconsistent from study to study.[3,49,50,51,52] There is no consensus on the discriminant value or interpretation of FeNO in severe asthma as compared with other asthma phenotypes.

Eosinophils in Airway

Eosinophil is an important biomarker of some key features of severe asthma. The presence of chronic airway obstruction has been linked to both increased eosinophils in sputum (≥ 2%, OR= 8.9)[20] and in blood (OR= 6.3).[31] Severe asthma can be characterized as eosinophil positive and eosinophil negative according to the presence or absence of eosinophils in the endobronchial biopsies.[29] The presence of eosinophils in the endobronchial biopsies from severe asthma patients despite chronic high-dose oral corticosteroid treatment indicate corticosteroid resistance. Fewer eosinophils in biopsies are seen in patients with early onset severe asthma than in typical early onset asthma. Eosinophil negative biopsies have predominance of neutrophils.

Mechanistic Observations in Severe Asthma

Interleukin-13 (IL-13) is a Th2 cytokine associated with allergic inflammation. Over expression of IL-13 is observed in sputum and bronchial biopsy specimens in severe asthma patients as compared with mild asthma and control groups.[53]

Lipoxins (lipoxygenase interaction products) are potent anti-inflammatory lipid mediators, which may attenuate allergic inflammation. Lipoxin blocks the Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF), which is a potent eosinophil survival factor. Defective lipoxin and lipoxin receptor generation may lead to enhanced eosinophil survival, persistent inflammation and poor response to steroids, and is a unique characteristic of severe asthma.[54,55]

Chitinase, a broad-spectrum protease, has been identified in airway samples from asthmatic patients and is quantitatively correlated with the degree of airway remodeling and asthma severity. Mammalian chitinase activates Protease-Activated Receptor Type-2 (PAR-2) in human airway epithelial cells, which lead to a variety of inflammatory processes.[56] YKL-40, a chitinase like protein, was elevated in patients with asthma and correlated with severity of disease, pulmonary function and thickness of the subepithelial basement membrane.[57] Moreover, elevated YKL-40 expression is under genetic control and CH13L1, the chitinase 3-like 1, gene that encodes YKL-40 has been identified.[58]

Mechanisms of Corticosteroid Insensitivity

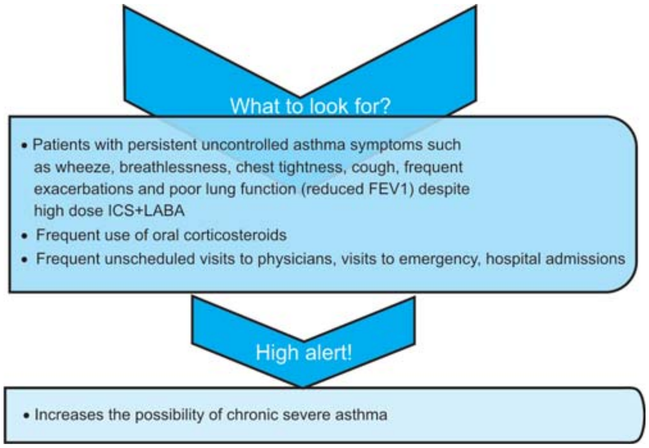
The reduction in corticosteroid responsiveness has been ascribed to the following factors:[5]

- Reduced number of glucocorticosteroid receptors (GR).
- Altered affinity of the ligand for GR.
- Reduced ability of the GR to bind to DNA because of phosphorylation.
- Increased expression of inflammatory transcription factors, such as AP-1, that competes for DNA binding.
- Deficiency of HDAC2 which is an important cofactor for GR function.
- Cigarette smoking is an oxidative stress that can affect GR nuclear translocation and expression of HDAC2.
- Neutrophilic inflammation.
- Respiratory viruses (adenovirus, rhinovirus) are implicated in corticosteroid resistance. The exact mechanism is not clear but oxidative stress, prevention of GR nuclear translocation and reduction in HDAC2 activity could be some of the reasons for corticosteroid insensitivity subsequent to viral infection.
- Airway remodeling.
- Overexpression of interferon regulatory factor (IRF) transcription factors activated by interferon.

Diagnosis

Diagnosis of chronic severe asthma is suspected from the presence of several important clues[59] (Fig. 69.2).

It is important to confirm whether the patient really has asthma or a disease that mimics asthma. The latter includes COPD, bronchiectasis, constrictive bronchiolitis, congestive heart failure, upper airway obstruction, dysfunctional breathing, vocal cord dysfunction, Allergic Bronchopulmonary Aspergillosis (ABPA), hypersensitivity pneumonitis, Churg-Strauss syndrome and eosinophilc pneumonia. Coexisting conditions such as tuberculosis, frequent respiratory infections including *C. pneumoniae* and *M. pneumoniae*, severe nasal and sinus



- Patients with persistent uncontrolled asthma symptoms such as wheeze, breathlessness, chest tightness, cough, frequent exacerbations and poor lung function (reduced FEV1) despite high dose ICS+LABA
- Frequent use of oral corticosteroids
- Frequent unscheduled visits to physicians, visits to emergency, hospital admissions

- Increases the possibility of chronic severe asthma

Fig. 69.2: Diagnostic algorithm for chronic severe asthma

disease, gastroesophageal reflux, psychological factors (anxiety, depression, panic and fear), obstructive sleep apnea and obesity can worsen asthma control. It is always good to look for unusual triggers such as occupational sensitizers, household irritants (e.g. mosquito repellants), food additives, smoking, drugs (aspirin, NSAID, ACE inhibitors), thyrotoxicosis and menstruation that can aggravate asthma.

Investigations

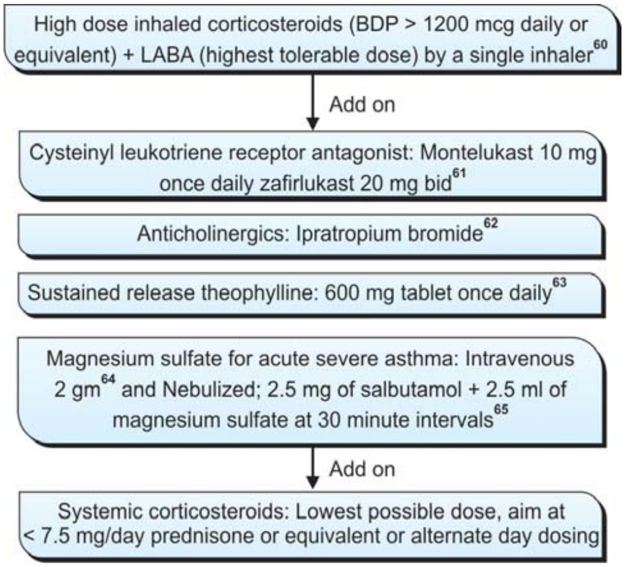
Various methods are given below by which investigation can be done:[7]

- Thorough medical history particularly for poor compliance with medication and under treatment
- Check inhaler technique
    - Blood Tests
    - Blood eosinophil count
    - Total serum IgE, allergen skin prick test
    - Bood theophylline levels or serum cortisol (to support adherence)
    - Other blood tests depending on clinical features (α1-antitrypsin, angiotensin-converting enzyme, immunoglobulins, antineutrophilic cytoplasmic antibody, aspergillus serology)
- *Pulmonary Function*
    - Spirometry: Bronchodilator reversibility, flow volume loop, lung volumes, transfer factor
    - Bronchial challenge test
- *Noninvasive Markers of Airway Inflammation*
    - Quantitative sputum cell counts
    - Exhaled nitric oxide
- *Radiography*
    - Chest X-ray
    - High resolution computed tomography of the lungs (to look for bronchiectasis, interstitial lung disease)
    - Computed tomography of nasal sinuses (to look for nasal disease)
- *Other Tests (As Clinically Indicated)*
    - Nasal endoscopy (to exclude polyps, rhinosinusitis)
    - Bronchoscopy (to look for tumors, foreign body)
    - Laryngoscopy during symptomatic episodes (to examine for vocal cord dysfunction)
    - Echocardiogram (to differentiate "wheeze" that may be due to cardiac causes)
    - Psychiatric assessment
    - Cardiopulmonary exercise testing (to evaluate whether exercise intolerance and exercise related symptoms have a pulmonary or a nonpulmonary origin)

Management

Treatment of chronic severe asthma should aim to achieve the best possible asthma control and quality of life with the least possible medication. The choice of therapy depends upon the severity of disease and includes:[41]

- Conventional pharmacotherapy (Fig. 69.3)
- Immunomodulating pharmacotherapy
- Biological therapy



High dose inhaled corticosteroids (BDP > 1200 mcg daily or equivalent) + LABA (highest tolerable dose) by a single inhaler[60]

Cysteinyl leukotriene receptor antagonist: Montelukast 10 mg once daily zafirlukast 20 mg bid[61]

Anticholinergics: Ipratropium bromide[62]

Sustained release theophylline: 600 mg tablet once daily[63]

Magnesium sulfate for acute severe asthma: Intravenous 2 gm[64] and Nebulized; 2.5 mg of salbutamol + 2.5 ml of magnesium sulfate at 30 minute intervals[65]

Systemic corticosteroids: Lowest possible dose, aim at < 7.5 mg/day prednisone or equivalent or alternate day dosing

Fig. 69.3: Conventional pharmacotherapy

Monitor Side Effects

LABA: Tachycardia, palpitations, tremors

ICS: Hoarseness, oral thrush, reflex cough

Systemic corticosteroids: Osteoporosis, diabetes, hypertension, cataract formation, gastrointestinal upsets (dysphagia, abdominal pain, gastrointestinal bleeding), Cushingoid features.

Laboratory Monitoring

Bone mineral density, fasting blood sugar, blood pressure.

Concomitant Therapy

Calcium, vitamin D and/or bisphosphonates, proton pump inhibitors.

Immunomodulating Pharmacotherapy

In order to minimize the chronic need for systemic corticosteroids and reduce their adverse effects, an exploratory trial for 24 to 36 weeks with alternative anti-inflammatory and immunomodulatory therapies, such as methotrexate, oral gold, cyclosporine, Intravenous γ-globulin (IVIG), macrolide antibacterials and azathioprine, should be considered. Regular monitoring of patients' symptoms and laboratory parameters are mandatory to avoid side effects.

Methotrexate: Methotrexate is a folate antagonist that retains its anti-inflammatory activity at a low dose of 5 to 25 mg/week. However, the mechanism of action remains unclear. Eleven clinical trials and three meta-analyses have evaluated oral or intramuscular methotrexate in the dose of 7.5 to 30 mg/week for 12 to 28 months.[41] In a recent study,[66] a substantial reduction (>50%) in the steroid dose was observed in the methotrexate group. Common side effects include liver function abnormalities, abdominal pain, diarrhea, nausea, oral ulcers and stomatitis, but they are usually transient and reversible and seldom life threatening.

Gold: Gold is an immunomodulatory agent whose mechanism of anti-inflammatory action is unknown. Three prospective studies have examined the efficacy of gold[67,68,69] administered for a duration of six to eight months. In the largest trial, the Auranofin Multicenter Drug Trial, 3 mg twice daily for eight months significantly reduced the daily oral corticosteroid dose by ≥ 50% in corticosteroid dependent asthma.[69] Gold is well tolerated and side effects, such as abdominal pain, diarrhea and pruritic rash are common, but self limited.

Cyclosporine: Cyclosporine is a fungal metabolite that has immunomodulatory and anti-inflammatory effects. To date, three small prospective randomized trials have examined the effect of cyclosporine (loading dose 5 mg/kg/day) in patients with steroid-dependent asthma for short periods of 3 to 11 months.[70,71,72] Serious side effects of dose-dependent nephrotoxicity were not observed at low doses in these trials, but several patients experienced hypertrichosis, worsening of preexisting hypertension, paresthesias, tremor, headache and flu like symptoms.

Intravenous Immunoglobulin (IVIG): There is very limited experience with IVIG therapy in asthma.[73] Two prospective trials have examined the effects of IVIG therapy (2 g/kg loading dose followed by 400 mg/kg infusion every three weeks for three months) in severe steroid dependent asthma, of which one trial was stopped prematurely. There was no significant reduction in the corticosteroid dose, but the post-hoc analysis did show a median reduction from 16.4 mg to 3 mg/day in patients needing high dose corticosteroid therapy.[74] Minor side effects include headache and nausea and are self limiting. Avoid IVIG therapy in patients with IgA deficiency. In addition to uncertainties on clinical efficacy, its high cost and limited availability in the global market are likely to prevent its widespread use.

Macrolide Antibacterials: Macrolide antibiotics particularly troleandomycin (14 mg/kg/day, maximum dose of 1 gm/day) for 12 to 24 months[75] and clarithromycin 500 mg twice daily for 12 months[76] have decreased corticosteroid requirements in steroid-dependent asthma that has correlated with a subjective improvement of symptoms. The improvement does not appear to be related to the direct antibacterial effect, but has been attributed to the inhibition of corticosteroid metabolism by the hepatic cytochrome P450 complex. Steroid related side effects are common with troleandomycin. Bacterial resistance has not been reported. Empirical treatment with macrolides especially clarithromycin may be considered in patients with severe corticosteroid dependent asthma as it has a better safety profile than troleandomycin.

Thiopurines: Azathioprine has a corticosteroid sparing effect in steroid refractory ulcerative colitis[77] and steroid-responsive vasculitis[78] in a dose of 2 to 2.5 mg/kg/day. However, there is very limited evidence to support the use of azathioprine as a steroid sparing agent in steroid dependent asthma and large, well designed, long-term studies are required before any recommendation in clinical practice can be made.[79]

Biologic Therapy

Asthma is a syndrome of airway inflammatory diseases. The immunological pathogenesis of this airway inflammation is becoming increasingly important and provides an opportunity for targeted biological intervention for patients who fail to respond to alternative anti-inflammatory and immunomodulatory therapies. Targeted therapies include strategies to activate dendritic cells through the TLR-9 receptors, to interrupt the action of TH2 cytokines with cytokine blockers and monoclonal antibodies, to promote development of TH1 responses, to block IgE mediated pathways and to block TNF-α.

Dendritic Cell-Based Therapies

The dendritic cell presents the antigen to pattern recognition receptors such as Toll-Like Receptors (TLRs).[80] A large number of animal studies have demonstrated that activation of TLR-9 can result in the skewing of immune response towards TH1.[81] Preliminary studies with TLR-9 agonists in allergic rhinitis have not been very convincing, but additional studies are underway in allergic asthma.[82,83]

TNF-α Inhibitors

TNF-α is important in innate immune response. It is a cytokine, principally produced by macrophages in response to the activation of toll-like receptors, but is also produced by other proinflammatory cells including monocytes, dendritic cells, B lymphocytes, T lymphocytes, neutrophils, mast cells and eosinophils, as well as structural cells including fibroblasts, epithelial cells and smooth muscle cells. TNF-α levels are higher in those with severe asthma. TNF-α promotes eosinophilic and neutrophilic inflammation, contributes to airway hyperresponsivenss and airway remodeling in asthma. Corticosteroids fail to reduce TNF-α in asthmatic airways and therefore TNF-α contributes to glucocorticosteroid resistance. Based on these observations, blocking TNF-α could represent an advance in the management of asthma patients who are resistant to corticosteroids.[84,85] Biologic agents targeting TNF-α include infliximab (a chimeric mouse/humanized monoclonal antibody), etanercept (a soluble fusion protein combining TNF-α receptors with an FC fragment of human IgG1) and adalimumab (a fully human monoclonal antibody).[86]

Preliminary clinical studies showed significant improvement in patients with severe asthma refractory to glucocorticosteroid treatment, but some studies reported negative findings. In two small studies in chronic severe asthma, etanercept (25 mg twice/week subcutaneous infusion for 2 to 3 months) improved bronchial hyperresponsiveness, FEV_1 and quality of life, but surprisingly did not affect airway inflammation.[87,88] Infliximab was not effective in mild to moderate asthma.[89]

TNF-α inhibitors are well tolerated with common side effects such as injection site rash, headache, nausea and abdominal pain. Serious and rare side-effects are infections, particularly tuberculosis, solid organ malignancies, multiple sclerosis and worsening of cardiac failure.[90] Small molecule inhibitors of TNF-α Converting Enzyme (TACE) have also been developed.[91] Large multicenter clinical trials with etanercept and other anti-TNF-α monoclonal antibodies are in progress.

Anti-IgE Monoclonal Antibodies

Omalizumab, an IgE-specific humanized IgG1 monoclonal antibody binds to the Fc-region of the IgE molecule, prevents IgE from interacting with high or low-affinity IgE receptors (FcεR1 and FcεR11) and results in rapid decreases in levels of circulating free IgE.[92] Omalizumab has been successfully used to treat severe allergic asthma patients who continue to remain symptomatic despite optimum combination treatment.[93] Omalizumab is administered as a subcutaneous injection in a dose of 150 to 300 mg once every two to four weeks. In a pooled analysis of several large clinical trials, omalizumab significantly reduced asthma exacerbations (by 38%), emergency department visits (by 61%) and hospital admissions (by 52%) and unscheduled doctor visits (by 47%) when compared to control subjects.[94,95]

Omalizumab is the only biological therapy that is approved for asthma at this time. Common side-effects include injection site reaction, headache and pharyngitis. Peak therapeutic response is achieved 16 weeks after starting treatment[96] and therefore a clinical assessment needs to be made at 16 weeks after the initiation of therapy to determine the need to continue therapy. Omalizumab is approved for clinical use but is a limited option because majority of patients with chronic severe asthma are nonatopic. Additionally, the high cost of the drug is another limiting factor.

Lumiliximab (anti-CD23) is a human monoclonal antibody directed against the low affinity IgE receptor CD23 (FcεR11) which is expressed on several cell including monocytes, alveolar macrophages, B cells and dendritic cells of allergic individuals. CD23 is believed to have a role in the IgE-mediated inflammatory processes and its activation can result in the increased production of proinflammatory cytokines. A Phase I single dose trial in patients with allergic asthma resulted in decreased IgE levels by 40%, and *in vitro* studies showed reduced production of proinflammatory cytokines (IL-1β and TNF-α).[97] Additional studies are needed to determine the true clinical efficacy of this agent in asthma.

Th2 Cytokine-Blocking Therapies

The cytokines (IL-4, IL-5, IL-9 and IL-13) produced by TH2 type lymphocytes, basophils and mast cells promote allergic inflammation in asthma. Human studies have targeted IL-4, IL-5, IL-9, IL-13 individually and joint targeting of IL-4 and IL-13.[98]

Targeting IL-4: In the presence of dendritic cell-presented allergen, IL-4 strongly influences the differentiation of TH0 cells into TH2 cells. Along with IL-13, IL-4 promotes the switch from IgM to IgE by the B lymphocyte. IL-4 also upregulates IgE expression on mast cells and basophils and contributes to the recruitment of inflammatory cells and goblet cell hyperplasia in asthma.[99]

The solubilized IL-4 receptor fragment altrakincept inhibits binding of IL-4 to its receptor. Preliminary studies[100,101] with nebulized altrakincept maintained asthma control despite withdrawal of corticosteroids but a larger, Phase III trial[102] failed to confirm this benefit.

Pascolizumab, an anti-IL-4 humanized monoclonal antibody, did not yield impressive results in asthma patients and further development was discontinued.[84]

Targeting IL-5: IL-5 stimulates the development and release of eosinophils from the bone marrow, their enhanced adhesion to endothelial cells lining the postcapillary venules and their persistence, activation and secretion into the airways.[103] Most of the airway inflammation in asthma is because of the inappropriate accumulation of eosinophils which release proinflammatory mediators such as cytokines and chemokines. Given its central role in regulating the development and release of eosinophils, blocking IL-5 with Monoclonal Antibodies (mAb) was a potentially attractive target to blunt the eosinophilic bronchitis in asthma. In contrast to several clinical trials in which anti IL-5 mAb, “mepolizumab” was not successful in asthma of varying severity,[104-106] two small proof of concept studies[107,108] reported a decrease in asthma exacerbations in a subset of asthmatic patients who have a persistent blood and sputum eosinophilia despite treatment with systemic corticosteroids. This finding indicates that this particular phenotype of asthmatics might stand to benefit from use of an anti-IL-5 monoclonal antibody.

Targeting IL-9: IL-9 has a direct effect on the development and activation of human mast cells, contributes to goblet cell hyperplasia in the airways and to airway remodeling.[109] Phase I studies with anti-IL-9 monoclonal antibody (MEDI-528) have been completed in healthy subjects without major adverse events. Phase II studies are currently in progress in patients with symptomatic moderate to severe asthma.[98]

Targeting IL-13: As IL-13 and IL-4 share the same receptor, IL-13 has many functions similar to those of IL-4 but in addition IL-13 is important for epithelial cell maturation, goblet cell hyperplasia and mucous production, generation of extracellular matrix proteins and enhanced contractility of airway smooth muscle cells[110-112] IL-13 is also involved in the recruitment of eosinophils, monocytes, macrophages and T-cells. Human anti-IL-13 specific monoclonal antibodies are in Phase I and II trials. A Phase I clinical trial with CAT-354 showed that increasing single doses of intravenously administered anti-IL-13 monoclonal antibody in patients with mild asthma were well tolerated at all doses with no safety concerns, but we have yet to await data related to asthma outcomes.[113]

Joint Targeting of IL-4 and IL-13: IL-4 and IL-13 signal through the same surface receptor, IL-4R α which then activates the transcription factor STAT-6 which is required for many of their biologic functions.[114] Recombinant human IL-4 variant, “pitrakinra” given either as a subcutaneous dose or via nebulization twice daily for four weeks blocked the shared receptor IL-4R α to block the effects of both IL-4 and IL-13 and improved asthma outcomes.[115] Further large scale studies are required to establish the effectiveness and safety of this treatment.

Targeting Thymic Stromal Lymphopoietin (TSLP), IL-33 and other allergen-independent cytokine pathways which promote TH2 type allergic inflammatory disease to block chronic allergic inflammation are currently under investigation in animal models of asthma.[116]

T-Cell Blocking Therapies

Daclizumab (anti-IL-2 receptor α subunit/anti -Tac, anti-CD25) monoclonal antibody decreases T-cell proliferation and cytokine (TH1 and TH2) production. A proof of concept study with daclizumab, administered IV every two weeks in patients with moderate to severe persistent asthma improved pulmonary function and decreased blood eosinophils.[117]

Keliximab is an anti-CD4 monoclonal antibody that showed a dose-dependent decrease in peripheral CD4 counts but no significant changes in asthma symptoms in patients with steroid-dependent asthma.[118,119]

Promoting TH1 Cytokines

IL-12 and IFNγ downregulate TH2 response and drive the differentiation of TH0 cells towards a TH1 phenotype and therefore, may be a therapeutic option for treatment of allergic asthma. Injection of IL-12 in patients with mild asthma decreased blood and sputum eosinophils after allergen challenge but had no effect on the late phase asthmatic responses or in airway hyperresponsiveness. This therapy was associated with flu-like symptoms, abnormal liver function tests and cardiac arrhythmia.[120]

TH17 Cells as a Target

TH17 cells are a distinct type of T-helper cells which produce IL-17 cytokines that increase neutrophil infiltration.[121] IL-17 is also associated with steroid resistance in asthma.[122] Targeting this pathway may prove to be effective treatment of neutrophilic asthma.

IL-25 is another member of the IL-17 family that provokes TH2 response. Animal studies have shown that a neutralizing antibody against IL-25 significantly reduces airway hyperresponsiveness, reduces IL-5 and IL-13 production, reduces tissue eosinophil infiltration, goblet cell hyperplasia and serum IgE.[123] While human studies have not yet been reported, this might be a potential therapeutic target.

Other Potential Therapies

Since oxidative and nitrative stress may drive the corticosteroid insensitivity by attenuating the HDAC activity, antioxidants such as N-acetyl cysteine, fudostein or inhibitors of inducible NOS_2 should reverse corticosteroid resistance. As PI3K contributes to the defect in HDAC and JNK and p38, MAPK cause defective GR nuclear translocation, add-on treatment of these inhibitors might be useful to restore corticosteroid sensitivity. Two new products CRx-170, a combination of budesonide and low dose nortriptyline[124] and a new combination of prednisone and di-dypridamole[125] has been tested in asthma patients and showed promising results.

Novel Steroids: “Dissociated corticosteroids,” called nonsteroidal Selective Glucocorticoid Receptor Agonists (SEGRA) are now in clinical development.[126] These novel agents have the anti-inflammatory capacity of corticosteroids but with reduced side effects. However, these have not been tested in severe refractory asthma.

Another new steroid, in phase II trials, is TPI 1020.[127] This molecule is based on the corticosteroid budesonide but superior to budesonide in protecting against narrowing of the airways and it also inhibits migration of neutrophils into the lung (32.6% decrease vs 3.7% increase for budesonide) and their subsequent activation.

Eotaxin: Eotaxin is a chemokine that promotes recruitment of eosinophils by binding to the receptor CCR3 that is expressed on eosinophils. CCR3 is also expressed on basophils, mast cells, activated TH2 cells and airway epithelial cells.[128] Small molecule CCR3 antagonists such as N-ureidoalkyl-benzpiperidines,[129] YM-344031[130] and YM-355179[131] inhibited eoisnophil infiltration into airways in animal models. Furthermore, CCR3 antagonists also reduced airway hyperresponsiveness, goblet cell hyperplasia and airway remodeling in mice.[132] Therefore, CCR3 antagonists may be a promising therapy in asthma.

Cell Adhesion Molecules: Leukocyte extravasation, migration into interstitium, activation and tissue retention are regulated by cell adhesion molecules such as selectins (L-selectin, P-selectin, E-selectin, ICAM-1, and VCAM-1) and integrins (α1 and α2). The selectin antagonist, TBC1269 was shown to be effective in the animal models of allergic asthma.[114] The proof of concept study in patients with asthma suggests that inhaled TBC1269 may be more effective than the intravenous formulation in inhibiting the late phase asthma reactions.[133,134] Most of the small molecule integrin α4β1 antagonists were ineffective in preventing asthma symptoms. However a recent phase II trial with valategrast significantly improved lung function and reduced exacerbations in asthma patients who had their steroid treatment withdrawn, but further development of this molecule was discontinued because of safety issues.[135]

Statins: Statins exhibit anti-inflammatory properties by inhibiting the prenylation (not adhered to cell membrane) of signaling molecules such as Rho GTPases.[136] *In vitro* and mouse models suggest that statins inhibit the proinflammatory cell accumulation activation.[137,138] One study showed that simvastatin was not effective in mild to moderate asthma patients who respond to inhaled corticosteroids.[139] Since, the pleiotropic effects of individual statins differ, treatment with different statins may produce different results.[119,120] Their effectiveness in asthma needs to be confirmed with well designed randomized clinical trials.

Although *in vitro* and animal models have identified promising molecules targeted at the inflammatory component of asthma, the overall development of novel anti-inflammatory therapy for asthma has been disappointing in the clinical setting because of the lack of efficacy and safety issues. The way forward may be to reexamine the concept of combination therapy that would have a synergistic effect rather than monotherapy (e.g. CCR3 antagonist + anti-IL5mAb would inhibit eosinophil infiltration into the asthmatic lung).[120]

Bronchial Thermoplasty

The first non-pharmacological treatment for difficult-to-control asthma has recently been developed. Many of the symptoms in severe asthma patients are due to the excessive accumulation of smooth muscle bundles in the submucosa of these patients. Current treatments do not reduce the excess smooth muscle mass that is present in the remodeled airway in chronic asthma. Bronchial thermoplasty reduces the thickness of the hypertrophied bronchial smooth muscle in the airways and improves a patient's ability to breathe.[140] This novel approach is intended for patients $\geq$ 18 years, whose severe and persistent asthma is not well-controlled with inhaled corticosteroids and long-acting beta agonist medications.[141] The equipment used for the procedure called the 'Alair' system (Asthmatx, Mountain View, CA, USA), has been approved in April 2010 by the US Food and Drug Administration.[141] The Alair Bronchial Thermoplasty System[140] is composed of a catheter with an electrode tip that delivers a form of electromagnetic energy, called radiofrequency thermal energy, directly to the airways to ablate the hypertrophied bronchial smooth muscle. A controller unit generates and controls the energy. To obtain maximal benefit from the procedure, patients need multiple sessions targeting different areas in the lungs.

The initial trials of bronchial thermoplasty technique in dogs[142] and in mild asthma patients demonstrated clinical and functional improvement with only few adverse effects. Subsequently, randomized trials to assess the efficacy and safety of bronchial thermoplasty in asthma patients were initiated. The Asthma Intervention Research (AIR) Trial[143] and The Research in Severe Asthma (RISA) Trial[144] showed that at the end of 1 year of follow up, patients who had undergone bronchial thermoplasty showed a clinical and statistically significant improvement in FEV1, use of rescue medication, and asthma control scores in quality of life questionnaires. Although the patients treated with thermoplasty more often experienced adverse effects, such as dyspnea, cough, and wheezing, most of these were mild in nature and usually resolved in less than one week. As both, the AIR Trial and the RISA trial were not blinded, a third trial designated as Asthma Intervention Research 2 (AIR2) Trial,[145] included a placebo group in which asthma patients were sham-treated. The AIR2 Trial confirmed that in comparison with the sham-treated patients, symptomatic patients with severe asthma treated with bronchial thermoplasty had a significantly better quality of life with fewer severe exacerbations. A 3 years follow up of bronchial thermoplasty patients from multiple studies do not demonstrate clinical complications or deterioration of pulmonary function, indicating long-term safety with this treatment.[146] An analysis of chest CT findings performed five years after treatment in 15 patients also revealed no significant anatomical changes, confirming the absence of late anatomical deformities. Bronchial thermoplasty is still an experimental procedure, and we have to await regulatory approval for its clinical use.

MANAGING SEVERE ASTHMA USING AIRWAY INFLAMMATORY

The conventional strategies described above rely on symptoms and lung function to guide treatment particularly anti-inflammatory treatment. It is presumed that increased symptoms and worsening airflow obstruction are associated with a steroid-responsive bronchitis. However, clinical recognition by physicians of the presence and type of bronchitis is very poor.[147] Quantitative cell counts in sputum provide the most reliable and comprehensive and relatively non-invasive method to assess bronchitis. The clinical applications of this technique are well described elsewhere.[148,149] Briefly, sputum examination in a patient with severe asthma can identify three types of phenotypes that is helpful to plan investigations and treatment: Eosinophilic bronchitis, neutrophilic bronchitis and patients with normal sputum cell counts but with moderate to severe airway hyper-responsiveness (PC20 methacholine less than 2 mg/ml).

Patients with eosinophilic bronchitis are steroid sensitive. A reasonable treatment strategy would be to increase the dose of inhaled and ingested steroid to the optimum dose to control sputum eosinophilia (to less than 1%) by monitoring sputum counts at six weekly intervals. After the optimum dose of steroids are identified, novel prednisone-sparing strategies can be initiated. This includes investigations for causes of persistent eosinophilia (hypereosinophilic syndrome, vasculitis, chronic eosinophilic pneumonias, parasitic infestations, chronic rhinosinusitis, etc.) and evalution of drugs such as hydroxyurea, imatinib (in patients with PDGFR-FIPLI mutation) or mepolizumab. In highly atopic patients, omalizumab is another option although currently no adequately powered randomized controlled studies has conclusively shown a convincing steroid-sparing effect. Radical treatment of chronic rhinosinusitis is recommended as chronic hyperplastic rhinosinusitis is one of the most important predictors of persistent airway eosinophilia.[150] Fraction of exhaled nitric oxide is not helpful in monitoring response to corticosteroids in these severe patients.[151]

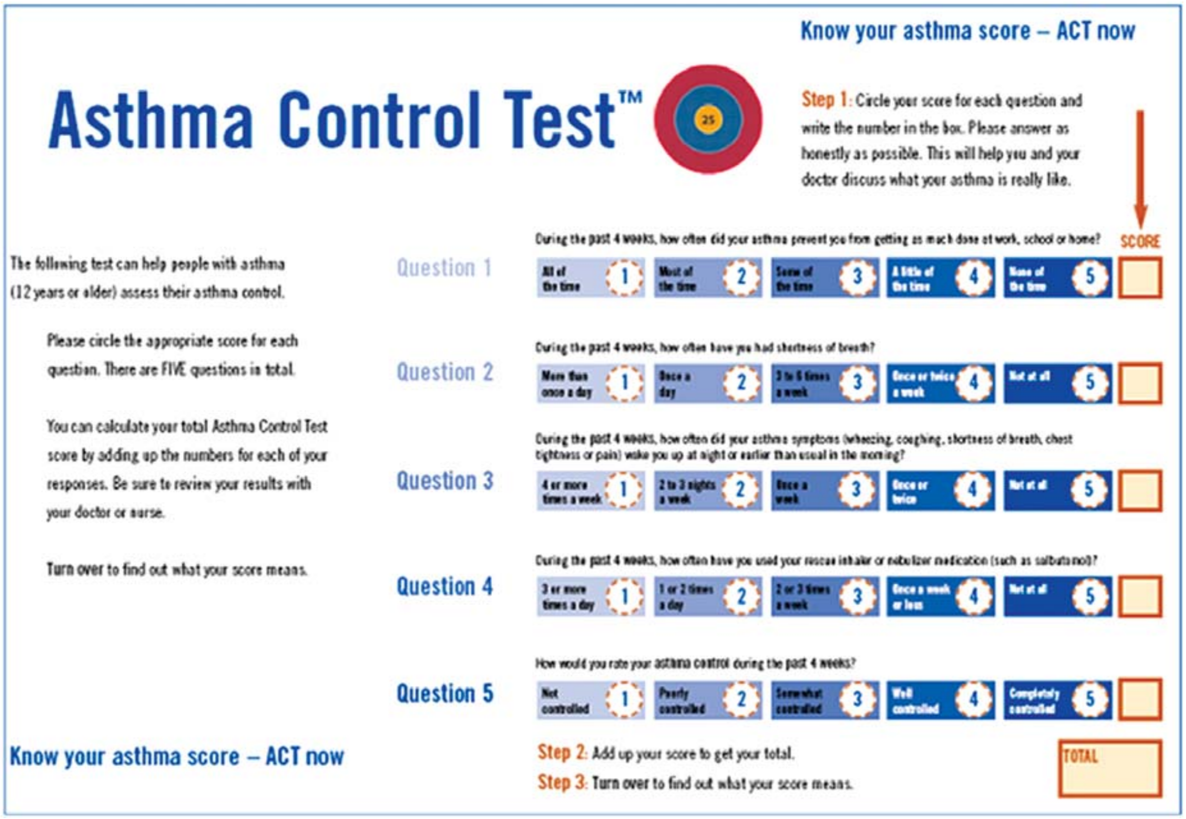
In patients with persistent neutrophilic bronchitis (total cell count greater than 25 million cells/g of sputum and neutrophils > 65%), high doses of corticosteroids are unncecessary. We would recommend reducing the dose of corticosteroids (by 5 mg decrease every 4-6 weeks) by carefully monitoring sputum cell counts to try and get patients off their corticosteroids or to the minimum dose to avoid adrenal suppression and concurrently investigate the cause of persistent neutrophilia.[152] These include detailed microbiology (including molecular diagnostic techniques for bacteria, viruses, fungi and *Chlamydia*), cystic fibrosis phenotype and genotype, innate immune deficiencies, neutrophil phagocytosis function defects, inflammatory bowel diseases, ciliary dysfunction, etc. Identification of specific causes help to institute specific therapies such as appropriate antimicrobial therapy, nebulized hypertonic saline, immunoglobulin replacement treatments, etc. Novel therapies directed against neutrophils and neutrophil activation products are currently being investigated for situations not associated with infective etiologies.

There is currently no specific therapies for patients with severe hyper-responsiveness not associated with a cellular bronchitis. Treatments directed against smooth muscle such as bronchial thermoplasty[145] is likely to be most beneficial for such patients. Other therapies that are likely to be beneficial in these patients are anti-TNF therapy, anti-leukotriene therapy and novel treatments that are currently being evaluated directed against IL-9 or IL-13.

MONITORING A PATIENT WITH DIFFICULT ASTHMA

It is unclear how best to monitor patients with difficult asthma. However, the following points should be considered:

- Regular follow-up
- Assess adherence to treatment, inhaler technique



Know your asthma score – ACT now

Asthma Control Test™

Step 1: Circle your score for each question and write the number in the box. Please answer as honestly as possible. This will help you and your doctor discuss what your asthma is really like.

The following test can help people with asthma (12 years or older) assess their asthma control.

Please circle the appropriate score for each question. There are FIVE questions in total.

You can calculate your total Asthma Control Test score by adding up the numbers for each of your responses. Be sure to review your results with your doctor or nurse.

Turn over to find out what your score means.

		1	2	3	4	5	SCORE
Question 1	During the past 4 weeks, how often did your asthma prevent you from getting as much done at work, school or home?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	☐
Question 2	During the past 4 weeks, how often have you had shortness of breath?	More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all	☐
Question 3	During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?	4 or more times a week	2 to 3 nights a week	Once a week	Once or twice	Not at all	☐
Question 4	During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as salbutamol)?	3 or more times a day	1 or 2 times a day	2 or 3 times a week	Once a week or less	Not at all	☐
Question 5	How would you rate your asthma control during the past 4 weeks?	Not controlled	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled	☐

Step 2: Add up your score to get your total.

Step 3: Turn over to find out what your score means.

TOTAL ☐

Know your asthma score – ACT now

Fig. 69.4: Asthma control test (Copyright 2002 by QualityMetric Incorporated. Asthma Control Test is a trademark of QualityMetric Incorporated)

- Encourage weight reduction, smoking cessation
- Assess asthma control using a validated test such as the Asthma Control Test (ACT). An ACT score more than 20 indicates well-controlled asthma and a score less than 19 indicates uncontrolled asthma[153] (Fig. 69.4)
- Monitor disease activity using tests of airway hyper responsiveness and noninvasive markers of airway inflammation.

Referral to a Specialist

Patients who do not respond to guideline-based treatment should be referred to a specialist especially if the diagnosis is in doubt or when excessive amounts of drugs, especially oral corticosteroids, are used.

CONCLUSION

Management of severe asthma is challenging. Patients can be difficult to control despite use of current standard of care therapy, including inhaled corticosteroids and long-acting beta agonists. Alternative diagnoses, noncompliance, poor inhaler technique and comorbidities, all can influence asthma control and response to currently available therapy. Severe asthma has a distinct pathophysiology including airway remodeling that contributes to the decreased effectiveness of standard therapy. Severe asthma has multiple phenotypes that likely require distinct therapeutic approaches to achieve control and improve long-term health outcomes. New therapeutic approaches to these distinct phenotypes will improve our understanding and treatment of this difficult to manage disease.

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Immunotherapy and Immunomodulators for Allergic Rhinitis and Asthma

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INTRODUCTION

Allergies occur as a result of aberrant immune reactivity against common harmless environmental proteins called allergens. A key component of the pathomechanisms of allergic diseases is the production of Th_2 cytokines, generation of allergen-specific Immunoglobulin E (IgE), cross-linking of the IgE molecules by allergen, activation of mast cells with the release of potent mediators which, in turn, elicit the acute allergic reactions and initiate the development of chronic inflammation. Most therapeutic approaches for allergic diseases focus primarily on the symptom control and suppression of inflammation. Nevertheless, none of the available drugs are capable of modifying the immune response and their effects vanish within few hours or days after discontinuation. Specific Allergen Immunotherapy (SIT) is the only disease-modifying treatment for allergic rhinitis and asthma, which benefits may persist years after treatment is discontinued.

Allergen immunotherapy has been used for almost a century as a desensitizing therapy for allergic diseases. It was introduced in 1911 based on the empiric concept that administering the substances, which produce clinical manifestations in the allergic subject, would result in a sort of vaccination with consequent clinical benefit. Despite the rationale was wrong, the results were favorable. With a better knowledge of the mechanisms of the specific immunotherapy (Fig. 70.1), the development of improved allergen extracts and the studies done using these, there has been a marked improvement in our understanding of immunotherapy. Furthermore, the standardization of allergenic extracts allowed the availability of vaccines of high quality and safety. In fact, in 1998, the World Health Organization (WHO) published a position paper on SIT,[1] and further recommendations for the use of immunotherapy were reported in the ARIA.[2]

The standard modality of administration of SIT is the subcutaneous route (SCIT), but in recent years also the sublingual route (SLIT) achieved credibility and is now considered a viable alternative to Subcutaneous Immunotherapy (SCIT). Specific immunotherapy, both subcutaneous and sublingual, is currently indicated for respiratory allergy (rhinitis/asthma); whereas for hymenoptera venom allergy, only SCIT is used.

SUBCUTANEOUS IMMUNOTHERAPY (SCIT)

SCIT is an allergen-specific therapy that induces long-term remission of allergic rhinitis and allergic asthma and

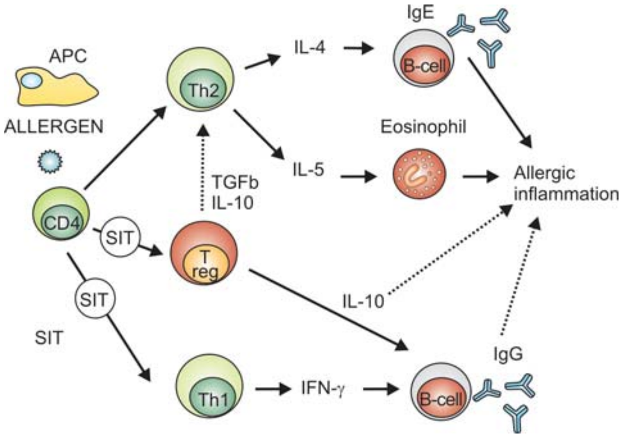

Fig. 70.1: Mechanisms of immunotherapy

in contrast to pharmacotherapy, i.e. symptomatic, SCIT prevents the onset of new sensitizations,[3,4] and reduces the progression of disease from allergic rhinitis to allergic asthma.[5] Such responses involve immunological memory and therefore direct and/or indirect effects on T and/or B lymphocytes.

Indications

- In ascertained IgE-mediated respiratory diseases (supported by a positive SPT/RAST) and when the causal role of the allergen(s) is well established.
- In patients with clinical symptoms due to a single or limited spectrum of allergies.
- In patients inadequately responding to drug treatment.
- In patients unwilling to use medication.
- In patients in whom pharmacotherapy induces undesirable side effects.

Contraindications

- Coexistent uncontrolled asthma/severe asthma
- Patients taking beta-blockers
- Patients with other medical/immunological diseases, including major cardiovascular disease, cancer or chronic infections
- Small children less than 5 years (relative contraindication)
- Pregnancy (maintenance injections may be continued during pregnancy, but it is recommended not to start induction phase in pregnancy)
- Patients unable to comply with the immunotherapy protocol or with psychiatric disorders

Efficacy

The clinical efficacy of SCIT is well established, both for rhinitis and asthma. A review of 43 Double-Blind Placebo-Controlled (DBPC) trials has confirmed an efficacy (improvement of symptoms greater than 30% as compared to placebo) in 75 to 80% of the studies.[6] This clinical efficacy is associated with a marked reduction in for the use of anti-allergic medications during the pollen season and with an improvement in patients' quality of life. In some studies it was shown that the efficacy is dose dependant.[7-24] SCIT is also effective in allergic asthma. A Cochrane meta-analysis of 62 randomized controlled trials performed between 1954 and 1998 demonstrated a significant improvement in symptoms, a reduction in the use of rescue medication and an improvement in both allergen-specific and nonspecific bronchial hyperresponsiveness.[25] The results were consistent across the trials, although the methodological quality of the studies was, on average, low. An updated grading of the strength of the experimental evidence for SCIT and Sublingual Immunotherapy (SLIT) is provided in Table 70.1.

TABLE 70.1: Grading of the strength of the experimental evidence for SCIT and SLIT

	SCIT	*SLIT*
Clinical efficacy: Rhinitis	Ib	Ia
Clinical efficacy: Asthma	Ia	Ia
Clinical efficacy: Children (rhinitis)	Ib	Ia
Prevention of new sensitizations	IIb	III
Long-term effect	Ib	IIa
Prevention of asthma	IIb	IIb

Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled trial without randomization
IIb	Evidence from at least one other type of quasi experimental trial
III	Evidence from nonexperimental descriptive studies (comparative, correlation, case-control)
IV	Evidence from panels of experts or clinical experience or authorities

Long-Term Benefit (Carry-over Effect)

Allergen immunotherapy has been shown in several studies to maintain a long-term benefit after discontinuation. For example, in one DBPC withdrawal study, 3–4 years grass pollen immunotherapy was shown to result in sustained reduction in symptoms and rescue medication for at least three years following discontinuation.[26] Other studies have confirmed long-term benefit in relation to cat allergy, ragweed, tree pollen allergy and venom allergy. Immunotherapy has also been shown capable of reducing the onset of new allergen sensitivities in children.[3,4] In a prospective randomized controlled trial of pollen immunotherapy in children with seasonal allergic rhinitis, development of asthma was followed up over a period of five years. Two years following cessation of immunotherapy, there was a marked reduction in the risk of development of physician-diagnosed asthma (odds ratio 2.7, 95% confidence intervals 1.3–5.6) as compared to controls.[5] Taken together, these studies emphasize the important prophylactic value of injection immunotherapy, which is in contrast to pharmacotherapy where relapse of symptoms occurs immediately following discontinuation.

Safety

The major drawback of SCIT is the risk of potential side effects, like systemic allergic reactions, occasional anaphylaxis and even, fatalities. Risk factors for systemic reactions include extremely high sensitivity, coseasonal allergen exposure, history of previous systemic reactions and most importantly, the presence of uncontrolled bronchial asthma.[1,2]

Immunotherapy must be performed only under the supervision of a trained physician/specialist with a trained staff and adequate facilities available[1] with an appropriate observation area, facilities for vaccine storage at 4°C and access to the resuscitation facilities.[1,2] Immunotherapy protocols, in general, involve an updosing (induction) phase with weekly injections for 8–16 weeks, followed by a monthly maintenance injection (empirically this interval has been extended in some centers to 6–8 weeks). The maintenance phase should last 3–5 years. At each immunotherapy visit, it is recommended to record the date, dose and volume of allergen vaccine given. Adrenaline should always be available immediately. The patient should be observed for atleast 30 minutes following injections.

Injections should be postponed in the presence of respiratory infection, intercurrent illness, current asthma or symptoms due to concomitant allergen exposure. Dosage reduction, according to standard guidelines, should be performed in relation to previous systemic or large local reactions, during increased allergen exposure and if there is an extended time interval since the previous injections. In a randomized DBPC study with grass and birch vaccines, systemic mild reactions with SCIT occurred in 3.3% of the injections with grass and in 0.7% of injections with birch,[27] but no specific predictor could be identified. A postmarketing surveillance study reported a rate of mild-to-moderate level systemic reactions of 0.9% of the total doses given and of 3.7% of patients.[28] Another survey on grass pollen SCIT reports an occurrence of systemic reactions in 2% of patients,[29] with no life-threatening side effects. In a survey of more than 500 subjects, an occurrence of severe reactions was reported in 5.2% of patients and 0.1% of doses.[30] A retrospective study[31] in 65 patients receiving multiple vaccines and rush immunotherapy reported a 38% rate of systemic reactions with one severe episode. An e-mail survey involving more than 17,000 physicians reported a high rate of errors in administration (wrong patient or wrong dose),[32] which confirms the importance of careful administration of SCIT as recommended by international guidelines.[1,2,33] In general, according to USA surveys, fatalities occur in less than 1 case per 2,000,000 injections.[1]

Management of Adverse Events

Local swelling following injections is common and no treatment is required other than reassurance, although occasional use of an antihistamine may be indicated. Systemic reactions should be recognized and treated promptly, according to recommended guidelines. A grading system for systemic adverse reactions has been recently developed by World Allergy Organization (WAO), American Academy of Allergy Asthma and Immunology (AAAAI) and American College of Allergy, Asthma and Immunology (ACAAI).[34] In general, mild rhinitis or wheezing is treated by an antihistamine or bronchodilator, prolonging the observation period. More severe reactions, including moderate asthma, urticaria or angioedema require intravenous hydrocortisone and antihistamine. Adrenaline, 0.5 mg, by the intramuscular route, is indicated in rapidly evolving systemic reactions which do not respond to these measures and in all patients where there is associated moderate/severe respiratory impairment or hypotension. In general, if in doubt, give adrenaline which is more effective when administered early during a systemic reaction. Delayed systemic reactions are almost always mild, involving mild urticaria or asthma and respond to antihistamines and/or inhaled bronchodilator therapy.

THE SUBLINGUAL ROUTE

Starting from the beginning of 1900s, SIT was administered only subcutaneously, although various mucosal routes of administration were anecdotally proposed. When serious concerns about the safety of immunotherapy were raised, the clinical research with noninjection routes rapidly developed. Since its introduction in 1986, SLIT was regarded as a favorite alternative candidate to SCIT, especially due to its optimal safety profile.

After more than 20 years of clinical trials, postmarketing surveys and mechanistic studies, SLIT is nowadays considered a real step forward in the management of respiratory allergy, since it currently represents the only realistic alternative to the traditional injection route (Table 70.2).[35] The clinical efficacy (in term of symptom improvement) has been demonstrated for the most common allergens in more than 60 clinical trials,[36] and confirmed in meta-analyses in adult and pediatric populations.[37,38] Although meta-analyses have serious limitations, essentially due to the great heterogeneity of the clinical trials, so far they are the only instrument available for attempting to achieve an overall evaluation of the results of numerous trials according to

TABLE 70.2: Main characteristics of SLIT

Mechanisms	It is an allergen-specific immunomodulatory treatment which affects the Th2/Th1 balance and induces regulatory cytokines.
Association with drugs	SLIT does not replace drugs but must be used in association. On the long term period reduces the need for rescue medications.
Additional effects	Sustained efficacy after discontinuation, prevention of asthma onset.
Indications	Respiratory allergy (mite, grass, birch, olive, paritaria, cat).
Pharmaceutical forms	Available as drops, predosed dispensers, monodose vials, tablets.
Use	To be taken in the morning before breakfast. Keep under the tongue for 1–2 minutes then swallow. The first dose must be given under medical supervision.
Regimens	Updosing phase 10–30 days. Maintenance for 3–5 years daily or on alternate days according to manufacturer. Can be used also without an updosing phase. Preseasonal (stop at the beginning of the pollen season); coseasonal (start at the beginning of the pollen season); pre-coseasonal (start before the pollen season and stop at the end).
Side effects	Itching/swelling of the oral mucosa or tongue. Usually self-limiting in few days. Nausea or abdominal pain is rarer. Systemic side effects are rare. Only six cases of anaphylaxis described in 25 years.
Starting and duration	At least four weeks before the pollen season. For mites can be started in every period of the year. Duration 3–5 years.

evidence-based principles. Some concerns about SLIT still remain including the extent or magnitude of the clinical efficacy and the optimal maintenance dose to be used.

In addition, due to the large variability of the doses of allergen employed in many clinical trials[39] and to the various schedules of administration, SLIT is less rigidly formalized than SCIT. On the other hand, the recent large clinical trials conducted with grass tablets[40,41] have consistently shown the dose-dependency of the clinical effects of SLIT. This fact strongly increases the proof of efficacy, according to the GRADE recommendations.[42] Of note, in both those clinical trials, the magnitude of the effect over placebo largely exceeded the 20% suggested threshold, required for defining immunotherapy as clinically effective.[43] Finally, taking into account the economic aspects, which are of relevance in the case of AR, SLIT has been formally shown capable of reducing both the direct and indirect costs of the disease.[44-46]

It is also important to consider the effects of SLIT in a broader sense and now clinical data demonstrate the preventive effects of SLIT, in particular, in reducing the risk of inception of asthma in children with allergic rhinitis.[47,48] The most recent open controlled study[48] on this aspect, conducted in more than 200 children, receiving either SLIT or pharmacotherapy only for three years, showed a 40% reduction of the onset of persistent asthma in the SLIT-treated subjects, associated with a significant decrease of the onset of new sensitisations. Concerning the safety, the most common side effects are local (oral itching/swelling or nausea), but they are mild and self resolving in few days. The satisfactory safety profile (only six cases of anaphylaxis in 20 years) has suggested the possibility of avoiding the induction phase. In fact, the more recent large trials used a no updosing regimen. The good safety profile of SLIT in children, even below the age of 5,[49] gives the window of opportunity to use this treatment, taking advantage of the preventative effects.[50]

Despite the optimistic results of studies so far conducted, some important points still need to be addressed, including the optimal dose for each allergen and the optimal duration of a SLIT course needed to achieve the maximum benefits and the longest duration of the effects. In this context, recent large trials have started to provide some valuable information, at least for grass allergens, suggesting that[51] an eight-week preseasonal treatment achieves the best benefits. The preliminary results of a 15-years follow-up study reported that the optimal duration of a SLIT course should be four years.[52]

Mechanisms of SCIT and SLIT

Subcutaneous Immunotherapy (SCIT)

Subcutaneous immunotherapy is associated with a transient increase in allergen-specific IgE followed by blunting of seasonal increases in IgE. These effects are accompanied by increases in allergen-specific IgG4 antibodies.[53-56] Studies confirm and extend these observations to include measurements of the biological effects of IgG. These include the IgG-dependent ability of post immunotherapy serum to inhibit allergen-IgE complexes to B cells, the blocking of subsequent IgE-facilitated allergen presentation and activation of allergen-specific T lymphocytes and the prevention of allergen-IgE dependent activation of peripheral basophils.[57-59] SCIT is accompanied by inhibition of the recruitment and/or activation of effector cells including mast cells and eosinophils. Studies before and after SCIT confirm the reduction of the numbers of nasal mucosal eosinophils, basophils and mast cells during the pollen season,[60-64] a reduction in mucosal expression of the Vascular Adhesion Molecule (VAM) and decrease in IL-4 and IL-13.[65]

There is a blunting of allergen-driven Th_2 responses with reductions in IL-4, IL-13, IL-5 and IL-9[64,66-71] and an immune deviation to Th_1 responses with overproduction of IFNγ and/or the emergence of a population of regulatory T lymphocytes which produce the inhibitory cytokines IL-10 and/or TGF-β.[53-57,72] It is hypothesized that these regulatory T cells act directly to suppress allergen-specific Th_2 responses. Alternatively IL-10 is a known switch factor for IgG4 production,[73] whereas TGF-β favors IgA.[56]

Sublingual Immunotherapy (SLIT)

Sublingual immunotherapy is associated with qualitatively similar events to SCIT including modest increase in IgG, a transient increase in IgE and suppression of eosinophil recruitment and activation in target organs.[74-78] On the contrary, other studies failed to demonstrate changes in systemic T-cell and cytokine response[79,80] or local changes in T cells or effector cells within the sublingual mucosa. Some studies report an increase in IL-10 production[81,82] and another shows suppression of allergen-specific T cell responses after 12 months of grass therapy.[83,84] A recent study shows in vitro that SLIT reduces the expression of IL-5 and enhances the expression of IL-10 in PBMC stimulated with the allergen.[85] Further studies are needed to determine whether the same or alternative mechanisms are important for the effects of SLIT.

FUTURE DEVELOPMENTS OF SIT

The more and more detailed immunological knowledge and the concerns on the possible side effects of SCIT have prompted the development of new routes of administration and of modified vaccines. For instance, there is preliminary evidence that both the intralymphatic and the epicutaneous delivery of vaccines is effective and could represent an additional therapeutic option.[86,87] The introduction of recombinant allergens undoubtedly would allow a better standardization of allergen extracts, envisages the possibility of a tailored treatment according to individual sensitizations. However, at present, the few published trials of recombinant allergens for immunotherapy suggest that their clinical efficacy is not superior to that of traditional extracts.[88,89]

Another possible approach is the use of adjuvants to enhance TH_1 lymphocyte responses. Alum is the traditional adjuvant widely used in Europe. Alum has the effect of delaying absorption and in contrast to murine studies, downregulates Th_2 responses in humans, shown in both in vitro and in vivo studies. Bacterial adjuvants include lipopolysaccharide and DNA oligonucleotides. Monophosphoryl lipid A (MPLA), derived from the bacterial wall of Salmonella, is widely used as an adjuvant in prophylactic vaccines for infectious diseases and induces preferential Th_1 responses. An immunotherapy product with MPLA adjuvant was proven to be effective and is currently commercialized in Europe.[90] Bacterial DNA oligonucleotides containing an abundance of CPG motifs were shown to promote Th_1 responses and also induce IL-10, possibly by inducing T regulatory cells.[19] Preliminary data in humans from controlled trials support the use of these adjuvants in allergen extracts for treating respiratory allergy, but further studies are required, especially to rule out possible side effects.

The use of allergen-derived peptides for immunotherapy has the potential to stimulate "protective" Th_1 and/or T regulatory responses whilst avoiding systemic side effects associated with cross-linking of IgE on mast cells and basophils, which is the risk associated with conventional whole allergen extracts. Initial studies in cat allergy are encouraging, although, further studies are required.

CONCLUSION

Immunotherapy is an effective treatment for respiratory allergy. Since the 2001 ARIA document, new studies have enhanced the knowledge about this form of therapy. SCIT acts by either inducing immune deviation of T lymphocyte responses in favor of Th_1 responses to allergens and/or by the downregulation of Th_2 responses probably via regulatory T cells. IgG antibodies are also involved and have functional significance. The clinical efficacy of SCIT in allergic rhinitis and allergic asthma has been confirmed for most of the relevant allergens (grasses, trees, weeds, cats and mites).

SCIT is safe, provided that recommendations to minimize/manage adverse reactions are followed.

Several studies show the long-term efficacy of SCIT and the preventive effect on the onset of sensitization to additional allergens as assessed by skin testing. One study demonstrated that SCIT in children with pollen-sensitive rhinitis may reduce the risk of progression from allergic rhinitis to asthma. SLIT is effective in allergic rhinitis in adults and children.[83] One meta-analysis confirmed the efficacy also in asthma. Current data indicates that SLIT is safe and the rate of adverse reactions is not greater in children below 5 years of age. Further SLIT studies are needed to identify the optimal maintenance dose for all the relevant allergens and to elucidate the mechanism of action. Novel approaches for various other forms of allergen immunotherapy currently under evaluation include the use of adjuvants, peptides, recombinant/engineered allergens and DNA-conjugated allergens.

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71

Allergen Desensitization

Vikram Jaggi

INTRODUCTION

The three main modalities of treatment of allergic diseases are avoidance, pharmacotherapy and immunotherapy. Avoidance of common allergens is at best difficult and at worst impossible. It has been often said that "asthma is neither curable nor preventable."[1] Harsh as this may sound, it is quite true. Pharmacotherapy is highly effective and predictable in most patients, but only for as long as it is being taken. This is true for both bronchodilators and for inhaled steroids. Immunotherapy fills the gaps left by avoidance and pharmacotherapy. It is the only treatment modality that has been shown to alter the natural history of asthma. It is often effective for years after stopping treatment. This has also been shown to prevent the development of asthma in patients with allergic rhinitis and to prevent the development of new sensitizations in patients with asthma. However, it is neither highly effective nor predictably effective in all patients.

DEFINITION

Allergen immunotherapy is the repeated administration of specific allergens to patients with IgE-mediated conditions, to protect against the allergic symptoms and inflammatory reactions associated with natural exposure to these allergens.[2] Other terms used for allergen immunotherapy include desensitization (which is almost never achieved), hyposensitization (which lacks specificity) and the lay terms "allergy shots" or "allergy injections." The currently preferred term is allergen immunotherapy, which is short, accurate and easily understood. From a humble beginning in 1911, when crude pollen extract were employed to treat seasonal allergic rhinitis (or hay fever),[3,4] it has come a long way and is now recognized as a scientific method to both treat patients with allergy and to prevent the progression of the "allergic-march." Allergen immunotherapy today would merit consideration in allergic rhinitis (both seasonal and perennial), allergic asthma, insect sting allergy (hymenoptera hypersensitivity) and in certain drug allergies.

For allergen immunotherapy to be successful, it is imperative that patient selection as clinically relevant and well standardized antigens should be used and mixing of too many allergens should be avoided. Only a trained and experienced physician should prescribe and practice immunotherapy.

To paraphrase William Osler, the father of American medicine, allergen immunotherapy is "an art based on science." The last decade has seen a vast accumulation of scientific evidence to support its use.

HISTORICAL BACKGROUND

There are accounts of "Vish-Kanyas" in the ancient Indian scripts where courtesan girls were given minute, but increasing doses of poison to render them immune to the lethal effects of the poison. Native American Indians were known to chew poison ivy to prevent severe skin rash or anaphylaxis. These were only practices based on observations; there was no scientific understanding or proof of how or why it worked. It was during 1910–1920 that immunotherapy found its roots in clinical practice. It was used first in allergic rhinitis and later in allergic asthma. It was thought at that time that subanaphylactic doses lead to "using up" or "exhausting" the antibodies responsible for causing allergy; although at that time IgE was unknown. IgE was discovered in 1965–1966, was later characterized and its role in type I hypersensitivity was elucidated.

In the last 15 years, there has been a vast accumulation of scientific evidence on the mechanisms and efficacy of allergen immunotherapy. The publication of the WHO Position Paper on Allergen Immunotherapy[5] in 1998 reaffirmed scientific faith in this time-tested treatment modality. Later, the Preventing Allergy Treatment (PAT) Study[6] showed that allergen immunotherapy could prevent the the development of asthma in patients with allergic rhinitis. PAT was an important prospective long-term (10 Years) study in children with allergic rhinitis: 205 allergic rhinitis patients in five European countries were given three years of subcutaneous immunotherapy and followed for a further period of seven years; 45% of children with allergic rhinitis not treated with imunotherapy developed asthma. The risk of developing asthma decreased by approximately 50% in the group of vaccinated children. This confirmed a long-held scientific belief that allergy vaccination early in the disease development could reduce the risk of the development of asthma in children suffering from allergic rhinitis.

MECHANISMS OF ALLERGEN IMMUNOTHERAPY

Asthma is a complex disease in which many cells and cellular elements play a role. The immune responses in asthma are skewed towards the abnormal TH_2 type responses and away from the normal TH_1 type of response. Immunotherapy is shown to lead to the complex series of changes in the cellular, cytokine and chemokine profile to steer the immune system away from the TH_2 response towards a TH_1 type of response.[7] The following changes in cells and mediators have been noted with successful immunotherapy:

1. *Allergen-Specific IgE:* In patients who receive allergen immunotherapy, initially there is an increase in specific IgE antibody levels followed by a gradual and sustained reduction in IgE levels.[8] Immunotherapy also blunts the seasonal increase in specific IgE levels that normally occurs due to seasonal exposure to the aeroallergens.[9] Consequent to the reduction in serum IgE levels, histamine release from the basophils and the mast cells is reduced.[10]
2. *Acute and Late Phase Reactants:* Allergen immunotherapy is shown to block both immediate- and late-phase allergic response.[11] It reduces the recruitment of mast cells, basophils and eosinophils in the skin, nose, eye and bronchial mucosa after provocation and after natural exposure to allergens.[12]
3. *Blocking Antibodies:* In successful immunotherapy, there is an increase in allergen specific IgA and IgG levels (particularly the IgG4 isotype). Allergen specific IgG induced by immunotherapy has been shown to "block" IgE-dependant histamine release and subsequent IgE-mediated antigen presentation to T cells.[13] However, there is a poor correlation between the rise in specific IgG levels and clinical improvement.[14]
4. *Interleukins:* There is an increased production of IL-12, a strong inducer of TH1 response.[15]

IL-10 is also increased. IL-10 reduces beta cell antigen specific IgE and increases the IgG4 levels, reduces proinflammatory cytokine release from mast cells, eosinophils and T-cells.[16]

Although the changes mentioned above are clinically measurable, the correlation between these change and clinical response is not consistent or strong. At present, these changes cannot be used to clinically monitor immunotherapy or its efficacy.[14]

Indications

There are three main indications for allergen immunotherapy (Table 71.1): Allergic rhinitis (both seasonal and perennial), allergic asthma and hymenoptera allergy. Randomized, prospective, double-blind, placebo-controlled studies have shown the effectiveness of allergen immunotherapy in allergic rhinitis and allergic asthma.[17,18]

Allergen immunotherapy will merit consideration in any patient who has natural aeroallergen exposure with the symptoms of upper and/or lower respiratory allergy

TABLE 71.1: Indications and contraindications of immunotherapy

A. Usual indications	Allergic rhinitis Allergic asthma Sting allergy
B. Usually not indicated	Food allergy Chronic idiopathic urticaria Angioedema atopic dermatitis
C. Caution required	Severe coronary artery disease Unstable angina Cancer unstable asthma Uncooperative patients Use of beta-blockers

symptoms with demonstrable evidence of specific IgE antibodies to the clinically relevant allergen(s). Allergen immunotherapy is recommended for patients who are unable to avoid the allergens (pollens or house dust mites for instance), have an inadequate response to avoidance and pharmacotherapy, have unacceptable side-effects of medicines or who do not wish to take noncurative medication indefinitely. The ideal candidate for allergen immunotherapy is the patient with moderate to severe rhinitis and mild to moderate asthma induced by a few selected seasonal or perennial allergens. In allergic rhinitis, the more severe the allergic rhinitis, the stronger is the reason to consider allergen immunotherapy. In asthma, on the other hand, severity is generally a reason not to consider allergen immunotherapy. Allergen immunotherapy in asthmatics should not be initiated unless the patient's asthma is stable with pharmacotherapy. Patients with severe or uncontrolled asthma are at an increased risk for systemic reactions to immunotherapy.[19]

Selection of Allergens for Immunotherapy

A carefully taken history, knowledge of local and regional aerobiology and corroboration with a properly performed Skin Prick Test (SPT) will guide the physician to select the relevant allergens to be included in the immunotherapy vaccine for a given patient. SPT information is to be interpreted judiciously with caution. The results are not to be taken at their face value. For most patients, it is possible to find out less than four or five important relevant allergens. If more than one pollen from the same family has tested positive, inclusion of only the representative, one of them would suffice. Cockroach and fungal antigens have the ability to cause proteolytic degradation of other allergens, particularly the pollens.[20,21] Hence, these should not be mixed. House dust mite antigen does not seem to have a similar deleterious effect on pollens, hence can be mixed with pollens.[22] A good allergy vaccine prescription should include comprehensive information (Table 71.2).

TABLE 71.2: Prescription requirements of a good, allergy vaccine

1. The relevant and confirmed allergens (not more than five usually; the lesser the better)
2. The starting dose (which is usually 0.1 ml of 1:5000 dilution w/v)
3. The projected therapeutic dose
4. The frequency of injections (usually once or twice in a week initially in the build-up phase, then fortnightly or monthly in the maintenance phase).

TABLE 71.3: Conditions which require a gradual doing schedule

1. The SPT has caused significant reactions
2. There is a history of anaphylaxis
3. There is a history of allergic reaction to allergen immunotherapy.
4. More severe forms of asthma
5. In the natural pollen season

Schedule

The general principle is to start a dilute dose, which is gradually built up in concentration to the dose that is maximally tolerated or which gives adequate clinical response (Build-up Phase). This dose is then continued initially weekly, then fortnightly and finally on a monthly basis for the maintenance phase. Certain patients would require a departure from this usual dosing schedule in that a more dilute dose is used initially and the increase in dose is more gradual (Table 71.3).

Delivery of Allergen Immunotherapy

The ideal venue for the allergen immunotherapy injections is the doctor's clinic. The doctor should be available at all times when the injections are being given. The staff giving injections should be suitably trained. A written informed consent of the patient should be obtained. The facility to store the vials at 4 degree centigrade should exist. A standardized color code and marking system of vials of different concentrations with the name of the patient should be clearly printed on it.

Measurement of Peak Expiratory Flow (PEF) should be done before the injection. A policy should be in place to either reduce or withhold the dose in case there is a significant (20-30%) fall in the PEF reading. Patient should be observed for 20 to 30 minutes after the injections. Resuscitation equipment, including adrenaline and oxygen should be available.

For the sake of convenience, the patient may take the injections from another physician near his home. This has been shown to be safe, provided all the prerequisites of safe immunotherapy mentioned above are met and are available there as well.[23] It is not advisable to take immunotherapy injections at the patient's residence.

Technique of Injections

The injections are given in the posterior portion of the upper 1/3rd of the arm where the deltoid meets the triceps muscle. Here the subcutaneous tissue is maximum. It is given subcutaneously (not intradermally or intramuscularly). The injections can be alternated between the two arms. After the injection, heavy exercise is to be avoided for one hour for this can lead to rapid absorption, which may precipitate a systemic allergic reaction.

Duration of Allergen Immunotherapy

Most patients, who show response to aeroallergen immunotherapy, demonstrate clinical improvement once the maintenance dose is reached in 6–9 month time. The response is maintained during immunotherapy. To prevent the relapse of symptoms on stopping allergen immunotherapy, it should be continued for three years in most patients.

After discontinuation, some patients experience sustained clinical remission while some relapse. At present there are no reliable or specific tests to predict as to which patient will relapse and which will maintain long-term remission after discontinuing effective immunotherapy. In a prospective controlled study, designed to look for the immunotherapy relapse rate during the three-year period after discontinuation of immunotherapy, 55% of 40 asthmatic patients who were treated with immunotherapy for 12–96 months, relapsed. The relapse rate was 62% in the group treated for less than 35 months as compared to 48% in the group treated for greater than 36 months.[24]

At the end of three years of effective immunotherapy, a decision has to be made whether allergen immunotherapy should be continued or stopped. The doctor and the patient should jointly decide keeping in mind the benefits and risks associated with continuing or discontinuing immunotherapy. Reasons to favor continuing immunotherapy are a good response to allergen immunotherapy; a maintenance dose of monthly injections; asthma rather than allergic rhinitis; and no major inconvenience to the patient of a monthly injection. Most patients who have benefited prefer to continue monthly immunotherapy. Reasons favoring a trial to stop allergen immunotherapy to see if remission is maintained are allergic rhinitis rather than asthma; less than optimum response to immunotherapy; and a major inconvenience of injections.

Efficacy

Many double-blind, placebo controlled, randomized clinical trials demonstrate a beneficial effect of allergen immunotherapy in the treatment of allergic rhinitis, allergic asthma and stinging insect hypersensitivity, it is effective in both children and adults.[17,18,25,26]

Bee Sting Allergy

Bee sting allergy is a “pure” reflection of a type I hypersensitivity reaction where allergy is demonstrated unequivocally to a single unambiguous allergen. Once the maintenance dose is achieved for venom immunotherapy, 80 to 98% of the individuals will be protected from a systemic reaction upon sting challenge. Allergen immunotherapy is generally given for five years for this indication. After discontinuation of allergen immunotherapy, the risk of a systemic reaction to sting is very low—about 10%.[25] The very high efficacy of allergen immunotherapy in bee sting allergy and its continued benefits even after stopping immunotherapy are good proof of the power of allergen immunotherapy per se, provided allergy is clearly demonstrated, a single allergen is incriminated and the vaccine is made using that single relevant allergen. This enhances confidence on the innate ability of allergen immunotherapy to be effective.

Allergic Rhinitis

The efficacy of allergen immunotherapy in allergic rhinitis has been clearly demonstrated in a large number of trials. These studies have shown significant improvements in symptoms, quality of life, medication use and in immunological parameters. Allergen immunotherapy is also shown to be beneficial for up to three to six years or more after completion of treatment. Allergen immunotherapy is shown to prevent the development of asthma in allergic rhinitis patients who receive immunotherapy.

Asthma

A Cochrane review of 75 trials with 3,188 patients revealed a significant reduction in symptoms and medication use and an improvement in bronchial hyperreactivity after immunotherapy.[18] Allergen immunotherapy also prevents the development of new allergen sensitization in monosensitized patients.[27]

Side Effects and Risks

There can be local and systemic side effects. Local reactions at the injection site, such as itching, redness and swelling are quite common. The patients in fact, welcome such reactions as an additional proof of allergy to that substance. They are generally less than 2–3 cm in diameter and subside on their own in a day. If

TABLE 71.4: Important reasons responsible for systemic reactions with immunotherapy

- Wrong dose or wrong injection
- Injection given at the height of the natural pollen season
- Uncontrolled asthma (FEV1 less than 70% of predicted)
- Patient on beta-blockers
- Patient having a natural exacerbation
- Injection from a new vial

troublesome, these can be managed by the local application of ice or with an oral antihistaminic. Such reactions generally do not require any reduction in the dose. Large reactions (greater than 2.5 cm) that occur repeatedly or after a day, may predict a more serious systemic reaction; a dose reduction to the previously tolerated dose may be required.

Systemic reactions in the form of increased upper or lower respiratory allergy symptoms, urticaria/ angioedema or hypotension can also occur rarely. A majority of such reactions occur within 30 minutes of the injection; hence the mandatory 30 minute waiting period in the clinic. Most of the reasons responsible for systemic reactions are predictable and avoidable (Table 71.4).

Very rarely, a severe reaction may occur in spite of all due diligence, due to the inherent high degree of allergic sensitivity. The physician must be prepared and equipped to handle these reactions. Systemic reactions are managed in the usual way with adrenaline, injectable antihistamine and steroid administration. Volume replacement is also required.

Fatalities during allergen immunotherapy, although extremely rare, are reported. There is no reliable data from India. The fatality rate in USA is one death per 2.5 million injections or an average of 3.4 deaths per year.[28] This has been constant on a per decade rate for the last three decades. Near fatal reactions, hypotension or respiratory arrest or both, are 2.5 times more common than fatal reactions.

Special Considerations in Various Patient Groups

Children Under 5 Years of Age

There have been reports of the efficacy of allergen immunotherapy in children of less than 5 years of age.[29] In children with allergic rhinitis, allergen immunotherapy might prevent the development of asthma.[30] Yet, most allergists hesitate to prescribe allergen immunotherapy to small children or toddlers for the following, very valid, reasons:

- Small children often outgrow their allergic symptoms on their own, as they grow older.
- The diagnosis of asthma sometimes cannot be made with confidence in a young wheezy child.
- Injections are traumatic to small children.
- Compliance with scheduled injections is not guaranteed in small children.
- Children may find it difficult to communicate the symptoms of impending allergic or anaphylactic reaction to allergen immunotherapy.

TABLE 71.5: Improvement in children following immunotherapy

1. Improvement in symptom control for asthma and allergic rhinitis.[30]
2. Increased PC_{20} to histamine.[31]
3. Decreased risk of development of asthma.[30]
4. Decreased development of new sensitizations.[32]

Older Children

Allergen immunotherapy in older children is effective and well tolerated. In general, the clinical indications are similar for adults and children. Recently, studies in children receiving allergen immunotherapy have shown improvement (Table 71.5). Most allergists agree that the response to allergen immunotherapy is better in children and young adults than in older adults.

Elderly Patients

Elderly patients generally respond less favorably to allergen immunotherapy. Further, presence of certain comorbid conditions like hypertension, coronary artery disease or cerebrovascular disease make them more prone to the risks of allergen immunotherapy. The fact that they may be taking beta-blockers may make resuscitation difficult if an allergic or anaphylactic reaction were to occur. However, elderly patients may also benefit therefore, age alone should not be the reason to deny allergen immunotherapy.[33]

Pregnancy

Allergen immunotherapy is effective in pregnancy. However, if an allergic or anaphylactic reaction occurs in pregnancy due to allergen immunotherapy, it could have serious consequences on the continuation of pregnancy. For these reasons, the general policy is:

- Allergen immunotherapy is not initiated in pregnancy.
- If allergen immunotherapy is being given and is well tolerated, it is not discontinued in pregnancy.
- If maintenance dose has already been reached, it is continued at the same dose.
- If maintenance dose has not been reached, dose escalation is generally not done during pregnancy.

Autoimmune Disorders

There are concerns regarding allergen immunotherapy aggravating autoimmune disorders by their uncertain effects on various parameters of immune modulation. These concerns are largely theoretical without any substantial evidence that such treatment is harmful in these diseases. Most allergists hesitate to prescribe allergen immunotherapy to patients with autoimmune diseases for the simple practical reason that the blame of even a spontaneous flare up, not uncommon in these diseases, would fall on immunotherapy if it happens during this period.

Sublingual Immunotherapy

The conventional route of immunotherapy has been through subcutaneous administration. Reports of an alternate (and a more convenient and safe) route, i.e. the sublingual route, appeared in literature, mostly from Europe, after 1985. This came to be called Sublingual Immunotherapy (SLIT), as opposed to conventional Subcutaneous Immunotherapy (SCIT).

Effectiveness of SLIT has been shown in both children and adults for both allergic rhinitis and asthma. It is effective against pollens (particularly grass pollen), house dust mites and cat antigens. It generally takes longer (1–2 years) before there is improvement in symptoms.[34] There is good theoretical support for the sublingual route for immunotherapy. The dendritic cells in the oral mucosa are different from he dendritic cells of the skin in that the oral dendritic cells have an increased expression of certain major histocompatibility complexes and costimulatory molecules, which make these cells particularly adept at antigen presentation. This may play an important role in directing subsequent immune effects.[35]

SLIT appears to a have a favorable safety profile as compared to SCIT. Local symptoms like itching and burning in the lips, tongue and mouth are common. Mild gastrointestinal symptoms are also commonly seen. Rarely, aggravation of rhinitis, or even more rarely of asthma symptoms may occur. Anaphylaxis is reported, but is extremely rare. No deaths have been reported so far.

SLIT is being widely used in Europe. There are a few questions, which remain to be answered before it is widely used:

The optimum dose and dosage schedules for each allergen need to be clearly defined. Moreover, trials with mixtures of antigens are required and long-term efficacy compared to SCIT remains to be seen. With growing experience, this has the potential for greater use in allergic rhinitis and asthma. Its major advantages are the obviously ease of administration (by the patient at the home), no waiting period in the doctor's clinic, very low incidence of side effects and lower costs.

There are many instances of poorly practiced immunotherapy, which need to improve (Table 71.6).

TABLE 71.6: Poor practices in allergen immunotherapy

1. Allergen immunotherapy being practiced by untrained or poorly trained physicians.
2. Immunotherapy being prescribed on the basis of serum specific IgE results without any correlation to clinical history.
3. Inclusion of too many antigens in the immunotherapy vaccine (many of them unnecessary or irrelevant).
4. Inclusion of more than one pollen of the same family where only one representative allergen would suffice.
5. Use of non-standardized allergens for allergy testing and vaccine preparation.
6. Allergens with ability to cause proteolytic degradation of other allergens (fungal spores and cockroach) being mixed with other allergens.
7. Maintenance dose that is too weak to give a full therapeutic response.
8. Immunotherapy, indiscriminately used in severe or chronic asthma with chronic airflow limitation where not much benefit is to be expected, but the risk of serious side effects is more.
9. Immunotherapy being used in conditions with no proven role: urticaria, angioedema, atopic dermatitis or food allergy.

FUTURE DIRECTIONS

Advances and improvements in allergen immunotherapy continue to occur. The existing practices of allergen immunotherapy need be optimized. The extracts to be used require standardization, at present only a few extracts are standardized. Today, it is possible to identify and monitor the chemical and cellular changes that occur with immunotherapy. The challenge lies in transforming this information into a clinically effective method of monitoring immunotherapy. Several approaches to modify immunotherapy have been tested, such as the use of allergoids, alum precipitates and most recently of peptides. Recombinant technology has provided a powerful technique both for sequencing proteins and producing allergens in commercial quantities. To reduce the risk of allergic reactions, recombinant protein can be modified so as to decrease the reactivity with IgE antibody while maintaining reactivity with T cells. The sublingual route of allergen immunotherapy is promising, likely to be more widely used.[36]

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Bronchodilators

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INTRODUCTION

Treatment of asthma with bronchodilatory drugs has a long, fascinating history. Ancient ayurvedic texts recommended inhaled therapy particularly with steam, cinnamon, castor oil and herbs such as *Atropa belladonna, Datura stramonium* or mixtures containing anticholinergic compounds (like atropine, hyoscyamine and scopolamine). These compounds were also used by the ancient Greeks with the help of specially made inhaler devices. The first evidence for use of sympathomimetics drugs is available from the traditional Chinese medicine (Ma huang, from the plant *Ephedra sinica* containing ephedrine). Some of the other remedies tried before the modern era that might or might not have been effective include owl's blood in wine, opium-induced vomiting and chicken soup.

The treatment of asthma achieved a landmark in 1897 when John Abel was able to prepare crude adrenal extract (*epinephrin*). Subsequently, in 1920s and 30s, many epinephrine analogs were synthesized, including isoproterenol. However, its beta selectivity was not known. Its use became widespread only in the middle part of the 20th century. Development of isoprenaline in inhalational form was a big step, but tragically caused thousands of deaths during the 1960s. The discovery by Lands and coworkers of β_1 and β_2 receptors led to the development of salbutamol in 1967.

It is safe to assume that most of the world population consumes (and has consumed for hundreds of years) either tea or coffee/cocoa or cola drinks. Tea leaves (*Thea sinensis)* contain theophylline (small amount), caffeine, and theobromine; cocoa and chocolate seeds (*Theobroma cacao)* contain theobromine and some caffeine; coffee fruit (*Coffea arabica)* and the nuts of *Cola acuminata* contain caffeine. All these plant alkaloids are known to possess mood elevating, stimulant and bronchodilating properties. Although theophylline was first extracted in the 19th century, its use as bronchodilator was first described only in 1922.[1]

The next paradigm shift in the treatment of asthma came in the 1960s with the use of anti-inflammatory drugs. Khellin, a naturally occurring chromone (*Ammi visnaga* extract) had been used in Egypt and the Eastern Mediterranean countries for centuries in the treatment of respiratory diseases. The synthesis of *Cromolyn* (Roger Altounyan) in 1965 was an attempt to improve the bronchodilator activity and reduce the adverse effects of khellin. The Nobel Prize winning discovery of Kendall, Reichstein and Hench "relating to the hormones of the adrenal cortex," was soon followed by observations that adrenocorticotropic hormone and cortisol helped in asthma. As the use of corticosteroids in bronchial asthma was appreciated, the physicians started becoming more aware of their adverse effects, need for topical preparation was realized and inhaled steroids were introduced in 1972.

Bronchodilators are broadly classified as below:

- Beta-2 adrenergic agonists: Short acting, long acting and ultra long acting
- Methylxanthines
- Anticholinergic agents.

BETA-2 ADRENERGIC AGONISTS

Beta-2 adrenergic agonists are the most efficacious and the most widely used bronchodilators. They can be used by inhalation or systemically, provide excellent smooth muscle relaxation and rapid bronchodilation with relatively few side effects, thus providing excellent risk-benefit ratio. The most preferred route when using these drugs is inhalational because the mast cells are located close to the airway lumen and more easily accessible to this route. However, less than 10% of the inhaled drug reaches the site of action, the remainder is swallowed. In order to reduce systemic adverse effects, the stress is on developing drugs that have low systemic bioavailability [poor absorption from the gastrointestinal tract (GIT) or high first-pass hepatic metabolism]. Another strategy is to increase the drug delivery to lungs and simultaneously decrease the amount of drug reaching the GIT; for example, by attaching a spacer to the Metered-Dose Inhaler (MDI).

Mechanism of action: Human lungs contain both alpha and beta adrenergic receptors; alpha receptors are not known to play any significant role in the regulation of the Airway Smooth Muscle (ASM) tone. On the other hand, beta adrenergic receptors, subtype-2, are the most important regulators of airway smooth muscle tone. Traditionally, the mechanism of action of beta-2 adrenergic agonists has concentrated on airway smooth muscle relaxation mediated through elevated cAMP levels (Fig. 72.1). Beta-2 agonists act through hetero-trimeric G-proteins leading to the stimulation of adenylyl cyclase. This in turn leads to the elevation of cAMP levels. Elevated cAMP activates Protein Kinase A (PKA). Activated PKA in turn phosphorylates myosin light chain kinase, thereby preventing airway smooth muscle contraction. While this concept still holds, several other mechanisms have been elucidated.[2] PKA may also bring about the activation of potassium channels leading to potassium efflux, which in turn causes hyperpolarization of airway smooth muscles. Cross activation of Protein Kinase G (PKG) may also lead to the relaxation of ASM.

Additionally, beta-2 adrenoceptors are expressed in inflammatory cells like mast cells, macrophages, neutrophils, eosinophils, as well as in type I and II alveolar cells. Activation of beta-2 adrenoceptors leads to the inhibition of these cells. This may additionally contribute to the benefits obtained with beta-2 adrenergic agonists.

Short-Acting Beta-2 Agonists (SABAs)

The agents of this group are used by inhalational route mainly. They are considered the most effective agents for relieving acute bronchospasm (Level A evidence). They are also indicated for preventing exercise-induced bronchospasm. Two epidemics of asthma deaths in the 1960s and 1970s in UK and New Zealand were attributed to the use of SABAs. Subsequently, the results of Mild Asthma Trial evaluated regular versus "as needed" albuterol in 255 patients with mild asthma.[3] Patients were randomized to 16 week treatment of "as needed" or regular use albuterol. Peak Expiratory Flow (PEF) variability, FEV_1, number of puffs of albuterol or symptoms were not different in the two groups. It was thus concluded that "as needed" therapy was preferable for the regular inhalation of bronchodilators. In a Cochrane review,[4] data from 31 outcomes were analyzable. There was little difference between the treatments for nearly all outcomes. In cross-over studies, evening peak flow was better with regular treatment. Bronchial hyperreactivity was slightly better in the "as needed" group. It was thus concluded that there was little advantage in using SABAs regularly.

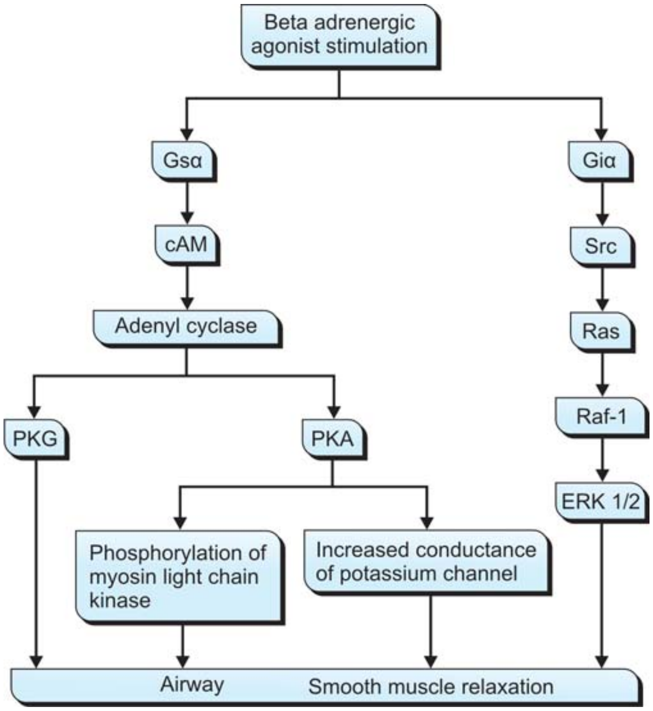
Beta adrenergic agonist stimulation
Gsα
cAM
Adenyl cyclase
PKG
PKA
Phosphorylation of myosin light chain kinase
Increased conductance of potassium channel
Giα
Src
Ras
Raf-1
ERK 1/2
Airway Smooth muscle relaxation

Fig. 72.1: Molecular mechanism of action of beta-2 adrenergic agonists

If SABAs are needed more than twice per week, it is considered to indicate the inadequate control of bronchial asthma. Use of more than one SABA canister for quick relief of bronchospasm in a period of one month indicates an increased possibility of emergency department visit. Pharmacogenomics have thrown some light on the variability in propensity to deterioration of lung function while taking SABAs, albuterol in particular.[5]

Polymorphism of beta-2 adrenoceptor gene may explain some of this variability. Patients homozygous for arginine at position 16 are more likely to experience the worsening of lung functions than those who are either Arg/Gly or Gly/Gly genotype at the same locus.

a. Salbutamol: Salbutamol (albuterol) is the prototype SABA. It is given by inhalation, orally and parenterally (but not in all countries). The preferred route of administration is inhalation, even though only 10% to 20% of the administered dose reaches the site of action while the rest is swallowed or left behind in the device.[6] Salbutamol, unintentionally, but invariably swallowed from the inhaler device or taken orally as tablet, is readily absorbed from the GIT. Peak plasma levels (Cmax) are seen considerably earlier with inhaled formulation (Tmax 0.2 h) as compared to oral administration (Tmax 1.8 h).[7] Salbutamol undergoes considerable first-pass metabolism in the liver and gut wall, but not in the lung and has no active metabolites. Its plasma half-life is 4–6 hours as it is rapidly excreted, primarily in the urine. Its metabolism is stereoselective and levosalbutamol [*R*(–)-enantiomer] is metabolized about eight times more rapidly than the *S*(+)-enantiomer (also has no bronchodilator effect).[8] This property has been utilized to develop and market levosalbutamol as a novel drug (approved by the Food and Drug Administration in 1999), with some evidence of fewer adverse effects.

Adverse drug reactions: Tremors and nervousness are the most common adverse effects, they are dose-dependent and seen in up to 20% of patients. Headache (7%), palpitations, tachycardia (5%), muscle cramps (3%), elevated blood pressure, insomnia, restlessness, weakness, nausea, dizziness, and chest discomfort/heartburn are also observed. Throat irritation or sore throat and nosebleeds can also occur. Other rare adverse effects, which are occasionally seen are: Allergic reactions, rash, hives, throat irritation itching; difficulty in breathing; tightness in the chest; swelling of the mouth, face, lips or tongue; chest pain; ear pain; fast or irregular heartbeat; new or worsened troubled breathing; pounding in the chest; red, swollen, blistered or peeling skin; severe headache or dizziness; unusual hoarseness; and wheezing, swelling, bronchospasm or anaphylaxis (shock). Worsening of diabetes and lowering of potassium have been also reported. In a rare patient, inhaled salbutamol can paradoxically precipitate life-threatening bronchospasm.

Salbutamol should be given with caution in hyperthyroidism, myocardial insufficiency, arrhythmias, susceptibility to QT-interval prolongation, hypertension and diabetes mellitus. Hypokalemia should be kept in mind in severe asthma as the hypoxia associated with the condition and the concomitant drugs used in the situation may exacerbate hypokalemia. There are reports of abuse of salbutamol among both asthmatic and nonasthmatic (especially) young persons.

Drug interactions: Though pharmacokinetic interactions are not remarkable, pharmacodynamic interactions may be of concern. Concomitant use with other beta-2 agonists, corticosteroids, diuretics and xanthines may cause increased risk of hypokalemia. A propensity to cause hypokalemia increases the predisposition to digitalis induced arrhythmias. There may be adverse cardiovascular additive effects such as hypertension and tachycardia (if combined with tricyclic antidepressants or monoamine oxidase inhibitors). Similar interaction can occur with other stimulant sympathomimetic drugs, especially in patients with underlying coronary heart disease. Beta-blockers (especially nonselective) block salbutamol effects and bronchospasm may occur.

Use in asthma: For the relief of acute bronchospasm, 1 or 2 inhalations of salbutamol 100 mcg may be given from a conventional metered-dose aerosol as required, up to four times daily. Two inhalations may also be given just before the exertion for the prophylaxis of exercise-induced bronchospasm. Due to environmental concerns with the use of chlorofluorocarbons (CFC), CFC-free aerosols have been developed. These contain hydrofluoroalkanes (HFA). These are also available as dry powder inhalers. A dose, double to that of conventional aerosol is often required when the drug is administered in the powder forms. Long term use of beta adrenergic agonists is known to reduce the efficacy of the agents. This has been attributed mainly to the process of receptor desensitization. Uncoupling of the receptor from Gs, receptor internalization, upregulation of cAMP phosphodiesterase and down-regulation of Gs are some of the reasons for receptor desensitization.

b. Bitolterol: A long-acting beta-adrenergic agonist, it is the prodrug of colterol – a long-acting beta-adrenergic agonist synthesized mainly in the lungs. Although it has a long duration of action (>5 hours), unlike other long-acting beta-adrenergic agonists, it can be given for acute exacerbations of bronchospasm because of its rapid onset of action (about 2 minutes).

c. Orciprenaline: Also known as metaproterenol, it is less selective for beta-2 receptors than salbutamol, therefore causes more adverse effects. When given by inhalation, its onset of action is 30 minutes and duration 1 to 5 hours.

Because of its nonselective action, it has been used orally or by slow Intravenous (IV) infusion in the treatment of bradycardia (like isoprenaline).

d. Pirbuterol: It is a selective beta-adrenergic agonist with properties similar to that of salbutamol. The onset occurs in 10 minutes and the action lasts for 5 hours.

e. Terbutaline: Terbutaline is similar to salbutamol in most aspects except that its half-life is longer (16–20 hours). It is given mainly for the relief of acute exacerbations. It is available for inhalational, parenteral and oral administration.

f. Fenoterol: It has a rapid onset (5 minutes) after inhalation. It was implicated in the asthma-related epidemic (increased morbidity and mortality) in New Zealand in 1970s and 1980s with similar reports from Canada and Japan. Subsequently, a meta-analysis concluded that the increase in asthma-related mortality associated with beta-adrenergic agonist was only slight.[9] Moreover, the link between asthma-related deaths and fenoterol remained controversial as it was proposed that patients who used the drug had more severe disease.

g. Oral beta agonists: Oral preparations of beta-2 agonists have the disadvantage of a worse side-effect profile compared to inhaled preparations. A brief course of albuterol or metaproterenol syrup may be considered in the children of less than 5 years of age who cannot manipulate MDIs and yet have occasional wheezing. In occasional patients with severe asthma exacerbations, in whom the aerosol delivery causes worsening of cough and bronchospasm; oral forms of albuterol, metaproterenol or terbutaline may still be effective.

Long-Acting Beta 2-Adrenergic Agonists (LABAs)

Long-acting beta 2-adrenergic agonists as well as ultra long-acting agents are used for the maintenance therapy of asthma. The mechanism of action is similar to that of SABAs.

a. Salmeterol: This LABA (duration of action 12 hours) is used for maintenance therapy in conjunction with corticosteroids. The onset occurs at 10–20 minutes, but the peak effect is delayed making it unsuitable for the treatment of acute spasm. Publication of the results of interim analysis of Salmeterol Multicenter Asthma Research Trial (SMART) showed a small and significant increase in asthma-related deaths with the use of salmeterol, mainly in African-Americans.[10] A meta-analysis of 19 trials showed a similar increased propensity to cause asthma-related deaths, increased incidence of hospitalization due to asthma exacerbations and life threatening asthma attacks in those treated with salmeterol.[11] Therefore, the current practice in chronic asthma is not to use salmeterol as a substitute to inhaled steroids, but to add it to inhaled corticosteroid rather than increasing the dose of inhaled corticosteroid.

b. Formoterol: Formoterol is a partial agonist, touted for lesser propensity to desensitization of the beta-agonist activity. Experimental studies, however, have demonstrated that at equally effective doses, all beta-2 agonists may be equally susceptible to desensitization.[12] Like salmeterol, it has to be used in conjunction with corticosteroids. Addition of long-acting beta-adrenergic agonist to low or high dose of inhaled corticosteroids reduces the risk of asthma exacerbation compared to inhaled corticosteroid given alone. Inhaled formoterol is rapidly absorbed after inhalation. The plasma half life of the drug after administration is around 10 hours.

c. Bambuterol: Bambuterol metabolizes to terbutaline, the active metabolite. As result of slow metabolism, its approximate duration of action is around 24 hours. It may cause an increase in nonfatal heart failure in elderly patients.

d. Clenbuterol: It is used in the dose of 20 mcg twice daily, by inhalation. It is being widely abused by sportsperson for improving performance and also by farmers for improving the muscle mass of livestock. These effects remain unproven.

Ultra (Very) Long-Acting Beta-2 Adrenergic Agonists (ULABAs or VLABAs)

Attempts to further increase the duration of action of beta-2 agonists have been made so as to get compounds suitable for once daily administration, which by improving compliance, may also improve the outcomes. Most of these compounds are R,R-enantiomers of existing drugs since it is likely that these isomers will have less desensitization. Arformoterol, the R,R-isomer of formoterol has been shown to have duration of action of 24 hours. However, studies have also indicated that clinically important difference may not exist between the duration of action of formoterol and arformoterol. Carmoterol is another ultra long-acting beta-agonist with the structural elements of both formoterol and procaterol. In clinical trials, it has been shown to be as effective as formoterol, but is not yet approved. Clinical trials have also demonstrated safety and efficacy of another ULABA, indacaterol. It has, in addition to prolonged duration of action, a quick onset of action. Some of these agents are likely to be marketed soon. Many of the beta-2 adrenergic agonists are available as fixed dose combinations with inhaled corticosteroids while some are available as fixed-dose combinations with once-daily long-acting muscarinic antagonists (LAMAs).

Besides asthma, LABAs and ULABAs are being evaluated in Chronic Obstructive Pulmonary Disease (COPD) as well. It is an issue of concern whether LABAs may increase the mortality in COPD, in view of the result of the increased mortality seen in the SMART.[11] On the other hand, the landmark trial, Towards a Revolution in COPD Health (TORCH)[13] showed that there was a 17% relative risk reduction (amounting to 2.6% absolute reduction); in all-cause mortality. However, a combination of inhaled steroid (fluticasone) and a long-acting agent (salmeterol) was used in this large (> 6000 patients), multinational (42 countries), randomized trial. The combination improved lung function, reduced the total number of exacerbations and reduced the yearly rate of decline in FEV_1 more than the two individual drugs. Importantly, monotherapy with salmeterol had better survival than placebo, although statistical significance was not achieved.

METHYLXANTHINES (XANTHINES)

Theophylline, theobromine and caffeine are three important methylxanthines (some non-methylated xanthines are under development). Aminophylline (theophylline-diamine) is a commonly used derivative of theophylline. The exact mode of action of xanthines is not known. The primary action (although at high concentrations, *in vitro*) is through inhibition of Phosphodiesterases Group of Enzymes (PDEs), which in turn prevent breakdown of cAMP and cGMP, leading to their accumulation and effects such as relaxation of smooth muscle, stimulation of cardiac function, and inhibition of release of cytokines and chemokines (TNF alpha, leukotrienes).

Although xanthines are nonselective inhibitors of PDEs (of which at least five types are known), the enzyme most likely responsible for their action is PDE4 (to a lesser extent, PDE5), located on bronchial smooth muscle and inflammatory cells. Attempts to make selective PDE4 inhibitors (“designer xanthines”) have not been successful, the development of at least three selective PDE4 inhibitors (roflumilast, cilomilast and tofimilast) has been stopped due to various toxicities seen at low doses.

The second important mechanism of action of xanthines is through competitive inhibition of adenosine receptors. Adenosine can modulate adenyl cyclase activity, cause bronchial smooth muscle contraction and histamine release leading to bronchoconstriction. Although considered important by some, it must be mentioned that enprofylline (xanthine without adenosine antagonistic action) also has bronchodilator effect. Deacetylation of histones by xanthines may decrease the recruitment of histone deacetylases by corticosteroids to areas where the transcription of proinflammatory genes occurs. This can actually lead to synergism between steroids and xanthines, a theoretical interaction that now has some clinical evidence since theophylline was able to restore responsiveness to steroids in (smoker) asthmatics. In conclusion, xanthines have both bronchodilatory and anti-inflammatory effects, but which one is more important remains unclear.

The other effects of xanthines include Central Nervous System (CNS) stimulation (especially with caffeine), positive chronotropic and inotropic effects on heart, stimulation of gastric acid and intestinal enzyme secretion, mild diuretic effect (especially with theophylline), and stimulation of skeletal muscle (including the diaphragm) contraction.

Theophylline

It is the prototype drug of the class available for oral and parenteral administration. Dosage of modified release formulations should be titrated for an individual patient. Parenteral preparations are seldom used. Elimination is primarily hepatic, the metabolites as well as the unchanged drug (10%) are excreted in urine except in neonates (50% excreted unchanged). Its half-life in healthy, nonsmoking adults is seven to nine hours, and three to five hours in children and smokers, but higher (10–30 hours) in neonates, premature infants, elderly nonsmokers and in patients with liver disease or heart failure.

Solutions or uncoated tablets of theophylline produce maximal concentration in plasma within 2 hours. Sustained release preparations have marked interpatient variability in their bioavailabilities and may warrant careful dose titration. Food drug interactions are also highly variable. These agents are widely distributed, may cross placenta and pass into breast milk. Allopurinol, macrolides, quinolones, oral contraceptives and albendazole are known to decrease the clearance of theophylline, thus its dose need to be reduced. On the other hand phenytoin, ritonavir, rifampicin and sulfinpyrazone may increase its clearance.

Therapeutic Drug Monitoring (TDM) may be needed with its use, it being a narrow therapeutic index drug and having multiple interactions. An optimum therapeutic concentration is generally considered to be between 10–30 micrograms/ml. Toxicity has been seen with the rapid intravenous administration of therapeutic doses of aminophylline resulting in cardiac arrhythmias.

The adverse effects commonly encountered with theophylline and xanthine derivatives irrespective of the route are gastrointestinal irritation and stimulation of the CNS. Serum concentrations of greater than 20 mcg/mL are associated with an increased risk of adverse effects. Overdosage may also cause agitation, diuresis, repeated vomiting, cardiac arrhythmias, hypotension, electrolyte disturbances (such as hypokalemia, hyperglycemia, hypomagnesemia), metabolic acidosis, rhabdomyolysis, convulsions and death.

Aminophylline

It is a prodrug of theophylline (joined with ethylenediamine), releases theophylline *in vivo*. It is given slowly intravenously by slow injection (or infusion) in acute severe bronchospasm, at a rate greater than 25 mg/minute. It is important to elicit drug history of the patients before the administration of intravenous aminophylline. In patients already on xanthine medication, it is safe to omit the loading dose or if possible, serum concentration estimated and the required dose calculated. It is also administered orally and rarely, rectally absorption from the latter route is erratic. Besides asthma, it is also used in the management of COPD, neonatal apnea and erectile dysfunction (local application). It has been also tried in motor neuron disease, methotrexate-induced neurotoxicity, and for removal of fat (locally).

Diprophylline

Unlike theophylline, diprophylline is largely cleared unchanged renally (half-life 2 hours) and does not need dose modification in patients with hepatic dysfunction. Unlike theophylline, drug interactions are uncommon. It is used in doses of 15mg/kg, three to four times a day.

Caffeine

Caffeine is a xanthine that is more widely acknowledged as a CNS stimulant. It increases alertness and reduces sleep. In doses of 5–10 mg/kg, it has a bronchodilator action that is weaker (40%) compared to theophylline, which is why it is hardly used in asthma.

Xanthines (particularly theophylline and aminophylline) were used as first-line bronchodilators in the past, but their position was taken by steroids and beta-2 agonists. Xanthines are less efficacious and have greater potential for adverse effects. There has been a resurgence of their use for their anti-inflammatory properties and because of the availability of slow-release preparations for nocturnal control.

ANTICHOLINERGIC AGENTS

Airway smooth muscles express both M2 and M3 muscarinic receptors. Besides in airway smooth muscles, muscarinic receptors are also present in glandular and surface epithelial cells, endothelial cells and various inflammatory cells in the airway. Acetylcholine produces bronchoconstriction predominantly by acting through M3 muscarinic receptors. Activation of these receptors leads to the activation of Phospholipase C (PLC) resulting in the formation of IP3 and DAG. Additionally, M2 receptors augment the contractile response mediated by M3 receptors. This is achieved by limiting adrenergic relaxation and inhibitory effects on calcium-activated potassium channels. M3 receptors are also involved in the stimulation of mucus secretion from submucosal glands and goblet cells.

There are several reviews on the usefulness of anticholinergics in acute and chronic bronchial asthma in children and adults. Mostly, it is shown that while the agents are useful in acute asthma, there is insufficient evidence for their role in chronic asthma.[14-17] Specifically, they were shown to cause significant reductions in hospital admissions with favorable symptom scores, particularly in the respect of daytime dyspnea and daily peak flow measurements. For the latter, the clinical significance was small and in terms of peak flow measurements, equated to approximately a modest 7% increase over placebo. The more clinically relevant comparison of a combination of anticholinergic plus SABA versus SABA alone gave no evidence in respect of symptom scores or peak flow rates of any significant differences between the two regimes. Thus, these drugs may be used to provide additive benefit to SABA in moderate-to-severe asthma exacerbations or may be used as alternative bronchodilators for patients who do not tolerate SABA.

Ipratropium Bromide

It is a quaternary ammonium antimuscarinic agent. When given by inhalation, it causes direct bronchodilatation. Ipratropium bromide provides additive benefit to SABAs in moderate-to-severe asthma exacerbations, leads to somewhat higher and prolonged effect compared to either agent used alone. It may also be used as an alternative bronchodilator for patients who do not tolerate SABAs. When ipratropium is used alone, the bronchodilation by onset is slower, the magnitude is lesser and more variable as compared to SABAs. The exact cause of variability in response to ipratropium is not known, may be related to the intrinsic parasympathetic tone in a particular patient as well as the contribution of parasympathetic system in causing bronchoconstriction.

Ipratropium is used by the inhalational route; 10% to 30% of the drug is deposited in the lungs, very small amount reaches the systemic circulation as it is not absorbed from the GIT. It is available as metered-dose inhalers (alone and in combination with beta-2 agonists), dry powder capsules and as nebulizer solution. The usual dose from an MDI is 1 or 2 inhalations (20–40 mcg) three or four times daily, but the total daily dose should not exceed 12 inhalations. Inhaled antimuscarinics have greater usefulness in COPD. Intranasal ipratropium is also used in the management of rhinitis (reduces rhinorrhea and sneezing).

Being an anticholinergic, it is associated with the dryness of mouth, constipation (rarely paralytic ileus), tachycardia, palpitations and arrhythmias. Rarely, it can cause urinary retention (especially in the presence of prostatic hyperplasia) and precipitation of angle closure glaucoma. Patients with glaucoma should be advised to be careful while using these agents to avoid the mist entering the eyes. Antimuscarinics cause impaired drainage of aqueous humor while beta-2 agonists increase the production of aqueous humor; their concomitant use (which is routinely done) may be potentially harmful in susceptible patients. Rarely, paradoxical bronchospasm (seen also with other bronchodilators, may be attributable to some preservative) and hypersensitivity reactions (urticaria, angioedema, rash and anaphylaxis) have been reported. There is some evidence of increased mortality in COPD seen with ipratropium while not seen in others.[18-20]

Tiotropium Bromide

It is a long-acting quaternary ammonium anticholinergic agent (duration of action 24 hours) available for aerosol administration. About one-fifth reaches systemic circulation after dry powder inhalation and about one-third after inhalation of the solution. Its half-life is five to six days, excreted by the kidneys and therefore its use in patients with renal impairment, especially if creatinine clearance is < 50 mL/min, should be avoided.

It should not be used for the initial treatment of acute bronchospasm, primarily used in the maintenance treatment of COPD, as well as of asthma. It is used once daily as two inhalations of 2.5 mcg from the MDI. Besides the adverse effects seen with other antimuscarinics, pharyngitis, sinusitis, rhinitis and epistaxis have been reported. Recently, a small increase in the risk of stroke (8 per 1,000 patients treated for one year compared with 6 per 1,000 patients on placebo) has been seen.[21] There have been case reports of dermatological adverse reactions such as cutaneous lupus and photosensitive lichenoid eruption.

Recent advances in anticholinergics have focused on the development of agents with lower systemic absorption and thereby having lesser adverse drug reactions, as well as on oral formulations. Aclidinium bromide is a long-acting anticholinergic agent selective for M3 receptors. The drug is being evaluated mainly for COPD and was shown to have bronchodilator effect lasting for 24 hours in healthy volunteers challenged with methacholine.[22] With better efficacy observed when anticholinergics are used in conjunction with beta-adrenergic agonists, certain fixed-dose combinations have been recently approved, several others, particularly with tiotropium, are under development.

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Patient Education in Asthma

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INTRODUCTION

With the availability of inhaled and modern means of therapy now, we have effective treatment options to reduce agony of asthmatic patients. Inspite of effective therapy for diseases such as asthma, many patients still suffer due to ignorance, lack of understanding and faulty perception of the disease. Patient education is the only means, which can impart skills to enable a patient to use modern therapy and to remove wrong notions. Patient education is an integral part of the treatment in almost all respiratory diseases, but its efficacy in evidence-based medicine is proved mainly in asthma. Patient education is also important for risk factor reduction, especially for the quit-tobacco plan. It is an essential component of respiratory rehabilitation, for example in patients with Chronic Obstructive Pulmonary Disease (COPD).

Recent guidelines have contributed significantly in the elucidation of this question in the terms of sound evidence base.[1,2] In patients with COPD, rehabilitation has been recognized as an established modality of treatment as it can increase functional capacity, lead to improvement in dyspnea and quality of life.[1] The role of rehabilitation in other respiratory disorders is gradually being scrutinized, however, further evidence is needed to have clear guidelines. (See chapter on Rehabilitation for more details).

Patients must become effective partners in their own care, for the treatment of a chronic respiratory disorder to become successful. Patient education in asthma is well supported by evidence based documents almost similar to the effectiveness of respiratory rehabilitation in COPD patients.[3] Asthma is one disease which starts in childhood and continues throughout life with marked fluctuations in severity. When a patient is sick, even to take a breath becomes a mounting task. In contrast, during symptom-free period, a patient considers himself as fit as a normal person. Patients must make day-to-day or even moment-to-moment decisions, in response to such fluctuations, mainly regarding self-medication or to ask for medical help. Factors like patient motivation, literacy and socioeconomic setup markedly influence such decisions.

Education need of the asthmatic patient, which often remains neglected by health care providers, is no less important than that of patients with coronary artery disease or diabetes mellitus. Asthma education is commonly practiced in the western countries, but there are hardly any organized asthma education programs in India except for the availability of some expert documents and reports on efficacy of asthma education.[4-7]

GOALS OF ASTHMA EDUCATION PROGRAMS

The primary aim of asthma education is to keep the patient well and to impart ability to adjust the doses of the medicines according to an action plan. Reducing the costs is the primary aim for the health care services. The Global Initiative for Asthma (GINA) treatment has recommended the following issues for discussion with a patient:[3]

- Asthma is a continuous disease
- Patient’s expectation from treatment
- Patient’s fears and apprehensions about asthma.

To achieve these goals, specific information with a practical goal should be given to change behavior. Teaching over several days, covering many general topics may not be as useful as regular review of basic principles. Frequent verification of understanding and application of learned behavior are important.

BENEFITS OF ASTHMA EDUCATION PROGRAMS

One of the earliest published, randomized clinical trial of an education program for patients with asthma was a study in 1973 which included adult, inner-city residents. Members of the treatment group participated in a single, small-group session. This project had led to conclusions, which have now become the mainstay of planning and evaluation in patient education and health promotion.[8] The model recognizes three sets of variables that must be considered in determining the type of educational interventions:

1. *Predisposing factors:* The knowledge, attitudes, beliefs, and perceptions make up a baseline on which an action can take place.
2. *Enabling factors:* Skills and resources required to be able to enact a motivated behavior.
3. *Reinforcing factors:* Make the behavior more or less likely to be repeated or sustained over time. This has led to popular concept of precede-proceed framework.[9]

Some of more recent studies underline the importance of behavioral change over education alone.[10] However, the main draw back of systematic reviews in the asthma education is the variability between the study interventions and their insufficient documentation, which requires a more uniform and standard approach in these studies.[11,12]

The recent National Asthma Education and Prevention Program (NAEPP) guidelines gave an evidence grade of A to the recommendation for asthma self-management education.[13] Asthma education should be provided at every patient encounter by all providers and at all points of care (evidence grade B). The guidelines also recommend written action plans that include specific treatments and actions to respond to changes in symptoms, especially for patients with moderate-to-severe asthma (evidence grade B).[14,15]

Several adult asthma education programs have also reported better correlation between knowledge and outcome. A Cochrane review of 36 trials that compared usual care to self-management plus regular review and an action plan found more regular physician visits, fewer emergency department visits, slightly better lung function and peak flow measurements, need of fewer drugs and rescue medication in later group.[16] Studies that involved less intensive interaction and monitoring, had less effect while written action plans had better outcomes.[17]

TABLE 73.1: Methods and benefits of asthma education[3,13]

Methods	*Improvements*
Small group sessions	Knowledge of asthma
Individual teaching	Feelings of control
Large group lectures	Positive attitudes
Problem-solving sessions	Physical activity
Booklets	Inhaler technique
Diaries	Use of peak flow meters
Computer games	Peak flow rates
Promotion of peak flow monitoring use	Asthma severity
	Reduction of school absenteeism
Repeated audits	Health care costs
Checklists	Emergency room visits/ hospitalizations

METHODS AND SETTINGS

Methods

No single teaching method or medium will work for all patients in all settings (Table 73.1). Many factors will influence the selection of methods. Written material allows the patients to understand information at their ease, and is on hand for future reference. Interactive computer programs are somehow individualized in approach and many are available on the Internet.[18] Videotapes are attractive for patients, but have the limitation of not being individualized. Utility of videotapes and other material ultimately depends upon individualized counseling, either in a one-on-one or group setting.

Settings

There is evidence of positive asthma-education outcomes in multiple settings.[19] Settings that provide follow-up visits, education-reinforcement and continuing asthma monitoring are associated with better asthma control. The NAEPP guidelines recommend asthma education at all points of care, so that the patient has multiple chances to learn about asthma and build up self-management skills.[13] It is quite interesting that the clinic setting would allow the best opportunity for an ongoing collaborative relationship between the patient and the provider, and better outcomes (evidence grade A).

Asthma education in the school is important because of the potential for reaching a large number of children. Comprehensive school-based asthma programs can improve symptom control and reduce acute-care utilization.[20,21] Home-based education programs can significantly impact allergen control (evidence grade A).[13] Decreasing allergen exposure reduces exacerbations, and should be a component of asthma education when allergens are an important trigger.

ASTHMA EDUCATION PROGRAM COMPONENTS

The written action plan is the single most important strategy of asthma education. Patients who recognize asthma symptoms, understand peak flow measurements and how to respond appropriately are more likely to maintain asthma control. The NAEPP guidelines include example action plans.[13]

What should be the content of asthma education?

Patient is educated to impart skills in following aspects of asthma:

- Diagnosis
- Inhaler medicines
- Difference between reliever and controller drugs
- Potential side effects of medicines
- Control of symptoms
- Early detection of exacerbation
- Monitoring control of asthma
- How and when to take medical assistance?

The two main components of asthma, i.e. inflammation and bronchoconstriction should be made clear to the patients. The differences between smooth muscle contraction and the inflammatory components should be explained with the use of figures. The patient must be able to distinguish between reliever (bronchodilators) and controller (anti-inflammatory) agents. They also should know that reliever act rapidly, but controller-steroids work more slowly. Importantly, patients must understand that the controller drugs will allow asthma control to be achieved and must be taken regularly instead of "on demand" basis.

The use of beta 2-agonists before exercise, exposure to irritants and cold air, should be suggested. Inhaler technique should be demonstrated and checked regularly, as should the use of spacer devices or dry powder inhalers. The key to achieving asthma control is the patient's understanding of what are the criteria of control or of loss of control of asthma, and how to monitor severity according to symptoms and expiratory peak flow rates.[22] Peak Expiratory Flow (PEF) monitoring may be beneficial because of the learning and reinforcement value of self-monitoring and the greater sense of control and self-efficacy that comes with self monitoring.[23]

After establishing the goals of therapy, corresponding symptom and peak flow end points, patients must know how to adjust medication and when to seek medical care according to the symptoms and PEF, using their action plans instead of relying solely on their physicians. Action plans have been developed and seem to reduce morbidity significantly, although it is difficult to dissociate their effects from treatment adjustments and other aspects of the education program.

Asthmatic patient should also receive general counseling about nutrition, sleep habits and relaxation methods, and they must have an opportunity to ask questions of general relevance to asthma management.

How to assess adequacy of teaching and understanding?

Evaluation can be made immediately after the teaching session by a questionnaire incorporating key issues. The level of confidence of the patient does not necessarily mean level of understanding of asthma management. The level of the control of asthma achieved, health services use (emergency visits, hospitalizations), quality of life evaluation of the asthmatic, and the level of airflow obstruction are useful parameters to determine long-term benefits of asthma education.[24] Overall assessment may be repeated after a few weeks, and then at intervals of three to six months.

PATIENT EDUCATION: PROBLEMS

Among the barriers to effective asthma education, one must include the limited time available for teaching in the physician's office, the use by physicians of terms that the patient does not understand, the tendency of medical personnel to concentrate on acute treatment instead of long-term control, and until recently, the fact that treatment emphasized symptomatic relief and not prolonged control of airway inflammation. Patients often report that it is difficult to discuss their illness during a hurried medical consultation, they may be embarrassed to ask questions, and likely to forget or confuse multiple recommendations if they are not written (Table 73.2).

Other problems relate to the acceptance and the understanding of asthma. As with other chronic diseases, there is often an initial denial of the problem; efforts should be made to help the asthmatic accept his condition, a prerequisite to effective control. False

TABLE 73.2: The barriers to effective asthma education [6,13]

Physician related

- Limited time available for teaching patients
- Use of terms that the patient will not understand
- Tendency to concentrate on acute treatment instead of long-term control.

Patients related

- Difficult to discuss their illness—hurried consultation, embarrassed to ask questions
- Likely to forget or confuse multiple recommendations if they are not written
- Problems with acceptance and understanding of asthma
- Misunderstanding the fundamental principles
  - Inadequate perception of symptoms, leading to non-application or delay in the application of principles taught
  - Inadequate perception of signs, e.g. misinterpretation of changes in peak flow
- False expectations and a desire to be “cured”
- Abrupt cessation of the medication. The patient should be advised stepping down instead of stopping suddenly
- Preconceived assumptions, fears and concerns, e.g. fear of steroids.

expectations are frequent. A desire to be cured may push patients to try different forms of treatment that offer a miraculous cure (e.g. popular fish therapy of South India). The importance of regular treatment, even when asthma is apparently controlled, is often not understood, leading to gross undertreatment.[25] Preconceived assumptions, fears and concerns, e.g. fear of steroids, and inadequate counseling from misinformed sources may also interfere with teaching.

CONCLUSION

Effective respiratory rehabilitation incorporates exercise schedules and patient education comprehensively to encompass treatment and other aspects needed to make any individual patient recover gradually from the deterioration of the condition and to remain in a fully functional state as far as possible. Patient education is one of the major components of asthma treatment and prevention. A variety of teaching programs have been developed to improve self-management skills. An action plan that incorporates objective measurements like peak flow has been more successful in improving control and reducing morbidity than that based on the improvement of only knowledge. Such measures are aimed at specifically preventing needless delays in treating exacerbations and improving compliance with preventive measures.

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Childhood Asthma

Meenu Singh

EPIDEMIOLOGY

Bronchial asthma is the most common chronic disease of childhood, affecting an estimated 6 million children. The burden of asthma affects the patients, their families, and the society in the terms of loss of work and school days, lessened quality of life, avoidable emergency department visits, hospitalizations and deaths. Improved scientific understanding of asthma has led to significant improvements in asthma care. The International Study of Asthma and Allergies in Children (ISAAC) study noted a significant variation in its prevalence in different parts of India with a range of 0.5% to 18% in a 12-month prevalence of self-reported asthma symptoms from a written questionnaire.[1] A 20 to 60 fold difference in the prevalence of symptoms was found between various centers involved in this study.

Although prevalence data of allergic disease in India is scarce, the little data that is available suggests that the patterns differ in different areas.[1-4] A study of 271 children from rural areas of Tamil Nadu reported a prevalence of breathing difficulty at any time in the past in 9%.[5] In the study from rural areas of North India, the prevalence of chronic cough among children aged 1–15 years (n = 2275) was 1.06%, and two-thirds were due to asthma.[3] Such variable patterns also exist across urban regions. Prevalence rates ranging from 1.9% to 15.7% have been reported. Such national variation, with almost 10–15 fold difference in the prevalence of allergic disorders, is probably unique to India. In a recently conducted study at our center under the aegis of the Asthma Task Force of the Indian Council of Medical Research, a survey was conducted on 10,028 school children (10–15 yeas of age) belonging to 39 randomly selected schools for the diagnosis of asthma and other atopic disease in Chandigarh. A total of 536 children were found to have a current clinical diagnosis of asthma, allergic rhinitis or eczema with a 3.3% prevalence of asthma. These findings were similar to those of ISAAC surveys conducted earlier at our center.

The comparative prevalence of wheeze in 13–14 year olds between the two South Asian cities (Galle, Sri Lanka and Chandigarh, India) representing each of the above archetypes has been studied.[5] The validated one page ISAAC questionnaire for 13–14 year olds was used for the study. Crude prevalence rates and odds ratios [with 95% two sides Confidence Intervals (CI) for the comparison of prevalence rates] were calculated. The prevalence rate for wheezing in Galle (28.7%) was higher than that of Chandigarh (12.5%). The Odd Ratios (ORs) for prevalence for Galle versus Chandigarh were: 2.3 (95% CI 1.8–2.9) for lifetime wheezing; 2.1 (95% CI 1.6–2.7) for wheezing in the previous year; 4.8 (95% CI 3.5-6.7) for exercise-related wheeze; and 1.7 (95%CI 1.2–2.3) for physician diagnosed wheeze, thus demonstrating significant differences in wheeze prevalence between the two cities ($P < 0.05$). The numbers of 13–14 year olds experiencing less than 12 wheezing episodes per year or sleep disturbance due to wheeze of less than one night per week were also significantly higher for Galle. Hence, a higher prevalence of wheeze was noticed in 13–14 year old children living in an old-fashioned, congested city (Galle) than in a clean city, Chandigarh.

DEFINITION

Clinically, asthma is a complex disorder characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness and an underlying inflammation. The interaction of these features determines the clinical manifestations and severity of asthma and the response to treatment.[6,7]

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: In particular, mast cells, eosinophils, neutrophils, T lymphocytes, macrophages and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing, particularly at night or early in the morning, wheezing, breathlessness and chest tightness. These episodes are usually associated with widespread, but variable airflow obstruction that is often reversible, either spontaneously or with treatment.

PATHOPHYSIOLOGY

Airflow limitation is caused by a variety of changes in the airway, all influenced by airway inflammation:

- Bronchoconstriction: Bronchial smooth muscle contraction that quickly narrows the airways in response to exposure to a variety of stimuli, including allergens or irritants.
- Airway hyperresponsiveness: An exaggerated bronchoconstrictor response to stimuli.
- Airway edema: As the disease becomes more persistent and inflammation becomes more progressive, the presence of mucosal edema, mucus hypersecretion and the formation of inspissated mucus plugs further limit airflow.

Reversibility of airflow limitation is incomplete in some patients. Persistent changes in airway structure occur, including sub-basement fibrosis, mucus hypersecretion, injury to the epithelial cells, smooth muscle hypertrophy and angiogenesis. Recent studies provide insights into different phenotypes of asthma that exist. Different manifestations of asthma may have specific and varying patterns of inflammation (e.g. varying intensity, cellular mediator pattern and therapeutic response). Further studies will determine if different treatment approaches benefit the different patterns of inflammation.

Immunobiology of Asthma

Airway obstruction in asthma is mediated by hyperresponsive bronchial smooth muscle, secreted airway glycoproteins, and inflammatory debris produced by airway goblet cells and other cells, as well as edema or swelling of the airway wall. The development of asthma involves the interplay between the host factors and the environmental exposures that occur at a crucial time in the development of the immune system. Genetic susceptibility also plays a crucial role in this interaction. A definitive cause of the inflammatory process leading to asthma is not yet established.

a. *Innate Immunity:* Numerous factors may affect the balance between Th1-type and Th2- type cytokine responses in early life and down-regulate the Th1 immune response that fights infection. Instead there is dominance of Th2 cells leading to the expression of allergic diseases and asthma. This is known as the "hygiene hypothesis," which postulates that certain infections early in life; exposure to other children (e.g. presence of older siblings and early enrolment in childcare, which have greater likelihood of exposure to respiratory infection); less frequent use of antibiotics, and "country living" are associated with a dominant Th1 response and lower incidence of asthma. On the other hand, the absence of these factors is associated with a persistent Th2 response and higher rates of asthma.

b. *Genetic Factors:* Asthma has an inheritance component, but the genetic factors, which are involved, remain complex. As the linkage of genetic factors to different asthma phenotypes becomes clearer, treatment approaches may become more directed to specific patient phenotypes and genotypes.

c. *Environmental Factors:* The two major factors that are important in the development, persistence and possibly the severity of asthma are:
    i. Airborne allergens (particularly sensitization and exposure to house dust-mite and Alternaria), and
    ii. Viral respiratory infections [including Respiratory Syncytial Virus (RSV) and rhinovirus].

    Other environmental factors under study are:
    i. Tobacco smoke (exposure "*in utero*" is associated with an increased risk of wheezing, but it is not certain that this is linked to subsequent development of asthma).
    ii. Air pollution (ozone and particular matter).
    iii. Diet (obesity or low intake of antioxidants and omega-3 fatty acids).

The association of these factors with the onset of asthma has not been clearly defined. A number of clinical trials have investigated dietary and environmental manipulations, but the trials have not been sufficiently conclusive to permit recommendations.

Knowledge of the importance of inflammation central to the pathogenesis of asthma continues to expand and underscores inflammation as the primary target of treatment. Numerous studies indicate that current therapeutic approaches are effective in controlling symptoms, reducing airflow limitation and preventing exacerbations, but currently available treatments do not appear to prevent the progression of asthma in children. As the various phenotypes of asthma are defined and inflammatory and genetic factors become more apparent, new therapeutic approaches will be developed that may allow more specific treatments to the individual patient's needs and circumstances.

DIAGNOSIS

To establish a diagnosis of asthma, the clinician should determine that symptoms of recurrent episodes of airflow obstruction or airway hyperresponsiveness are present; airflow obstruction is at least partially reversible; and alternative diagnoses are excluded.[7]

Key Symptom Indicators for Considering a Diagnosis of Asthma

The presence of multiple key indicators increases the probability of asthma:

- Wheezing is a high-pitched whistling sound that comes out while breathing out, especially in children. A lack of wheezing and a normal chest examination do not exclude asthma.
- History of any of the following:
  - Cough (worse, particularly at night)
  - Recurrent wheeze
  - Recurrent difficulty in breathing
  - Recurrent chest tightness.
- Symptoms occur or worsen in the presence of:
  - Exercise
  - Viral infection
  - Inhalant allergens (e.g. animals with fur or hair, house dust-mites, mold, pollen)
  - Irritants (tobacco or wood smoke, airborne chemicals)
  - Changes in weather
  - Strong emotional expression (laughing or crying hard)
  - Stress
  - Menstrual cycles.
- Symptoms occur or worsen at night, awakening the patient.

Recommended Methods to Establish the Diagnosis According to Expert Panel Report III

1. Detailed medical history.
2. Physical examination: It may reveal findings that increase the probability of asthma, but the absence of these findings does not rule out asthma because the disease is variable and signs may be absent between episodes. The examination focuses on:
   - Upper respiratory tract (increased nasal secretion, mucosal swelling, and/or nasal polyps);
   - Chest (sounds of wheezing during normal breathing or prolonged phase of forced exhalation, hyperexpansion of the thorax, use of accessory muscles, appearance of hunched shoulders, chest deformity); and
   - Skin (atopic dermatitis, eczema).
3. Spirometry can demonstrate obstruction and assess reversibility in patients of more than 5 years of age. Patients' perceptions of airflow obstruction are highly variable. Spirometry is an essential objective measure to establish the diagnosis of asthma, because the medical history and physical examination are not reliable means of excluding other diagnoses or of assessing lung status. Spirometry is generally recommended, rather than measurements by a peak flow meter, due to wide variability in peak flow meters and reference values. Peak flow meters are designed for monitoring, not as diagnostic tools.

   A differential diagnosis of asthma should be considered. Recurrent episodes of cough and wheezing most often are due to asthma in both children and adults; however, other significant causes of airway obstruction leading to wheeze must be considered both in the initial diagnosis and if there is no clear response to initial therapy.
4. Additional studies are not routinely necessary, but may be useful when considering alternative diagnoses.
5. Additional pulmonary function studies, such as diffusing capacity, measures of lung volumes and evaluation of inspiratory flow-volume loops will help if there are questions about other diseases such as a restrictive defect, vocal cord dysfunction or bullous lung diseases.
6. Bronchoprovocation with methacholine, histamine, cold air or exercise challenge may be useful when asthma is suspected and spirometry is normal or near normal. For safety reasons, bronchoprovocation should be carried out only by a trained individual. A positive test for airway hyperresponsiveness, which is a characteristic feature of asthma is diagnostic, but

can also be present in other conditions. Thus, a positive test is consistent with asthma, but a negative test may be more helpful to rule out asthma.

7. Chest X-ray may be needed to exclude other diagnoses.
8. Biomarkers of inflammation are currently being evaluated for their usefulness in the diagnosis and assessment of asthma. Biomarkers include total and differential cell count and mediator assays in sputum, blood, urine and exhaled air.

Common Diagnostic Challenges

1. Cough Variant Asthma: Cough can be the principal or only manifestation of asthma, especially in young children. Monitoring of Peak Expiratory Flow (PEF) or bronchoprovocation may be helpful. Diagnosis is confirmed by a positive response to asthma medications.
2. Vocal Cord Dysfunction (VCD), which is seen commonly in adolescent girls, can mimic asthma, but it is a distinct disorder. Vocal cord dysfunction may coexist with asthma. Asthma medications typically do little to relieve VCD symptoms. Variable flattening of the inspiratory flow loop on spirometry is strongly suggestive of VCD. Diagnosis of VCD is made from indirect or direct vocal cord visualization during an episode, during which the abnormal adduction can be documented. VCD should be considered in difficult-to-treat, atypical asthma patients and in athletes who have exercise-related breathlessness unresponsive to asthma medication.
3. Gastroesophageal Reflux Disease (GERD), Obstructive Sleep Apnea (OSA) and Allergic Bronchopulmonary Aspergillosis (ABPA) may coexist with asthma and complicate diagnosis.
4. Children in the age group of 0 to 4 years pose particularly a challenge. Diagnosis in infants and young children is elusive, complicated by the difficulty in obtaining objective measurements of lung function in this age group. Caution is needed to avoid giving inappropriate, prolonged asthma therapy. However, it is important to avoid under-diagnosing asthma by using such labels as "wheezy bronchitis," "recurrent pneumonia," or "Reactive Airway Disease (RAD)," thereby missing the opportunity to treat a child. The chronic airway inflammatory response and structural changes that are characteristic of asthma can develop in the preschool years, and appropriate asthma treatment will reduce morbidity.

Guideline-Based Management of Asthma

National Asthma Education and Prevention Program (NAEPP) is dedicated to translating research findings into clinical practice. The first NAEPP guidelines were published in 1991, and updates were made in 1997, 2002 and in 2007. Important gains have been made in reducing morbidity and mortality rates due to asthma; however, challenges remain. Several guidelines have been made in India for adults as well as for children.

The goal of NAEPP, EPR3 2007 guideline,[7] is to help people with asthma control their disease so that they are active all day and sleep well at night. New focus of management is on monitoring asthma control as the goal for asthma therapy and distinguishing between classifying asthma severity and monitoring asthma control (Fig. 74.1). The impairment and the risk are the two key domains of assessment of severity and control. The domains represent different manifestations of asthma, they may not correlate with each other, and may respond differentially to treatment. Impairment represents the frequency and intensity of symptoms and functional limitations, the patient is experiencing currently or has recently experienced. Risk represents the likelihood of either asthma exacerbations, progressive decline in lung function or for children, lung growth; or risk of adverse effects from medication. Modifications have been made in the stepwise approach to managing long-term asthma.

Treatment recommendations are presented for three age groups (0–4 years of age, 5–11 years of age, and youths more than 12 years of age and adults) because of several different reasons:

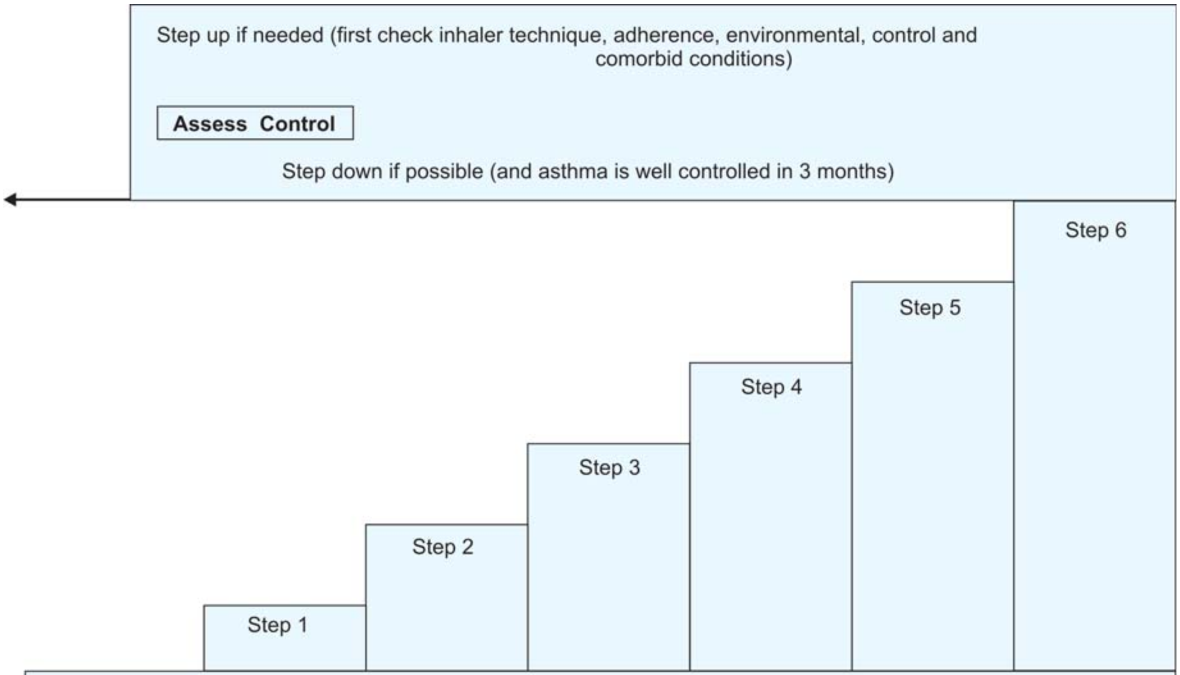
i. The course of the disease may change over time;
ii. The relevance of different measures of impairment or risk and the potential short- and long-term impact of medications may be age related; and
iii. Varied levels of scientific evidence are available for these three age groups.

The stepwise approach expands to six steps to simplify the actions within each step (Fig. 74.2). Previous guidelines had several progressive actions within different steps; these are now separated into different steps. Medications also have been repositioned within the six steps of care. The new emphasis is made on multifaceted approaches to patient education and to the control of environmental factors or comorbid conditions that affect asthma. Modifications to treatment strategies for managing asthma exacerbations have also been improvised.

Components of severity		Assessing asthma control and adjusting therapy in children					
		Well controlled		Not well controlled		Very poorly controlled	
		Ages 0–5	Ages 5–11	Ages 0–5	Ages 5–11	Ages 0–5	Ages 5–11
Impairment	Symptoms	≤ 2 days/week. But not more than once on each day		2 days/week or multiple times on < 2 days/week		Throughout the day	
	Night-time awakenings	≤ 1x/month		>1x/month	≥ 2x/month	>1x/week	≥ 2x/week
	Interference with normal activity	None		Some limitation		Extremely limited	
	Short-acting beta$_2$-agonist use for symptom control (Prevention for EBI)	≤ 2 days/week		>2 days/week		Several times per day	
	Lung function • FEV_1 predicted or peak flow (Personal best) • FEV_1/FVC	N/A	> 80% > 80%	N/A	60-80% 75-80%	N/A	< 60% < 80%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1x/year		> 2–3x/year	> 2x/year	> 3x/year	≥ 2x/year
	Reduce in lung growth	N/A	Requires long-term follow-ups	N/A		N/A	
	Treatment related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.					
Recommended action for treatment (see "Stepwise Approach for Managing Asthma" for treated steps) The stepwise approach is meant to assist, not replace the clinical decision making required to meet individual patient needs.		• Maintain current step • Regular follow-up every 1–6 months • Consider step down if well controlled for at least 3 months.		Step up 1 step	Step up at least 1 step	• Consider short course of oral systemic corticosteroids • Step up 1–2 steps.	
				• Before step up: Review adherence to medication, inhaler technique and environmental control. If alternative treatment was used, discontinue It and use preferred treatment for that step. • Re-evaluate the level of asthma control in 2–6 months to achieve control, every 1–6 months to maintain control. Children 0–4 years old: if no clear benefit is observed in 4–6 weeks, consider alternative diagnoses or adjusting therapy. Children 5–11 years old: Adjust therapy accordingly. • For side effects, consider alternative treatment options.			

Adapted from EPR 3 guidelines for asthma

Fig. 74.1: Assessing asthma control and adjusting therapy in children


Step up if needed (first check inhaler technique, adherence, environmental, control and comorbid conditions)
Assess Control
Step down if possible (and asthma is well controlled in 3 months)
Step 6
Step 5
Step 4
Step 3
Step 2
Step 1

Children 0–4 Years of Age						
	Intermittent Asthma	Persistent Asthma: Daily Medication Consult with Asthma Specialist if step 3 care or higher is required: consider Consultation at step 2				
Preferred	SABA PRN	Low dose ICS	Medium dose ICS	Medium dose ICS + LABA or montelukast	High dose ICS + LABA or montelukast	High dose ICS + LABA or Montelukast + oral corticosteroids ICS
Alternative		Cromotyn or Montelukast				
	Each step: Patient education and environmental control					
Quick-relief medication	• SABA as needed for symptoms: Intensity of treatment depends on severity of symptoms. • With viral respiratory symptoms: SABA q 4–6 hours up to 24 hours (longer with physician consultation). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations. Caution: Frequent use of SABA may indicate the need to step up treatment. See next for recommendation initiating long-term-control therapy.					

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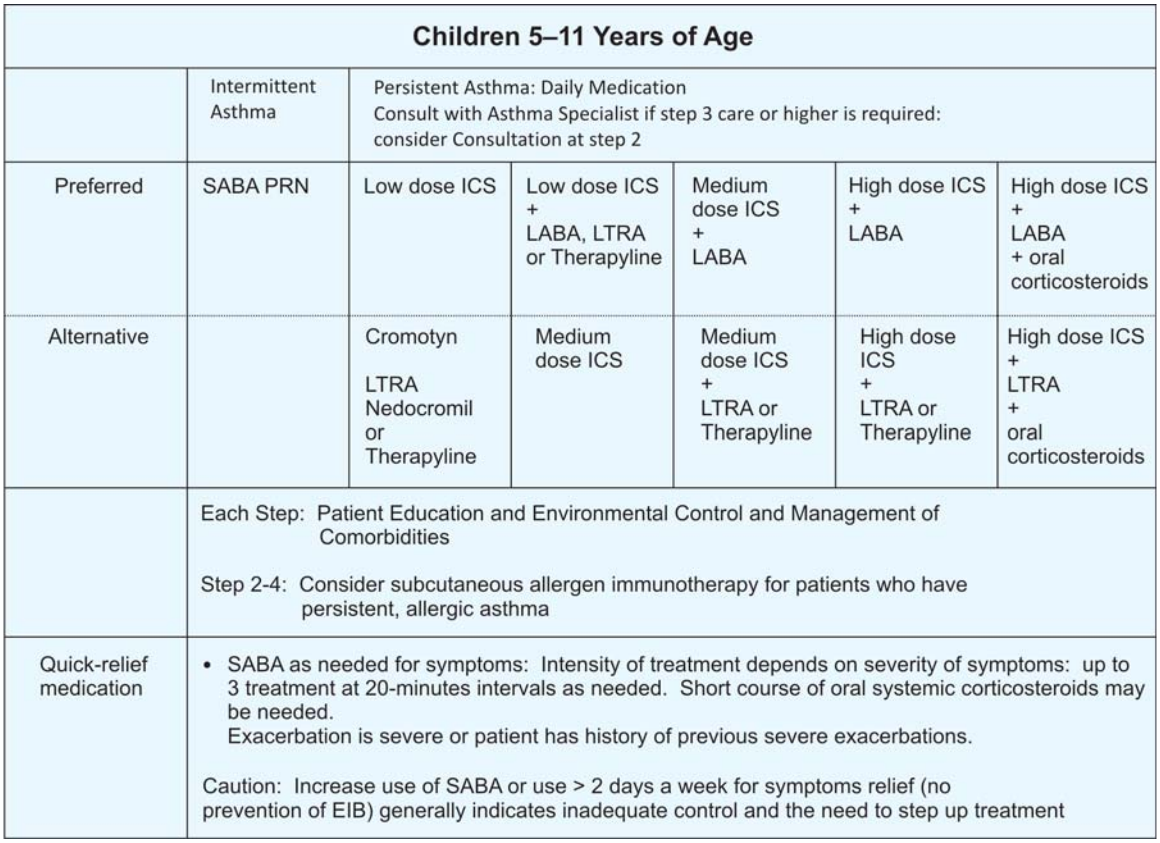

Children 5–11 Years of Age

	Intermittent Asthma	Persistent Asthma: Daily Medication Consult with Asthma Specialist if step 3 care or higher is required: consider Consultation at step 2				
Preferred	SABA PRN	Low dose ICS	Low dose ICS + LABA, LTRA or Therapyline	Medium dose ICS + LABA	High dose ICS + LABA	High dose ICS + LABA + oral corticosteroids
Alternative		Cromotyn LTRA Nedocromil or Therapyline	Medium dose ICS	Medium dose ICS + LTRA or Therapyline	High dose ICS + LTRA or Therapyline	High dose ICS + LTRA + oral corticosteroids
	Each Step: Patient Education and Environmental Control and Management of Comorbidities Step 2-4: Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma					
Quick-relief medication	• SABA as needed for symptoms: Intensity of treatment depends on severity of symptoms: up to 3 treatment at 20-minutes intervals as needed. Short course of oral systemic corticosteroids may be needed. Exacerbation is severe or patient has history of previous severe exacerbations. Caution: Increase use of SABA or use > 2 days a week for symptoms relief (no prevention of EIB) generally indicates inadequate control and the need to step up treatment					

Fig. 74.2: Step-wise approach for managing asthma in children, 0–4 years and 5–11 years of age

Management

Goal of Therapy: Control of Asthma

a. *Reduce impairment*

- Prevent chronic and troublesome symptoms (e.g. coughing or breathlessness in the daytime, in the night, or after exertion)
- Require infrequent use (≤ 2 days a week) of inhaled Short-Acting Beta Agonists (SABA) for quick relief of symptoms [not including prevention of Exercise-Induced Bronchospasm (EIB)]
- Maintain (near) normal pulmonary function
- Maintain normal activity levels (including exercise and other physical activity and attendance at school or work)
- Meet patients' and families' expectations of and satisfaction with asthma care.

b. *Reduce risk*

- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
- Prevent loss of lung function; for children, prevent reduced lung growth
- Provide optimal pharmacotherapy with minimal or no adverse effects of therapy.

Achieving and Maintaining Asthma Control Requires Four Components of Care

1. Assessment and monitoring.
2. Education for a partnership in care.
3. Control of environmental factors and comorbid conditions.
4. Medications.

A step-wise approach to asthma management incorporates these four components, emphasizing that pharmacologic therapy is initiated based on asthma severity and adjusted (stepped up or down) based on the level of asthma control. Special considerations of therapeutic options within the stepwise approach may be necessary for situations such as Exercise-Induced Bronchospasm (EIB), surgery and others. This approach is used for assessing a patient's overall asthma severity, once the most optimal asthma control is achieved and maintained, or for population-based evaluations.

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Allergic Bronchopulmonary Aspergillosis

Ritesh Agarwal

INTRODUCTION

Allergic Bronchopulmonary Aspergillosis (ABPA) is a complex immunological pulmonary disorder caused by hypersensitivity to *Aspergillus* species mainly *Aspergillus fumigatus*, with resultant systemic immune activation, chronic asthma, recurrent pulmonary infiltrates and bronchiectasis.[1,2] Allergic aspergillosis primarily complicates the course of patients with bronchial asthma and Cystic Fibrosis (CF).[3] The disease remains underdiagnosed in many countries, and as many as one-third of all cases are initially misdiagnosed as pulmonary tuberculosis in the developing countries.[4-7] The condition has immunologic features of immediate hypersensitivity (type I), antigen-antibody complexes (type III), and eosinophil-rich inflammatory cell responses (type IVb), based on the revised Gell and Coombs classification of immunologic hypersensitivity.[8, 9] The disorder was first described by Hinson in 1952 in the United Kingdom,[10] in 1957 in Australia[11] and in 1958 in the United States.[12] From India, the first case was described in 1971.[13] The disease presents with varied clinical and radiological manifestations ranging from an asymptomatic patient with or without pulmonary infiltrates to severe uncontrolled asthma with or without Central Bronchiectasis (CB) and pulmonary fibrosis.[14-21] A lung biopsy is generally not required, and the diagnosis can often be made on clinical, radiologic and serologic grounds. An early diagnosis is not difficult in the presence of an increased clinical suspicion. However, there are reports of mean diagnostic latency of as long as 10 years between the occurrence of first symptoms and the diagnosis.[22] In the past two decades, there has been an increase in the number of cases possibly due to the heightened physician awareness and the availability of serologic assays for the diagnosis of ABPA.[4-6,23,24] This chapter summarizes the current concepts in the pathogenesis, diagnosis and management of this complex entity.

Characterization of Aspergillus Species

Aspergillus was first catalogued in 1729 by the Italian priest and biologist Pietro Antonio Micheli and the species *Aspergillus fumigatus* was described in 1863 by Johann Baptist Georg Wolfgang Fresenius. There are approximately 250 species of *Aspergillus*, but only a few are known to be pathogenic for humans.[25] *A. fumigatus*, *A. flavus*, and *A. niger* are the most commonly encountered pathogenic species.[26] It is of interest to note that only pathogenic species (for example, *A. fumigatus*, *A. flavus* and others) can grow at body temperature. *Aspergillus* is a ubiquitous mold found in organic debris, dust, compost, foods, spices and rotted plants. It is also one of the most common indoor molds especially in the attics and basements, bedding, curtains, floor mats and house dust. Worldwide surveys have found that *Aspergillus* species represent between 0.1% and 22% of the total air spores sampled.[27] *Aspergillus* species are thermotolerant and capable of growing at a wide range of temperatures. These fungi can be cultured using Sabouraud's agar medium at 37°C in contrast to many other fungi whose growth is inhibited beyond 35º Celsius. The spores of *A. fumigatus* (2 to 3.5 µm in size) are in the respirable range, and can thus easily enter the airways. In susceptible persons, spores germinate into hyphae, which colonize the bronchi. *Aspergillus* is recognized by its filamentous, septate hyphae appearance of approximately 3 to 7 µm wide with Y-shaped branching in tissue preparations.

The clinical, radiological and histological manifestations of bronchopulmonary aspergillosis are due to a complex interplay between the number and virulence of the organisms and the patient's immune response.[28] Depending on the host immunity and the organism virulence, *Aspergillus* can cause a variety of respiratory diseases, which include simple colonization, aspergilloma, hypersensitivity pneumonitis, Immunoglobulin E (IgE)-dependent asthma, severe asthma with fungal sensitization, ABPA, chronic necrotizing pulmonary aspergillosis, invasive airway aspergillosis and invasive pulmonary aspergillosis.[29-31] ABPA is currently the best recognized manifestation of *Aspergillus*-associated hypersensitivity disorders. An ABPA-like syndrome can also be caused by numerous fungi other than *A. fumigatus*, and is known as Allergic Bronchopulmonary Mycosis (ABPM).[32]

EPIDEMIOLOGY OF ABPA

Aspergillus hypersensitivity (AH) is defined as the presence of an immediate-type cutaneous hypersensitivity to commercial (or an indigenously prepared) extracts of *Aspergillus* or an increase in *Aspergillus*-specific IgE levels.[33] ABPA can be conceptualized as an exaggerated form of AH, and AH is currently considered as the first step in the development of ABPA.[34] However, only a small proportion of patients with AH develop the complete clinical picture of ABPA.[5-7,34] Despite the numerous published case series on ABPA, the exact prevalence of AH and/or ABPA in patients with bronchial asthma remains unknown.[35] The prevalence of AH is difficult to ascertain due to the variability of the skin tests (intracutaneous vs prick tests), the diverse antigens (commercial vs locally prepared) used for the performance of these skin tests, the lack of standardized diagnostic criteria and the absence of optimum disease-specific cut-off values for various serological tests that are used. The incidence of AH is not clear because of the lack of population-based data for this purpose. The population prevalence of ABPA is generally stated to be about 1 to 2% in patients with bronchial asthma and 2 to 15% in patients with CF.[2,21,36,37] The population prevalence of ABPA in asthma is based on the inference of three studies (one peer-reviewed and two non-peer reviewed studies), and may not be entirely correct.[38,39] In the only peer-reviewed study, 14 patients with allergic bronchopulmonary mycosis were identified from a total of 1,390 new referrals in a catchment area population of around half a million, estimating a period prevalence of just above 1%.[38] In a questionnaire-based study carried out in 2.4 million people (Orange County, California), there were 143 cases of ABPA under the care of pulmonary and allergy specialists.[39] In another analysis conducted in 1991, the ABPA Committee of the American Academy of Allergy, Asthma and Immunology (AAAAI) performed a survey among the members of academy to find the number of ABPA cases under their treatment. Of the 33% respondents, it was observed that 703 patients with ABPA were under current care, and other physicians shared 49% of them. If the same case rate is assumed amongst non-respondents, then this figure might increase to 2,000. Both the above surveys from the United States projected the maximum number of ABPA patients as around 11,000, which in 1991 (in the 260 million US population), represented 1% of the estimated 12 million asthma patients in the United States.

The prevalence of ABPA in patients with asthma is likely to be much higher than currently believed. In a recently published systematic review, we demonstrated a pooled prevalence of AH and ABPA of 28% (95% CI, 24 to 34) and 12.9% (95% CI, 7.9 to 18.9) respectively.[35] The only limitation of this analysis was that all studies were performed in specialized chest or asthma clinics, which represent a selection bias as only the most symptomatic patients are likely to reach these clinics, and thus does not represent the population prevalence of ABPA. The prevalence of ABPA in bronchial asthma reported in six large studies in the last decade is summarized in Table 75.1.[6,7,40-43] The prevalence of AH and ABPA is even higher in patients with severe acute asthma. In a recent study of 57 patients with severe acute asthma admitted to a respiratory intensive care unit, we found the prevalence of AH and ABPA of around 51% and 39% respectively compared to the outpatient bronchial asthma prevalence of 39% and 21% respectively.[44]

TABLE 75.1: Studies describing the prevalence of *Aspergillus* hypersensitivity and/or allergic bronchopulmonary aspergillosis in patients with bronchial asthma over the last decade

Study	*Type of study*	*Type of skin test*	*Type of antigen*	*Criteria used for diagnosis of ABPA*	*Prevalence of AH in asthma (n/N)*	*Prevalence of ABPA in asthma (n/N)*
Eaton et al[40]	Prospective	Prick	Commercial (Hollister-Stier)	Major (A/R/T/E/P/I/C/S)	47/255	9/35
Kumar et al[41]	Prospective	Intradermal	Locally prepared	Major (A/R/T/E/P/I/C/S) Minor (C/S/B)	47/200	32/200
Maurya et al[42]	Prospective	Intradermal	Locally prepared	Major (A/R/T/E/P/I/C/S) Minor (C/S)	30/105	8/105
Agarwal et al[6]	Prospective	Intradermal	Commercial (Hollister-Stier)	Major (A/R/T/E/P/I/C/S) Minor (S/B)	291/755	155/755
Prasad et al[43]	Prospective	Intradermal	Not available	Major (A/R/T/E/P/I/C/S) Minor (C/S/B)	74/244	18/244
Agarwal et al[7]	Prospective	Intradermal	Locally prepared	Major (A/R/T/E/P/I/C/S)	87/242	54/242

Criteria for ABPA-Major (A-asthma, R-radiologic opacities, T-immediate positive skin test, E-eosinophilia, P-precipitins to *A. fumigatus*, I-IgE elevated, C-central bronchiectasis, S-specific IgG/IgE to *A. fumigatus*); Minor (C-sputum cultures of *A. fumigatus*, S-type III skin test positivity, B-brownish black mucus plugs)

PATHOGENESIS OF ABPA

The reason why only a minority of asthmatics develop ABPA is not fully understood.[3] In healthy individuals, *Aspergillus* is rapidly cleared by alveolar macrophages utilizing oxidase-dependent killing mechanisms.[45] Exposure to high concentrations of *A. fumigatus* spores from garbage dump sites, agricultural conditions, bird droppings and smoking moldy marijuana have been reported to cause ABPA.[10,46-49] Environmental factors are however, currently not considered to be the main pathogenetic factors in causation of ABPA because not all asthmatics develop ABPA despite being exposed to the same environment. It is likely that on a background of genetic susceptibility,[50-62] (Table 75.2), inhaled conidia of *A. fumigatus* and occasionally other fungi are able to germinate, leading to the growth of hyphae in mucus plugs. The fungi release antigens and exoproteases that compromise mucociliary clearance, stimulate and breach the airway epithelial barrier and activate the innate immune system of the lung, including the epithelial and the alveolar production of several inflammatory cytokines.[63-66] This leads to influx of the inflammatory cells, including the neutrophils and the eosinophils with resultant early and late-phase inflammatory reactions.[67,68] The antigens are further processed by the antigen-presenting cells and presented to T-cells. There is activation of both Th1 and Th2 responses, but heavily skewed towards a Th2 CD4+ T-cell response with release of IL-4, IL-5 and IL-13.[50,69-71] The Th2 cytokines lead to total and *A. fumigatus*-specific IgE synthesis, mast cell degranulation and promotion of a strong eosinophilic response. The inflammatory cells (partly contributed by fungal proteases) lead to tissue injury and the characteristic pathology of ABPA. In fact, animal models suggest the necessity of both IgE and IgG anti-*Aspergillus* antibodies in the pathogenesis of the disease.[72,73]

TABLE 75.2: Genetic factors associated with allergic bronchopulmonary aspergillosis

- Presence of HLA DR-2 and absence of HLA-DQ2 sequences[50,52,53]
- Interleukin 10 promoter polymorphisms[57]
- Surfactant protein A gene polymorphisms[56,61]
- CFTR gene mutation[51,54,55]
- Interleukin 15 polymorphisms[60]
- Tumor necrosis factor-α polymorphisms[60]
- Mannose-binding lectins polymorphisms[61]
- Interleukin 4 receptor polymorphisms[59]
- Interleukin 13 polymorphisms[58]
- Toll-like receptor gene polymorphisms[62]

PATHOLOGY OF ABPA

The pathology of ABPA varies from patient-to-patient (Table 75.3) and is different in different areas of the lung in the same patient.[74] Although the clinical picture of ABPA is well documented, detailed information is not available on its pathology, which reflects the fact that the diagnosis is primarily based on the serology and only a minority of patients requires lung biopsy. The finding of proximal bronchiectasis, i.e. the involvement of segmental and subsegmental bronchi with sparing of the distal branches is typical of ABPA.[75] The bronchi are filled with thick tenacious mucus plugs of dense

TABLE 75.3: Pathologic findings encountered in allergic bronchopulmonary aspergillosis

- Bronchiectasis involving segmental and subsegmental bronchi with sparing of distal bronchi
- Eosinophilic pneumonia
- Eosinophilic bronchitis
- Granulomatous bronchiolitis or bronchocentric granulomatosis
- Bronchiolitis obliterans with organizing pneumonia
- Localized tissue invasion by *A. fumigatus* without vascular invasion

eosinophilic material with many cells and granular debris. Histopathological examination reveals the presence of mucus, fibrin, Curschmann's spirals, Charcot-Leyden crystals and inflammatory cells. Scanty hyphae can often be demonstrated by in the bronchiectatic cavities. The bronchial wall in ABPA is usually infiltrated by inflammatory cells, primarily the eosinophils.[75] The peribronchial parenchyma contains a mixed chronic inflammatory response, often with conspicuous eosinophilia. Recurrent or transient parenchymal opacities are generally the result of an eosinophilic pneumonia. Occasionally, fungal growth in the lung parenchyma can occur in some patients with ABPA.[76] Patients can also demonstrate a pattern similar to that of bronchiolitis obliterans with organizing pneumonia.[77] A prominent feature is the presence of noncaseating granulomatous inflammation containing eosinophils and multinucleated giant cells centered on the airways, referred to as bronchocentric granulomatosis.[78,79] Fungal hyphae may be identified in the centers of some granulomas in the peribronchial tissue. The pathologic appearance is quite distinct from that of necrotizing pneumonia with vascular invasion described in patients with invasive aspergillosis. In patients with ABPA and localized tissue invasion, the host response seems to be able to limit the growth of the fungus and severe tissue destruction does not occur. Rarely, cases of invasive aspergillosis complicating the course of ABPA have been described in the literature.[80-85]

Clinical Features

Most patients are diagnosed in the third to fourth decades, and there is no gender predilection.[86] Although the initial descriptions involved mainly adults, an increasing awareness of the disorder by both the pulmonary and the nonpulmonary physicians has led to recognition of the disease in infancy[87] and early childhood.[88] The clinical features of ABPA encountered in three large series[4,6,7] published from the author's institute are summarized in Table 75.4. Patients are generally symptomatic with low-grade fever, wheezing, bronchial hyperreactivity, hemoptysis or productive cough. One clinical clue to the diagnosis of ABPA is the presence of asthma, which is poorly controlled with drugs.[89, 90] Patients can also present with the episodes of systemic illness with fever, weight loss and malaise. Expectoration of brownish black mucus plugs believed to a characteristic symptom is seen in 31 to 69% of patients.[4,6,41] The symptoms of hemoptysis and expectoration of brownish-black mucus plugs and a history of pulmonary opacities in an asthmatic strongly points towards the diagnosis of ABPA. However,

TABLE 75.4: Clinical features encountered in three large case series of allergic bronchopulmonary aspergillosis published from the author's institute

	Chakrabarti et al[4]	*Agarwal et al*[6]	*Agarwal et al*[7]
Number of patients	89	155	54
Male:Female	53:35	79:76	29:25
Mean age (years)	36.4	33.4	34.3
Mean duration of asthma (years)	12.1	8.9	10.9
History of asthma	90%	100%	100%
Expectoration of sputum plugs	69%	46.5%	27.8%
Mean eosinophil count (per µL)	–	1264	1146
AEC more than 500/µL (%)	100%	76%	74%
Fleeting shadows	74%	40%	35%
History of intake of antituberculous drugs	29%	45%	33%
Skin test against *Aspergillus*			
Type 1	85%	100%	100%
Type 3	16.9%	83.2%	70.4%
Mean IgE levels (mean)	Not done	6,434	7,829
Elevated *Aspergillus*-specific IgE/IgG	Not done	100%	100%
Serum precipitins against *Aspergillus*	71.9%	86.5%	78%
Central bronchiectasis	69%	76%	82%

patients with ABPA can often be asymptomatic and the disorder is diagnosed on routine screening of apparently well controlled asthmatics.[5,6,40] In a series of 155 cases of ABPA, almost 19% of patients with ABPA had well controlled asthma, and ABPA should be suspected in all asthmatics whatever the severity.[5,6] There are no characteristic findings on physical examination. Physical examination can be normal or may reveal findings of polyphonic wheeze. Clubbing is seen in only 16% of patients, usually those with long-standing bronchiectasis. On auscultation, coarse crackles can be heard in 15% of patients.[6] Wheeze on physical examination and pulmonary opacities on chest radiograph may suggest ABPA. Physical examination also detects complications of ABPA such as pulmonary hypertension and/or respiratory failure. During exacerbations of ABPA, localized findings of consolidation (localized crackles, bronchial breath sounds) and atelectasis (diminished breath sounds) can occur and needs to be differentiated from other pulmonary diseases. Clinically, it is often difficult to differentiate these conditions based on clinical assessment alone. In these settings, serological investigations are of great value in differential diagnosis.

Laboratory Findings

Aspergillus skin test: An immediate cutaneous hypersensitivity to *A. fumigatus* antigens is a hallmark of ABPA. The test can be performed using either a Skin Prick Test (SPT) or by intradermal injection of the antigen. A positive reaction is characterized by the development of a wheal and erythema within one minute, which reaches a maximum after 10 to 20 minutes, and resolves within 1 to 2 hours. A positive test result is found in virtually all patients with ABPA. However, almost 40% of asthmatic patients without ABPA can also demonstrate immediate skin reactivity to *Aspergillus* antigen.[91] Although theoretically both the intradermal and SPTs should perform in a similar manner, it has been shown that intradermal tests are generally more sensitive than SPTs.[92,93] The higher prevalence of AH with intradermal testing compared to prick test has been previously described in patients with ABPA.[92] In a meta-analysis we had observed that the prevalence of AH in bronchial asthma was higher with an intradermal test versus SPT (28.7% vs 24.8%). The intradermal test is also believed to be associated with a higher complication rate than SPT. However, in our experience of more than 5,000 intradermal tests, we have not encountered any complication.[4-7,23,44,94] Thus, if technically feasible, a prick test should be performed for *Aspergillus* skin testing, and if the prick test is negative it should be confirmed by an intradermal test.

Total serum IgE levels: The total IgE level is the most useful test for diagnosis and follow-up of ABPA. A normal serum IgE level excludes ABPA as the cause of patient's current symptoms, if the patient is not taking glucocorticoids. There is a controversy on what should be the cut-off value of IgE level that should be used for the diagnosis of ABPA. One Kilo Unit (KU) of IgE per liter is equivalent to one IU per milliliter and in turn is equal to 2.42 nanograms per milliliter.[95,96] Most studies have used a cut-off value of 1000 International Units (IUs) per milliliter,[5,6,16,17,97-100] but some authors use a cut-off value of 500 IU per milliliter.[2,37,40,41] We believe that a cut-off of 500 IU per milliliter will lead to overdiagnosis of ABPA as these levels are often seen in patients with AH without ABPA. As this will lead to unwarranted steroid therapy, hence we use a cut-off value of 1000 IU per milliliter. After treatment with glucocorticoids, the serum IgE level starts declining, but in most patients the level does not reach normal value. A 25 to 35% decline in IgE levels is taken as criteria for remission.[7,101] Repeated measurements of IgE levels need to be performed to determine the "new" baseline value for an individual patient during remission. The serum IgE also represents an important clinical tool in the follow-up of patients. A doubling of the patient's baseline IgE level signifies relapse of the disease.

Serum IgE and IgG antibodies specific to A. fumigatus: An elevated level of specific antibodies to *A. fumigatus* is considered the hallmark of disease and is measured by fluorescent enzyme immunoassay tests.[5] A cut-off value of IgG/IgE more than twice the pooled serum samples from patients with *Aspergillus*-hypersensitive asthma can help in the diagnosis of ABPA from patients with asthma and AH.[97] We currently use a cut-off of 0.35 kUA per liter of *A. fumigatus* specific IgE for the diagnosis of ABPA [the mean plus two standard deviation values of *A. fumigatus* specific IgE level of 25 patients with AH and asthma was found to be 0.245 kUA per liter using the fluorescent enzyme immunoassay (UniCAP Systems; Pharmacia and Upjohn Diagnostics; Stockholm, Sweden).]

Radiological investigations: A wide spectrum of radiographic abnormalities is encountered in ABPA (Table 75.5). The chest radiographic findings of ABPA include transient or fixed pulmonary opacities, which are often described as consolidation (Fig. 75.1).[102,103] Other findings include the presence of tramline shadows, finger-in-glove opacities and toothpaste shadows.[103-105] All these findings are due to mucus impaction of the bronchiectatic cavities.[106] On follow-up of these patients, there can be fibrosis and collapse mainly affecting the upper lobes[106] although there are no unique

TABLE 75.5: Radiologic findings (in order of frequency) encountered in patients with allergic bronchopulmonary aspergillosis

Chest radiographic findings

Patchy areas of consolidation, radiologic infiltrates – "toothpaste" and "gloved finger" shadows due to mucoid impaction in dilated bronchi, collapse - lobar or segmental, parallel-line shadows representing bronchial widening, ring-shadows representing dilated bronchi en face, fibrotic scarred upper lobes with cavitation, bronchial wall thickening – "tramline" shadows, air-fluid levels from dilated central bronchi filled with fluid, perihilar infiltrates simulating adenopathy, massive consolidation—unilateral or bilateral, small nodules, pleural effusions, pleural thickening.

High-resolution computed tomographic findings

Central bronchiectasis, mucus plugging with bronchoceles, consolidation, centrilobular nodules with tree-in-bud opacities, bronchial wall thickening, areas of atelectasis, mosaic perfusion with air-trapping on expiration, high-attenuation mucus (finding most helpful in differential diagnosis), pleural involvement, randomly scattered nodular opacities.

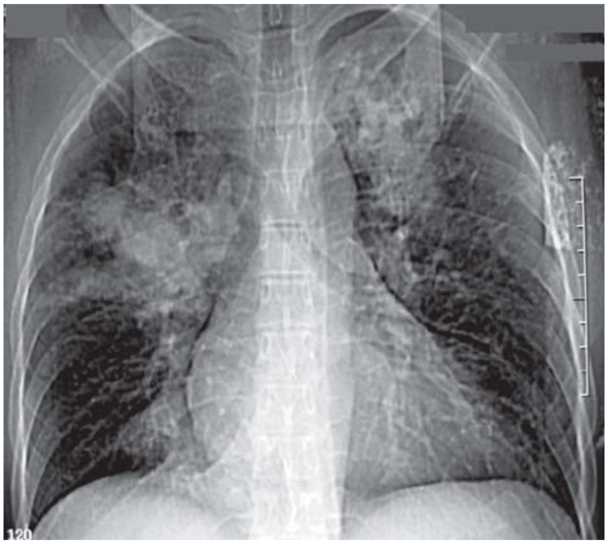

Fig. 75.1: Chest radiograph showing multifocal areas of consolidation

roentgenographic findings to define a particular stage.[107] Central bronchiectasis with peripheral tapering of bronchi is believed to be a sine qua non for the diagnosis of ABPA.[108] However, almost 40% of the bronchiectatic segments also have associated peripheral bronchiectasis.[5] Patients with ABPA who have CB are classified as ABPA-CB and those who meet all other criteria, but do not have central bronchiectasis are labeled as serologic ABPA (ABPA-S). The prevalence of CB in ABPA ranges from 69 to 76% in different studies (Table 75.4). High Resolution Computed Tomography (HRCT) has replaced bronchography as the imaging modality of choice for the diagnosis of bronchiectasis.[109] Findings on HRCT include the presence of central bronchiectasis, mucoid impaction, mosaic attenuation, presence of centrilobular nodules and tree-in-bud opacities (Fig. 75.2).[110,111] Mucoid impaction in ABPA can be of normal density or high density.[6] High-attenuation mucoid impaction, which is mucus visually denser than the paraspinal skeletal muscle, is a pathognomonic finding encountered in patients with ABPA (Fig. 75.3).[6,112-118] Although minimal bronchiectasis can be seen on HRCT in patients with bronchial asthma,[119,120] the findings of bronchiectasis affecting three or more lobes, centrilobular nodules and mucoid impaction are findings that are highly suggestive of ABPA.[121] The uncommon radiologic manifestations include miliary nodular opacities,[122] perihilar opacities simulating hilar lymphadenopathy,[88,103,123] pleural effusions,[124-126] pulmonary masses[127-132] and whole lung collapse.[133]

Serum precipitins against A. fumigatus: The precipitating IgG antibodies are elicited from crude extracts of *A. fumigatus* and other fungi and can be demonstrated using Ouchterlony double gel diffusion techniques of Longbottom and Pepys.[134] Present in almost 85% of the patients with ABPA, they probably indicate the continued growth of fungus in bronchi or body tissues.[135] These precipitins are however not specific as they are also present in 1 to 10% of normal subjects, hospitalized patients and other pulmonary disorders; and thus represent supportive, not diagnostic evidence for ABPA.[134-136]

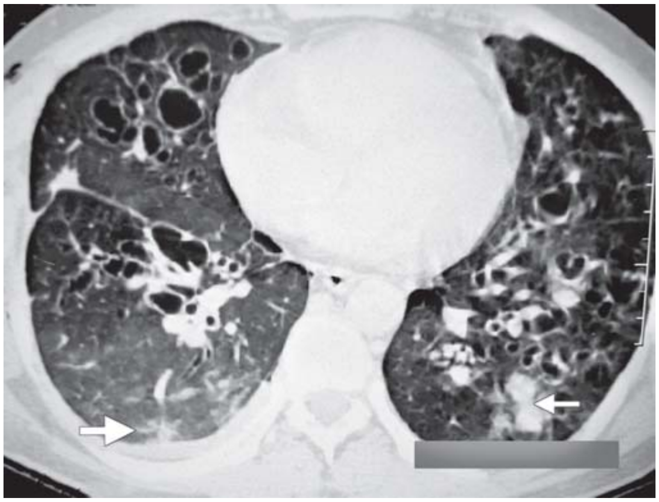

Fig. 75.2: High resolution computed tomographic image of a patient with allergic bronchopulmonary aspergillosis showing bilateral central bronchiectasis with centrilobular nodules (bold arrow) and mucus plugging (thin arrow)

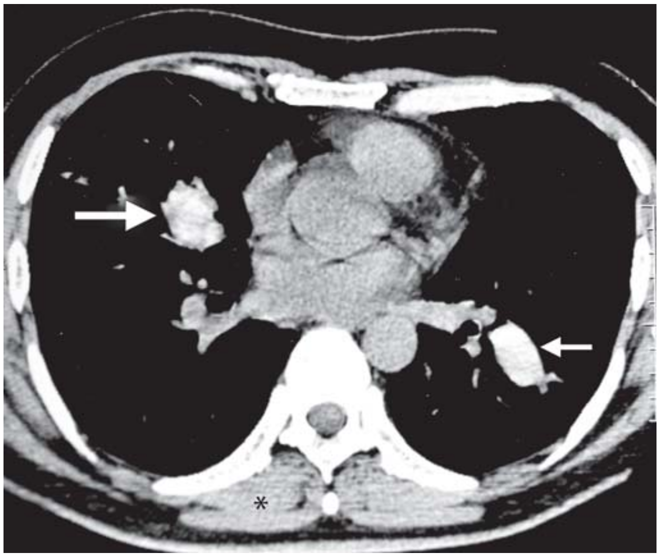

Fig. 75.3: Computed tomographic image of high-attenuation mucoid impaction (bold arrows). The mucoid impaction is visually denser than the paraspinal skeletal muscle (asterisk)

Peripheral eosinophilia: A blood absolute eosinophil count greater than 1000 cells per microliter is also taken as a major criterion for the diagnosis of ABPA. However, 53% of patients in one series[5] had an absolute eosinophil count less than 1000 cells per microliter and thus a low eosinophil count does not exclude the diagnosis of ABPA.

Sputum cultures for A. fumigatus: Culture of *A. fumigatus* in the sputum is supportive, but not diagnostic of ABPA. The fungus can also be grown in patients with other pulmonary diseases due to ubiquitous nature of the fungi. We do not perform sputum cultures for the diagnosis of ABPA.

Pulmonary function tests: These tests have no diagnostic value in ABPA, but help in categorizing the severity of asthma and/or the underlying lung disease. Bronchial challenge with *Aspergillus* antigens have been used in the past, but are not recommended as they can lead to acute bronchospasm, which can be fatal.[137] The pulmonary function tests generally show obstructive physiology with varying severity and reduction in diffusion capacity.[89,90,138] Pulmonary function tests can be normal in ABPA, and need not constitute the basis for screening.[5] Hence, it is recommended that all patients with bronchial asthma should be screened routinely for ABPA whatever the clinical severity or the lung function in physiological laboratories.[2,19,21,37,135-137,139-150]

Role of specific aspergillus antigens: Patients with ABPA are mostly evaluated with crude extracts from *Aspergillus.* These antigens lack reproducibility and consistency and frequently cross react with other antigens.[151] Advances in molecular techniques have enabled detection of almost 20 specific *Aspergillus* antigens with diverse biochemical nature and function. In fact, a number of allergens from *A. fumigatus* have been cloned. A number of these antigens have also been evaluated for the diagnosis of ABPA both in patients with asthma and cystic fibrosis. The recombinant allergens Asp f1, Asp f2, Asp f3, Asp f4 and Asp f6 have been evaluated for their diagnostic performance in serological studies in asthmatic patients[152-155] and in patients with CF.[154,156-158] Preliminary data suggest a promising role of these antigens in the diagnosis of ABPA. Further studies are required before they can be implemented in routine clinical practice.

Diagnosis and Diagnostic Criteria

The Rosenberg-Patterson criteria are most often used for the diagnosis (Table 75.6). The criteria continue to be challenged and modified.[3] The presence of six out of eight major Rosenberg criteria makes the diagnosis almost certain. There are also a set of minimal diagnostic criteria for ABPA using which the diagnosis of ABPA may be secured, possibly at an earlier stage.[40,159] The differentiation of patients with ABPA from patients with AH can also be problematic. Serum precipitins to *A. fumigatus* is present in 69 to 90% of patients with ABPA,[6,89,134,160,161] but also in 9% of asthmatics.[134] Central bronchiectasis can be seen in patients with asthma without ABPA.[119-121] The total IgE levels are elevated in the sera in all patients with ABPA, and reflect disease activity,[162,163] however, a moderate rise in IgE levels is also noted in patients with asthma without ABPA.[164] The use of IgE and IgG levels specific to *A. fumigatus* can help in diagnosis as they are significantly raised only in patients with ABPA when compared to asthmatic patients. In fact, values of IgG/IgE more than twice the pooled serum samples from patients with asthma who have AH can greatly help in diagnosis of ABPA.[135,165] We have recently proposed new criteria to simplify the diagnosis of ABPA (Table 75.6).

While investigating a patient with asthma, we first perform an *Aspergillus* skin test. Once it is positive, the total serum IgE levels are done. If the value is more than 1000 IU per milliliter, we perform the other tests, which include a HRCT of the chest, IgE and IgG specific to *A. fumigatus*, absolute eosinophil count and serum

TABLE 75.6: Criteria used for the diagnosis of allergic bronchopulmonary aspergillosis

Rosenberg-Patterson criteria[14,17]

Major criteria

- Bronchial asthma
- Immediate cutaneous hyperreactivity to *Aspergillus* antigen
- Elevated serum IgE levels (>1000 IU/mL)
- Elevated levels of *A. fumigatus*-specific IgG and/or IgE in serum
- Central bronchiectasis
- Fleeting pulmonary opacities on chest radiograph
- Peripheral eosinophilia (>1000/μL)
- Elevated serum precipitins against *Aspergillus*
- Precipitating antibodies (IgG) in serum

Minor criteria

- Expectoration of brownish-black mucus plugs
- Delayed cutaneous hypersensitivity to *Aspergillus* antigen
- Presence of *Aspergillus* in sputum
- The presence of six out eight major criteria makes the diagnosis almost certain. The disease is further classified as ABPA-S or ABPA- CB on the absence or presence of CB respectively

Agarwal criteria for allergic bronchopulmonary aspergillosis[94]

Predisposing conditions

- Bronchial asthma
- Cystic fibrosis
- Chronic obstructive pulmonary disease
- Others (hyper-IgE syndrome, chronic granulomatous disease, Kartagener's syndrome)

Obligatory criteria

- Elevated total IgE levels (more than 1000 IU per milliliter)
- Elevated IgE and/or IgG levels against *A. fumigatus*

Other criteria (at least three of five)

- Immediate cutaneous hypersensitivity to *Aspergillus* antigen
- Presence of serum precipitating antibodies against *A. fumigatus*
- Radiographic pulmonary opacities (fixed/transient)
- Absolute eosinophil count more than 1000 cells per microliter
- Central bronchiectasis on HRCT

precipitins to *A. fumigatus*. If the value is between 500 and 1000 IU per milliliter, the next step is analysis of *A. fumigatus* specific IgE and IgG antibodies. If the levels are raised, the patient is followed every six weeks with total IgE levels. If the absolute value rises above 1000 IU per milliliter or there is a rising trend with clinical/ radiologic deterioration, the treatment is started. If the value is between 500 and 1000 IU per milliliter and IgE and IgG specific to A. fumigatus are not raised, the patient is followed up with a yearly total IgE levels.[94]

Natural History

The natural history of ABPA is currently not well characterized and is often difficult to predict because spontaneous improvement of symptoms and pulmonary opacities characterize an important aspect of the disease.[17,98,166-169] ABPA is most often a non-acute respiratory syndrome that lingers on for years without diagnosis. Rarely, the condition presents in an acute fashion.[133, 170, 171] However, if the disease is not recognized, the chronic inflammatory process can progress inexorably and result in irreversible pulmonary dysfunction due to bronchiectasis and/or pulmonary fibrosis, and ultimately respiratory failure and cor pulmonale.[20] Thus, an early diagnosis and initiation of systemic corticosteroids are essential for the treatment of ABPA to prevent bronchiectasis and/or pulmonary fibrosis.[172] The natural history of ABPA is characterized by recurrent episodes of remissions and relapses. It can be best understood if we understand the clinical and radiological classification schemes of ABPA (Table 75.7).

Clinical staging of ABPA: Although ABPA has been classified into five stages a patient does not necessarily progress from one stage to the other in a sequential fashion (Table 75.7). Patients who present with acute to subacute symptoms are generally in **stage I or III** depending on whether or not the disorder has been previously diagnosed. The patient usually presents with radiographic infiltrates, elevated IgE (generally between 5500-7500 IU per milliliter) and *A. fumigatus*-specific IgG/ IgE levels.[6] There is clearing of radiographic opacities in most patients with 25 to 40% decline in IgE levels by six weeks after the institution of glucocorticoids.[7] By the end of three months almost all patients show at least 50% decline in the total IgE levels and the patient is said to be in remission or in **stage II**. Almost 50% of the patients have relapse/exacerbation of the disease (**stage III**), which is defined as doubling of the baseline IgE levels usually with worsening of patient's symptoms or the appearance of radiologic infiltrates.[5,16,17] If the patient does not have any additional ABPA exacerbations over the next three months after stopping therapy, we give an additional label of "complete remission." Patients who are in complete remission are followed up by measuring IgE levels every six months for the first year and then annually, modified depending on the clinical status of the patient. Even in patients who have achieved complete remission, the IgE levels do not return to normal values.[166] This is an important point because the aim of glucocorticoid therapy is not the achievement of normal IgE levels, but a 25 to 50% decline by six weeks to three months.[101] Some patients in stage III may enter into prolonged or even a permanent remission. A complete remission, however, does not imply a permanent remission as exacerbations of the disease have been documented for as long as seven years after remission.[168]

TABLE 75.7: Classification of allergic bronchopulmonary aspergillosis

Clinical classification of ABPA[5,16]	
Patterson stage	
I	Acute phase
II	Remission
III	Exacerbation
IV	Glucocorticoid-dependent ABPA
V	End-stage (Fibrotic) ABPA
Radiologic classification of ABPA[20,174]	
Greenberger classification	
Seropositive ABPA (ABPA-S)	All the diagnostic features of ABPA, but no evidence of central bronchiectasis on HRCT. Patients with ABPA-S may be classified as Patterson stages I to IV. These patients may have recurrent exacerbations and may also be classified as stage III
ABPA with central bronchiectasis (ABPA-CB)	All findings of ABPA, including CB on HRCT. Patients with ABPA-CB may belong to any of the Patterson stages
Kumar classification	
ABPA-S	ABPA without CB
ABPA-CB	ABPA with CB
ABPA-CB-other radiologic findings (ABPA-CB-ORF)	ABPA with CB other radiologic features, such as pulmonary fibrosis, bleb, bullae, pneumothorax, parenchymal scarring, emphysematous change, multiple cyst, fibrocavitary lesions, aspergilloma, ground-glass appearance, collapse, mediastinal lymph node, pleural effusion and pleural thickening
Agarwal classification (submitted for publication)	
ABPA-S	ABPA without CB
ABPA-CB	ABPA with CB
ABPA-CB-high attenuation mucus (ABPA-CB-HAM)	ABPA with CB and high attenuation mucus

Patients in **stage IV** (glucocorticoid-dependent disease) are of two types. The first group (glucocorticoid-dependent asthma) includes patients who require oral glucocorticoids for the treatment of persistent asthma, but in whom the IgE levels do not vary significantly overtime. In the other group of patients (glucocorticoid-dependent ABPA), the IgE levels rise once the steroids are tapered and continuous glucocorticoid therapy is required for the control of ABPA.[5,18] Patients in **stage V** are those with widespread bronchiectasis and varying degrees of pulmonary dysfunction on lung function tests although there are no specific criteria for the classification of this stage. We currently define patients in stage V only if they have type II respiratory failure and/or cor pulmonale. It is important to remember that the IgE level declines to below 1000 IU per milliliter in only a minority of patients with stages II and V (less than 10 to 15% of stages II and V).[98,166] Even in stage V ABPA, the disease can be clinically as well as immunologically active, and long-term glucocorticoid therapy may be required for the control of asthma and/or ABPA.[169,173]

Radiological classification of ABPA: ABPA is also classified as ABPA-S or ABPA-CB respectively depending on the absence or presence of bronchiectasis (Table 75.7). Patients with ABPA-S probably represent the earliest stage of the disorder. It is also believed that patients with ABPA-S have a milder clinical course and less severe immunologic findings when compared to ABPA-CB.[20,174,175] In the largest of these three studies (76 patients), which was also the first study which suggested that ABPA-S is less severe immunologically, only the *A. fumigatus*-specific IgG levels were higher in patients with ABPA-CB compared to ABPA-S. Other immunologic parameters were not significantly different between the two groups.[20] One author has also classified the disease into three groups; ABPA-S (mild), ABPA-CB (moderate) and ABPA-CB-Other Radiologic Findings (ORFs). However, this was a single study and included only 18 patients.[174] Also, the findings included in the categorization of ABPA-CB-ORF were pulmonary fibrosis, bleb, bullae, pneumothorax, parenchymal scarring, emphysematous change, multiple cyst, fibrocavitary lesions and pleural thickening; which are all changes representing the fibrotic stage of the disease. In ABPA-S there is active ongoing inflammation with progressive immunologic damage, and understandably the immunologic findings will not be very different from those in ABPA-CB. Recently, we have re-evaluated the clinical and serological severity of both these classifications using data from a large set of patients and propose a new classification scheme based on High-Attenuation Mucus (HAM) (unpublished data). The classification scheme by Greenberg et al. showed immunological severity in some parameters (eosinophil count and *A. fumigatus*-specific IgE levels), but not in others (total IgE levels). Moreover, on excluding patients with HAM, the immunological severity was restricted only to eosinophil counts. Interestingly, in the Kumar classification, the immunological markers were most severe in patients with ABPA-CB and not ABPA-CB-ORF. This suggests that ORF does not determine serological severity and probably represents the burnt out phase of the disease. The HAM classification was most consistent with the immunological severity persisting even after removal of patients (Table 75.7). Based on the results of this study, we believe that ABPA should be classified as ABPA-S, ABPA-CB and ABPA-CB-HAM because this classification not only suggests immunological severity, but also predicts patients who are likely to have frequent relapses.

The course of patients with ABPA-S is likely to be less severe when compared to those with ABPA-CB. In two separate multivariate analyses of 155 and 54 patients with ABPA, we demonstrated that the severity of bronchiectasis and presence of hyperattenuating mucoid impaction on HRCT predicted relapses of ABPA and the severity of bronchiectasis was an independent predictor of failure to achieve long-term remission.[6,7] This is an important observation and suggests that an early diagnosis of ABPA is essential because one not only prevents permanent lung damage, but also improves the likelihood of a smoother course of this relapsing-remitting disorder. Thus, it remains prudent to diagnose and treat ABPA early so as to prevent the development of bronchiectasis.

Management

The management of ABPA includes two important aspects: Institution of immunosuppressive therapy, primarily glucocorticoids to control the immunologic activity, and close monitoring for the detection of relapses. Another possible target is to use antifungal agents to attenuate the fungal burden secondary to the fungal colonization in the airways.

TABLE 75.8: Glucocorticoid protocols for the management of ABPA

Regime 1[2]
Prednisolone 0.5 mg/kg/day for one to two weeks, then on alternate days for six to eight weeks. Then taper by 5-10 mg every 2 weeks and discontinue. Repeat total serum IgE levels and chest X-ray every six to eight weeks to determine the baseline IgE concentrations.

Regime 2[5,135]
Prednisolone, 0.75 mg/kg for 6 weeks, 0.5 mg/kg for 6 weeks, then tapered by 5 mg every 6 weeks to continue for a total duration of at least 6 to 12 months. The total IgE levels are repeated every six to eight weeks for one year to determine the baseline IgE concentrations.

Systemic glucocorticoid therapy: Oral corticosteroids are the treatment of choice for ABPA. They not only suppress the immune hyperfunction, but are also anti-inflammatory. However, different regimens of glucocorticoids have been used as there is no robust data to guide the dose and duration of glucocorticoids (Table 75.8). The use of lower doses of glucocorticoids (regime 1 in Table 75.8) is associated with frequent relapses or corticosteroid dependence (45%).[17] We use a higher dosage of glucocorticoids for a longer duration (regime 2 in Table 75.8), and observed a higher remission rates and a lower prevalence of glucocorticoid-dependent ABPA (13.5%).[5] This raises the possibility of a higher dose and prolonged duration of corticosteroid therapy being associated with better outcomes. However, there are no direct comparisons between the two regimens and the selection is a matter of personal preference. Currently, a randomized controlled trial is underway to assess the efficacy of two different glucocorticoid regimens in ABPA.

The clinical effectiveness of steroid therapy is reflected by decrease in the patient's total serum IgE levels (there seems to be no correlation between serum levels of *A. fumigatus*-specific IgE levels and disease activity[176]) along with symptom and radiographic improvements. The goal of therapy is not to attempt normalization of IgE levels, but to decrease the IgE levels by 25 to 50%, which in most cases leads to clinical and radiographic improvement. One should also aim to establish a stable baseline serum level of total IgE, which serves as a guide to future detection of relapse and helps in follow-up of the patient.

Inhaled corticosteroids: Although small case studies suggest some benefit of inhaled corticosteroids in management of ABPA,[177-180] a double blind multicenter placebo controlled trial in 32 patients suggested no superiority over placebo.[181] Currently, there is no role of inhaled corticosteroids in the management of ABPA. We use inhaled corticosteroids only for the control of asthma, once the oral prednisolone dose is reduced to below 10 milligrams per day.

Oral itraconazole: The use of specific antifungal agents in ABPA has the advantage of modifying the immune response by removing/reducing the antigenic stimulus consequent to a decreased fungal burden. Ketoconazole has been tried in the past[182] and has been replaced by the less toxic agent, itraconazole.[100,176,183-195] However, only two randomized controlled studies (84 patients) have evaluated the role of itraconazole in ABPA.[100,191] In one study, 55 patients with "glucocorticoid-dependent" ABPA were randomized to receive either itraconazole 200 milligrams twice a day versus placebo. While the difference between the two groups was significant in the terms of overall response [reduction in the dose of corticosteroid by 50% or more; and decrease in the total IgE concentration by 25% or more; and at least one of the following (increase in exercise tolerance by at least 25%, improvement by 25% in results of the pulmonary function tests, resolution of pulmonary infiltrates)], but failed to reach statistical significance when each of the outcomes were examined separately.[191] The other study included 29 "clinically stable" ABPA patients randomized to receive itraconazole or placebo. Interestingly, majority of the patients did not receive glucocorticoids. There were significant decline in sputum inflammatory markers and serum IgE levels. The study also demonstrated a decrease in the number of exacerbations warranting glucocorticoid usage.[100] Pooled analysis showed that itraconazole could significantly decrease the IgE levels by 25% or more when compared to placebo, but did not cause significant improvement in lung function.[196] A major limitation was that neither of the study reported long-term outcomes in the terms of relapses of ABPA. Thus, long-term trials are required before a firm recommendation can be made for the use of itraconazole as adjunctive treatment for patients with ABPA. We currently use itraconazole only after the first relapse of ABPA despite glucocorticoid therapy or in patients with glucocorticoid-dependent ABPA. In the limited numbers of patients in whom we have used the drug, there was no observable advantage.[5]

Itraconazole also has numerous adverse effects. In a study of 189 patients treated with itraconazole (average, 400 milligrams per day), adverse effects occurred in almost 39% of patients.[197] There are also numerous drug interactions with the use of itraconazole. Most notably it may inhibit the hepatic metabolism of terfenadine, astemizole and cisapride, prolonging the electrocardiographic QT interval thus increasing the risk for cardiac arrhythmia. Caution should also be exercised when treating concomitantly with glucocorticoids. Itraconazole inhibits the metabolism of methylprednisolone (but not prednisolone) and can lead to the increased frequency of side-effects of steroids, including profound adrenal insufficiency.[198]Adrenal suppression has also been reported with the concomitant use of itraconazole and inhaled budesonide.[199,200]

Other Therapies: Numerous other therapies have been tried in ABPA. They can be tried in an individual patient, but should not be used as a routine measure. There is a single patient case report of ABPA treated with inhaled amphotericin and budesonide.[201] Similarly, there are numerous case records on the use of omalizumab for the management of ABPA.[171,202-207] Pulse doses of intravenous methylprednisolone have also been used in the treatment of severe ABPA.[170,171,208,209] Recently, voriconazole has also been tried in the treatment of ABPA.[210-213] We also use methotrexate as steroid-sparing agent in patients with steroid-dependent ABPA or in patients where steroids are absolutely contraindicated, such as cystoid macular edema, which is a potentially sight-threatening condition.

Differential Diagnosis

The diagnosis of the condition rests on clinical suspicion and performance of serological and radiological tests, including HRCT of the chest. Occasionally, the disorder needs to be differentiated from the following conditions: Pulmonary tuberculosis in endemic areas, community-acquired pneumonia (especially acute presentations of ABPA), and other inflammatory pulmonary disorders such as eosinophilic pneumonia, bronchocentric granulomatosis and Churg-Strauss syndrome.

Complications

The complications of ABPA include recurrent asthma exacerbations, and if untreated it leads to the development of bronchiectasis with the occurrence of pulmonary hypertension and type 2 respiratory failure. We have also encountered a patient who has developed secondary amyloidosis due to the bronchiectasis associated with ABPA. In fact, this is the reason why routine screening is recommended in bronchial asthma to prevent the aforementioned complications.

ABPA without Bronchial Asthma

ABPA is most commonly known to complicate the course of pre-existing bronchial asthma. However, ABPA may occasionally develop in an individual without pre-existing bronchial asthma. In a systematic review for the occurrence of ABPA without bronchial asthma, we found 36 cases reported across the globe.[122] Two cases demonstrated bronchodilator reversibility,[214] and one showed airway hyperresponsiveness to methacholine challenge.[215] Majority of the cases demonstrated hypersensitivity to *A. fumigatus*, but three cases showed hypersensitivity to *Helminthosporium*,[214] and one case each to *A. niger*.[216,217] Because of the absence of bronchial asthma, these cases are often mistaken initially for other pulmonary disorders like bronchogenic carcinoma [217-219] or pulmonary tuberculosis.

ABPA in Cystic Fibrosis

The association of ABPA and CF was first reported in 1965 by Mearns et al who reported two cases of ABPA in CF.[220] ABPA is now recognized as a potential complication in patients with CF.[221] The pathogenesis is similar to that of bronchial asthma, and a key element in the immunopathogenesis may be exposure of the bronchial lymphoid tissue to high levels of *Aspergillus* allergens, perhaps because of abnormal mucus properties resulting from the CF transmembrane conductance regulator mutations.[222] Unlike asthma, the recognition of ABPA in CF is difficult as ABPA shares many clinical characteristics with poorly controlled CF lung disease. Presence of wheezing (due to intercurrent infections), transient pulmonary infiltrates, bronchiectasis and mucus plugging are common manifestations of CF-related pulmonary disease with or without ABPA.

Numerous studies have described the prevalence of AH and/or ABPA in patients with CF.[188,223-249] A meta-analysis of these studies suggest the prevalence of AH in CF of 34% (95% CI, 27 to 41) and the prevalence of ABPA of 7.8% (95% CI, 5.8 to 10).[1] There was however, no uniformity in the diagnostic criteria with varying criteria used for the diagnosis of AH and ABPA in different studies. This fact was also reported in a questionnaire-based study, which revealed a considerable variability in the criteria used for the diagnosis of ABPA in CF.[250] Therefore, prospective reporting of cases with uniform criteria would be the only way to reliably identify the true prevalence of ABPA in CF, and it is likely that database surveys may have overestimated the true prevalence. Atopy seems to be an important risk factor for ABPA in CF. In cystic fibrosis, ABPA was seen in 22% of atopic patients and only 2% of nonatopic patients.[188,238,240,245]

Although, a number of patients with CF develop sensitization to *A. fumigatus* with an increase in total and *A. fumigatus*-specific IgE levels; the surprising aspect is that many a patient demonstrate a spontaneous decrease in many immunologic parameters, including IgE levels.[234] Thus, the diagnosis of ABPA in CF should not be based solely on serology and skin test results as patients with CF may demonstrate variable responses to *A. fumigatus* and prolonged testing might be required to make a definite diagnosis (Table 75.9). It is important to identify the development of ABPA in patients with CF as it has been shown that the deterioration of lung function is most strikingly pronounced in patients with ABPA compared with a control group of CF patients not sensitized to *A. fumigatus*.[188,247,251] Also patients with ABPA and CF were demonstrated to have higher rates of microbial colonization, pneumothorax, massive hemoptysis and poorer nutritional status.[242]

The treatment of ABPA in CF is not very different from that of ABPA in bronchial asthma except the fact that there is minimal data to formulate conclusive treatment recommendations for ABPA in CF. The treatment issues are further complicated by the fact that pulmonary exacerbations in a patient with ABPA and CF could be related to ABPA, pulmonary infection, and hence continuous assessment may be required over months with repeat performance of all the serological investigations for ABPA before a decision to treat an individual case is made.[221]

Coexistence of ABPA and Aspergilloma

The serological findings of ABPA has also been reported in patients with aspergilloma[252-262] and chronic necrotizing pulmonary aspergillosis.[263] This ABPA-like syndrome can be true hypersensitivity reaction consequent to the colonization of *Aspergillus* in long-standing pulmonary cavities of pulmonary diseases like tuberculosis or sarcoidosis.[252,253] Probably there is a continuous release of *Aspergillus* antigens, which leads to immunologic activation in a genetically predisposed

TABLE 75.9: Consensus conference proposed diagnostic and screening criteria for ABPA in CF[221]

Classic diagnostic criteria

1. Acute or subacute clinical deterioration (cough, wheeze and other pulmonary symptoms) not explained by another etiology
2. Serum total IgE levels >1000 IU/mL
3. Immediate cutaneous reactivity to *Aspergillus* or presence of serum IgE antibody to *A. fumigatus*
4. Precipitating antibodies to *A. fumigatus* or serum IgG antibody to *A. fumigatus*
5. New or recent abnormalities on chest radiography or chest CT that have not cleared with antibiotics and standard physiotherapy

Minimal diagnostic criteria

1. Acute or subacute clinical deterioration (cough, wheeze and other pulmonary symptoms) not explained by another etiology
2. Total serum IgE levels >500 IU/mL. If total IgE level is 200-500 IU/mL, repeat testing in 1-3 months is recommended
3. Immediate cutaneous reactivity to *Aspergillus* or presence of serum IgE antibody to *A. fumigatus*
4. One of the following: (a) precipitins to *A. fumigatus* or demonstration of IgG antibody to *A. fumigatus*; or (b) new or recent abnormalities on chest radiography (on chest radiography or chest CT that have not cleared with antibiotics and standard physiotherapy

Screening for ABPA in CF

1. Maintain a high level of suspicion for ABPA in patients with CF
2. Determine the total serum IgE levels annually. If the total serum IgE levels is >500 IU/mL perform *A. fumigatus* skin test or use an IgE antibody to *A. fumigatus*. If results are positive, consider diagnosis on the basis of minimal criteria
3. If the total serum IgE levels is 200-500 IU/mL, repeat the measurement if there is increased suspicion for ABPA and perform further diagnostic tests (immediate skin test reactivity to *A. fumigatus*, IgE antibody to *A. fumigatus*, *A. fumigatus* precipitins, or serum IgG antibody to *A. fumigatus* and chest radiography)

individual, thus leading to serological manifestations of ABPA. On the other hand, it can also represent saprophytic *Aspergillus* colonization and subsequent aspergilloma formation in bronchiectatic cavities of ABPA.[261,262] Whatever, the predisposing causes, most patients show brisk response to glucocorticoids.[252-255,262]

Allergic Bronchopulmonary Mycosis

Allergic bronchopulmonary mycosis is the occurrence of ABPA-like syndrome due to non-*Aspergillus fumigatus* fungal organisms. A variety of fungal agents (Table 75.10) have been reported to cause this syndrome, but the frequency is far less when compared to ABPA.[256,264-278]

ABPA Complicating Other Conditions

ABPA is mainly described in patients with bronchial asthma or cystic fibrosis. Occasionally, ABPA has been reported to complicate other lung diseases like idiopathic bronchiectasis,[279] post-tubercular bronchiectasis,[280] bronchiectasis secondary to Kartagener's syndrome,[281] chronic obstructive pulmonary disease,[94,282] and in patients with chronic granulomatous disease and hyper IgE syndrome.[283] However, these are single patient case reports or small case studies, and larger observations are required to definitely establish an association.

TABLE 75.10: Fungi implicated in the causation of allergic bronchopulmonary mycosis

Aspergillus niger[256]
Helminthosporium spp[264]
Penicillium spp[265]
Aspergillus ochraceus[266]
Stemphylium spp[267]
Aspergillus terreus[268]
Drechslera spp[269]
Torulopsis spp[270]
Mucor-like spp[271]
Candida spp[272]
Pseudallescheria spp[273]
Bipolaris spp[274]
Curvularia spp[274]
Schizophyllum spp[275]
Fusarium spp[276]
Cladosporium spp [277]
Saccharomyces spp [278]

Sinobronchial Allergic Mycosis (SAM) Syndrome

The presence of concomitant allergic fungal sinusitis and ABPM in the same patient represents an expression of the same process of fungal hypersensitivity involving the upper and lower airways and is called the SAM syndrome.[35] Allergic *Aspergillus* Sinusitis (AAS), is an entity in which mucoid impaction similar to that of ABPA occurs in the paranasal sinuses.[284] The pathogenesis is similar to ABPA and represents an allergic hypersensitivity response to the presence of fungi within the sinus cavity.[285] It can also be regarded as the upper airway analog of ABPA. The patient can be asymptomatic or manifest with symptoms of nasal obstruction, rhinorrhea, headache and epistaxis. In clinical practice, it may not be possible to confirm the diagnosis of AAS in many patients as they decline to undergo the procedures required to establish the diagnosis. We currently label patients with ABPA as having concomitant AAS if there is a combination of hyperattenuating mucus and/or bony erosion on a paranasal CT scan. Treatment is initiated for ABPA with patients receiving additional intranasal glucocorticoids. If the symptoms persist or are troublesome, surgical management may be required for the management of AAS.

Occasionally, the inflammatory mass (fungocele) from the sinus may extend into adjacent spaces, such as orbit and manifest as proptosis.[286] Some patients can also have an intracranial extradural spread. Histopathological examination can show findings of branching septate fungi interspersed with eosinophilic mucin and Charcot-Leyden crystals without the fungal invasion of soft tissue, with intracranial extension.[287] It is important to differentiate this entity from invasive rhinocerebral aspergillosis as many patients are inadvertently treated with intravenous amphotericin when in fact they should be treated with minimally invasive surgery and glucocorticoid therapy (with or without concomitant azole therapy).[287]

CONCLUSION

A high index of suspicion for ABPA should be maintained while managing any patient with bronchial asthma whatever the severity or the level of control. Host immunologic responses are central to the pathogenesis and are the primary determinants of the clinical, biological, pathological and radiological features of this disorder. ABPA may precede the clinical recognition of the disorder for many years or even decades, and is often misdiagnosed for a variety of pulmonary diseases. As a patient with ABPA can be minimally symptomatic or asymptomatic, all patients with bronchial asthma should be routinely screened with an *Aspergillus* skin test. In patients with *Aspergillus* hypersensitivity further immunologic studies are warranted to diagnose ABPA before the development of bronchiectasis as bronchiectasis is a poor prognostic marker in the natural history of this disease.

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Section

10

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Sundeep Salvi

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Chronic Obstructive Pulmonary Disease: The Neglected Epidemic

Sundeep Salvi

MORTALITY DUE TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic Obstructive Pulmonary Disease (COPD) is a growing global epidemic that is estimated to kill around three million people every year. It is currently the fourth largest killer disease in the world and expected to climb to the third position by the year 2030. The numbers of deaths due to coronary heart disease, stroke and other cardiovascular diseases have reduced substantially over the years, whereas COPD is the only disease whose mortality rates have increased substantially. The WHO has estimated that mortality rates due to COPD will increase by around 160% in the Southeast Asian region over the next two decades. Half a million people are estimated to die due to COPD in India every year, the second largest number in the world after China. A recent report has indicated that COPD is already the leading cause of mortality in the state of Maharashtra and causes even more deaths than those due to coronary heart disease and stroke.

MORBIDITY DUE TO COPD

The World Health Organization (WHO) has estimated that 600 million people worldwide have COPD. It affects around 5% to 10% of the population over the age of 40 years, although there are wide variations in the prevalence between countries. Although a gross underestimate of the COPD prevalence in India has been estimated as 17 million and it is anticipated to increase by over 30% in the next decade. COPD is a common and leading cause of morbidity that is associated with the worsening of quality of life; 80% of patients hospitalized following an exacerbation report a health status rated by a physician as being worse than death. The patients who survive their first COPD-related hospitalization, up to 50% are reported to be readmitted within six months of discharge.

THE ECONOMIC BURDEN OF COPD

COPD is associated with a huge economic loss, not only for the patient but also for the nation. The economic burden of COPD is estimated as 38.8 billion US$ for US and 38.6 billion US$ for Europe. The estimated economic burden due to COPD for India is ` 30,000 crores (7.5 billion US$). Up to 84% of the direct costs associated with COPD are due to inpatient hospitalizations; lost productivity due to COPD accounts for between 40% and 67% of the overall costs across the world. COPD is, therefore, a major economic burden for countries throughout the world.

RISK FACTORS FOR COPD

Tobacco smoking is believed to be the biggest risk factor for COPD globally, accounting for between 80% to 85% of all COPD cases in the developed world. Tobacco smoking is steadily growing in most of the developing countries. In India and other Southeast Asian countries, bidi smoking is more popular than cigarette smoking mainly because of its low cost. In the bidi, tobacco is packed inside dried tendu leaves and although the amount of nicotine is about one-third to one-fourth the amount present in cigarettes, the amount of tar it produces is about five times more; therefore, from a COPD risk point of view, one bidi is as harmful as one cigarette. In India, other forms of tobacco smoking also exist, such as hookah and chillum. A recent study that compared the differences in lung oxidative stress mediated by different types of smoking devices showed that the hookah and chillum elicited greater amounts of lung oxidative stress than bidis and cigarettes, suggesting that hookahs and chillums are more harmful than bidis and cigarettes.

Recent emerging evidence suggests, if not more, that other nonsmoking risk factors may be equally important than tobacco smoking. It has been recently argued that exposure to biomass fuel smoke is perhaps the biggest risk factor for COPD globally. Compared to 1.1 billion smokers worldwide, three billion people (about half of the world's population) are exposed to the high levels of indoor air pollution due to the burning of biomass fuel smoke. Around 70% of homes in India are estimated to use biomass fuel for cooking and/or heating purposes, most of which are poorly ventilated. During her lifetime, every woman who spends two to three hours for cooking, every day inhales a volume of 25 million liters of highly polluted air, thereby exposing to her to extremely high levels of particulate matter and gaseous air pollutants. Exposure to biomass fuels has been shown to be as great a risk factor for COPD as active smoking and a greater threat than passive smoking, thus matching and beating two factors traditionally considered to be the major causes of COPD.

A previous history of pulmonary tuberculosis has been shown to be an independent and strong risk factor for the development of "obstructive airways disease," which is more of the COPD phenotype. In countries from Africa, Asia and Southeast Asia, where tuberculosis is highly prevalent, the burden of COPD due to a prior history of pulmonary tuberculosis is expected to be very high. In fact, a history of tuberculosis has been shown to be a bigger risk factor for COPD than tobacco smoking in studies from Africa and Asia.

Chronic poorly treated persistent asthma has also been identified as an important risk factor for COPD and its contribution to the overall prevalence of COPD is expected to be high in developing countries, where asthma still remains poorly diagnosed and treated. The other risk factors for COPD that have been identified are occupational causes, nutritional factors and poor socioeconomic status and these have been discussed in detail in the Chapter on "Risk Factors for COPD." Genetic factors have attracted more attention recently because of rapid advancements in the field of genomics. Alpha-1 antitrypsin deficiency remains one of the important genetic diseases associated with the development of COPD that roughly affects about 1% of the COPD population and it seems likely that more COPD genes will be identified in the near future.

As most clinicians from India and the Southeast Asia-Pacific region read textbooks of respiratory medicine authored by British and American authors, the concept of COPD in nonsmokers is not as much highlighted as it deserves. We almost take it for granted that if the patient who comes to the clinic with symptoms suggestive of COPD, but does not smoke, does not have COPD; because we have been lead to believe that COPD is almost always caused by tobacco smoking. This mind set now needs to change with the new evidence that almost half the COPD population in this part of the world occur due to nonsmoking causes.

COPD Remains Poorly Recognized

Despite such a huge and growing health and economic burden, COPD remains poorly recognized in clinical practice and underappreciated by health care providers, researchers and policy makers. One of the main reasons for this has been an "identity crisis" for this disease terminology. COPD has been previously known as "chronic bronchitis", "emphysema", "chronic obstructive lung disease", "chronic airflow limitation", "chronic obstructive respiratory disease", "chronic obstructive bronchopulmonary disease", "nonspecific chronic pulmonary disease", "diffuse obstructive pulmonary syndrome" and "chronic obstructive airways disease." These different names created a lot of confusion amongst clinicians and policy makers. Moreover, none of the terms were actually helpful in diagnosing the disease in clinical practice.

One of the other reasons why COPD as a disease remained unrecognized and unimportant was the attitude by the health care providers that this was a disease that was "self inflicted" because of its strong association with tobacco smoking. The patients were, therefore, thought to deserve the suffering brought about by their smoking habit. Moreover, there were no powerful medications that could bring about significant improvements in symptoms and prevent the rapid decline in lung function that accompanied the disease. There was no remarkable treatment that a physician could offer to patients suffering with COPD. As a result, the overall approach was very "nihilistic" towards this disease.

COPD Remains Underdiagnosed in Clinical Practice

COPD remains grossly underdiagnosed in clinical practice. This is mainly because of underuse of spirometry. Studies from US, UK and other European countries have indicated that if history and clinical examination are the only tools used to diagnose COPD in clinical practice, more than half of the COPD patients will remain underdiagnosed. Despite this realization, spirometry continues to be underused in clinics and even hospital settings. There are several reasons that have been suggested for this and include the lack of training during undergraduate and postgraduate medical curriculum about spirometry, the perception that spirometry is a difficult and time consuming test to perform and interpret, and the fact that spirometers are expensive (although this is no longer true since the cost of spirometers have come down dramatically over the years). Clinicians who are involved in managing patients with COPD should, therefore, be encouraged to use spirometry routinely, not only for arriving at a diagnosis, but also for evaluating the response to treatment.

More recently, the role of the Impulse Oscillometer (IOS) has attracted attention as a useful diagnostic tool for measuring airflow obstruction. This tool measures airflow resistance by passing in sound waves into the lungs at different frequencies and measuring the resistance offered for the passage of these sound waves. By using sound waves of different frequencies, we can measure the presence of airflow obstruction proximally as well as distally. The unique advantage of this instrument is that it measures these parameters during normal tidal breathing. This instrument is considerably more expensive than the spirometer as its use will continue to increase the prices are anticipated to go down.

Body box plethysmography and carbon monoxide lung diffusion studies help to measure the total lung capacity and the function of the lung alveolar-capillary diffusion apparatus. Although useful to diagnose emphysema, the degree of air trapping and the loss of alveolar surface area in COPD, they are not available even in some of the tertiary care specialist hospitals. These instruments are particularly helpful in determining surgical operability and estimating the potential benefit of Lung Volume Reduction Surgery (LVRS) for COPD. Tertiary care hospitals should, therefore, be encouraged to procure these instruments for the benefit of COPD patients.

PRIMARY AND SECONDARY PREVENTION OF COPD

From a pharmacotherapy point of view, many new drugs are currently in the development phase and are awaited with interest. However, the key management step is the reduction in further exposure to environmental insults. Smoking cessation for those who have developed COPD due to tobacco smoking is a crucial component of COPD management. Apart from some antidepressant drugs that have shown some promising effects on smoking cessation, the key intervention still remains proper and in-depth patient counseling. For those who have developed COPD due to exposure to indoor and outdoor air pollutants, secondary prevention is important to prevent the further progression of the disease. With the realization that exposure to biomass fuel smoke is perhaps a greater risk factor for COPD in this part of the world, primary prevention strategies in the form of patient awareness programs and governmental intervention programs through policy change may go a long way in reducing the burden of COPD.

COPD Exacerbations

COPD exacerbations, usually caused by bacterial or viral infection and exposure to air pollutants, are the single most important factor that determines the quality of life and survival of the patient. Every effort should, therefore, be made to prevent COPD exacerbations and to treat them effectively and soon enough as and when they occur. Many of these exacerbations will require the use of appropriate antibiotics, along with oral corticosteroids, bronchodilators and ventilator support, if required. Not only do these exacerbations accelerate the decline in lung function and worsen the quality of life, but they also drain off financial resources. Many need to live a life full of compromises. Patient education and pulmonary rehabilitation play a crucial role in ensuring that the patient copes up with the underlying physiological derangement and lives a better quality of life. Nonetheless, many of the COPD patients will ultimately need to be counseled about the end-of-life issues. This needs to be done very carefully with a bit of imagination, sensitivity and better communication skills.

CONCLUSION

COPD is a disease that will certainly grow in the forthcoming decades and we need to build up an action plan to halt this progress. Both primary and secondary prevention strategies need to be in place. For this, we need to educate lay people, health care providers and public health personnel. We also need to generate new knowledge to understand the risk factors better, their mechanisms and explore opportunities for new interventions that will help to reduce the suffering that is associated with this debilitating disease. We also need to improve our diagnostic abilities by increasing the use of spirometry in clinical practice. More importantly, we need to approach our COPD patients with “justified optimism” and give them the best possible care that is currently available. There is a lot we can offer to these patients than what was available before. In order to prevent COPD from becoming a major killer disease in our country, we need to develop an appropriate infrastructure and action plan that will need to be implemented carefully and meticulously. It is time to have a National COPD Control Program in place, before it gets too late.

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Health and Economic Burden of Chronic Obstructive Pulmonary Disease

Monica Barne, Sundeep Salvi

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of morbidity and mortality in the developed as well as developing countries. It makes a person lose precious years of his life and also contributes significantly to the global economic burden. The abatement of the main risk factors for respiratory diseases, in particular tobacco smoking, environmental tobacco smoke, indoor biomass fuels, outdoor air pollution and unhealthy diet, can achieve huge heal in decreasing the disease burden.[1] Knowledge of the burden of a disease also helps in calculating the economic impact of the disease on the country so that cost-effective measures can be planned and implemented based on this understanding.

MORTALITY DUE TO COPD

Global Mortality

According to the World Health Organization (WHO), more than three million people die of COPD every year, which corresponds to almost 5% of all deaths globally. In 2002, COPD was the fifth leading cause of deaths worldwide and by the year 2030, it is predicted to become the third leading cause of deaths.[2] India alone contributes to over half a million of deaths, second only to China which is responsible for an estimated 1.3 million deaths (Fig. 77.1). The United States and Western Europe, each account for about 1,40,000 COPD deaths every year.[3] These mortality rates are projected to increase by over 30% every decade.

COPD Mortality in the United States of America

The United States has been tracking the mortality rates from various communicable and noncommunicable diseases over the last 50 years. Although coronary heart disease, cancer and stroke occupy the top three positions amongst all the causes of deaths, their mortality rates have reduced dramatically over the last three decades, unlike the mortality rates due to COPD which have, in fact, increased by over 160% (Figs 77.2 and 77.3).[4]

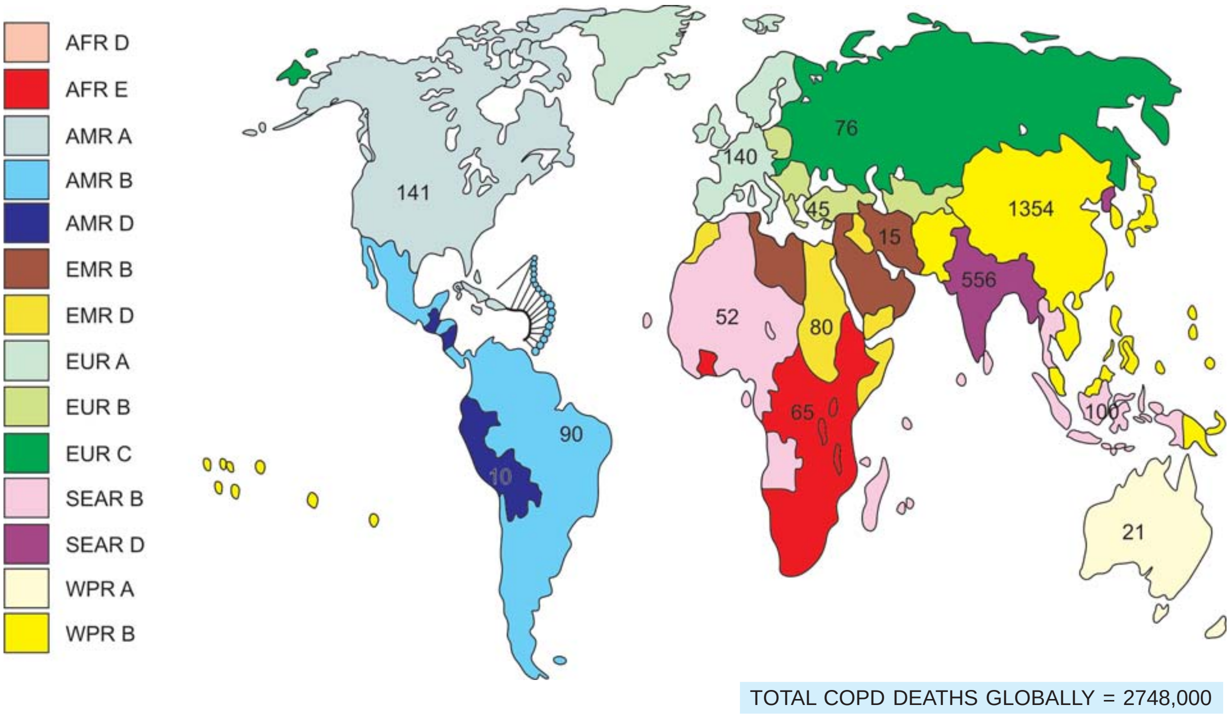
COPD Mortality in the Southeast Asian Region

Although tuberculosis and malaria are still major causes of death in the Southeast Asian Region, their mortality rates are anticipated to reduce from 4,00,000 and 2,00,000 per year, respectively to almost half by the year 2030[5] (Fig. 77.4). In contrast, mortality rates due to COPD, which are over two-fold greater than those due to tuberculosis currently (9,00,000), are estimated to increase by over 160% by the year 2030, which is almost similar to the increase in mortality rates of COPD in the US.

These observations clearly highlight the fact that mortality rates due to COPD are increasing both in the developed as well as developing world.[5]

COPD Mortality in India

As a result of industrialization, socioeconomic development, urbanization, changing age structure and changing lifestyles, India is facing a growing burden of noncommunicable diseases. Of all the noncommunicable diseases, chronic respiratory diseases have been shown


AFR D
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141
76
140
45
15
1354
556
52
80
65
90
10
100
21
TOTAL COPD DEATHS GLOBALLY = 2748,000

AFR: Africa; **AMR**: America; **EMR**: Eastern Mediterranean; **EUR**: Europe; **SEAR**: Southeast Asian Region; **WPR**: Western Pacific Region; **A:** Very low child and adult mortality; **B:** Low child and adult mortality; **C:** Low child mortality and high adult mortality; **D:** High child and adult mortality; **E:** High child mortality and very high adult mortality. Figure created from data in reference 3.

Fig. 77.1: Estimated COPD deaths (in thousands) by WHO region, 2002

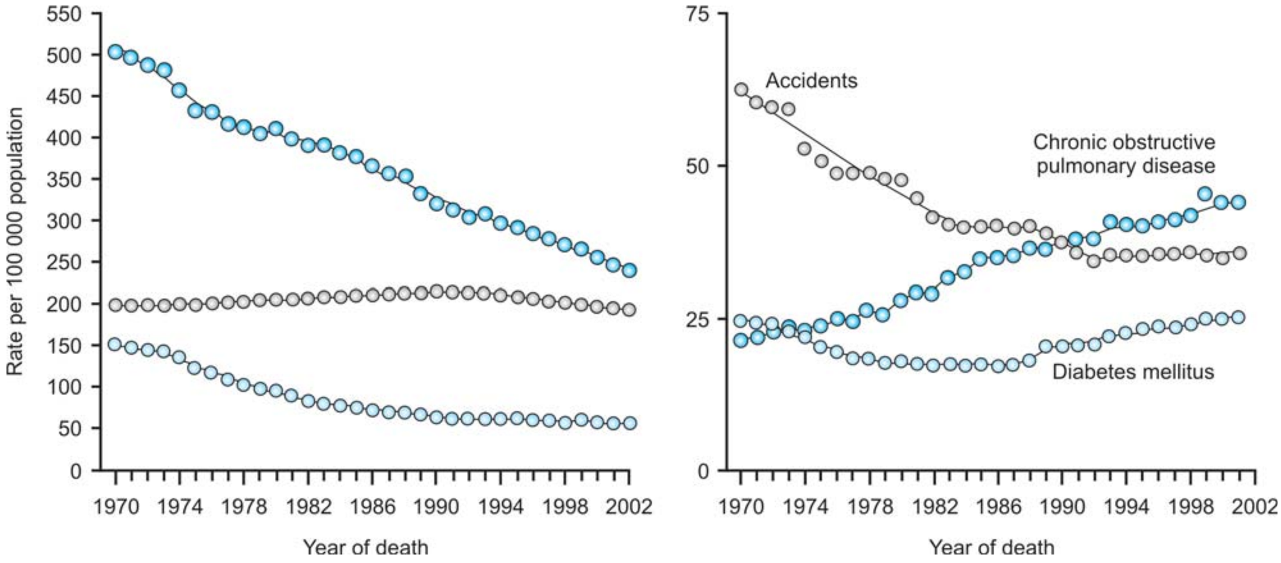
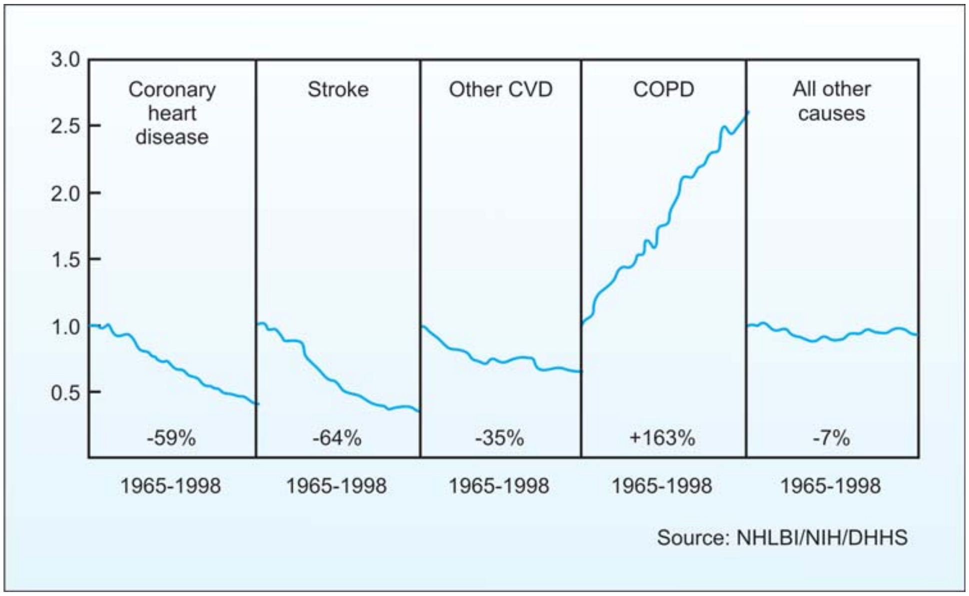


Fig. 77.2: Trends in age standardized death rates for the six leading causes of deaths in the United States, 1970-2002
Source: Jemal A, Ward E, Hao Y, et al. Trends in the Leading Causes of Death in the United States, 1970-2002. JAMA. 2005; 294:1255-9. *(Reproduced here with permission from the JAMA)*



Source: NHLBI/NIH/DHHS

Fig. 77.3: Percentage change in age adjusted death rates in the United States, 1965-1998

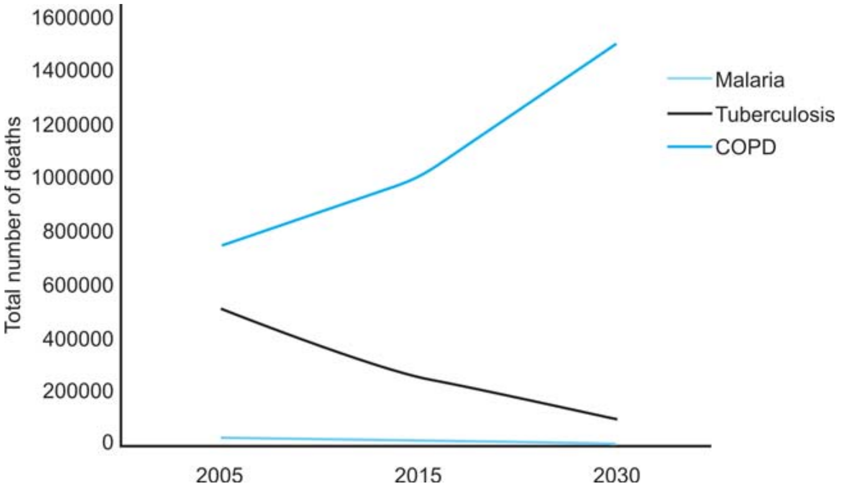


Fig. 77.4: Trends of mortality statistics in Southeast Asian Region for malaria, tuberculosis and COPD

to be the second biggest cause of mortality (5,77,837 deaths) in India, second only to injuries (Fig. 77.5).[6] The WHO estimates quote a figure of almost 5,56,000 deaths attributable to COPD in the Southeast Asian Region, which majorly comprises India.[3] Thus, almost 95% of the mortality due to chronic respiratory diseases in India can be attributed to COPD.

The above figures seem to be corroborated by another study that examined the leading causes of death in rural India.[7] The data gathered from the "Survey of Causes of Death (rural)," Annual reports of Registrar General of India (RGI), Census of India 2001, National Family Health Survey I and II and various other community-based studies clearly indicated that bronchitis and asthma were the leading cause of death in rural India (Fig. 77.6)[7] overtaking those due to coronary heart disease, cardiovascular disease and even other communicable diseases such as tuberculosis, pneumonias and gastrointestinal infections. Bronchitis and asthma together were recorded as the leading cause of death in both the sexes in all the states studied (Fig. 77.6).

Chronic obstructive pulmonary disease is primarily described by its prototype "chronic bronchitis" in most of the epidemiological studies and as per current

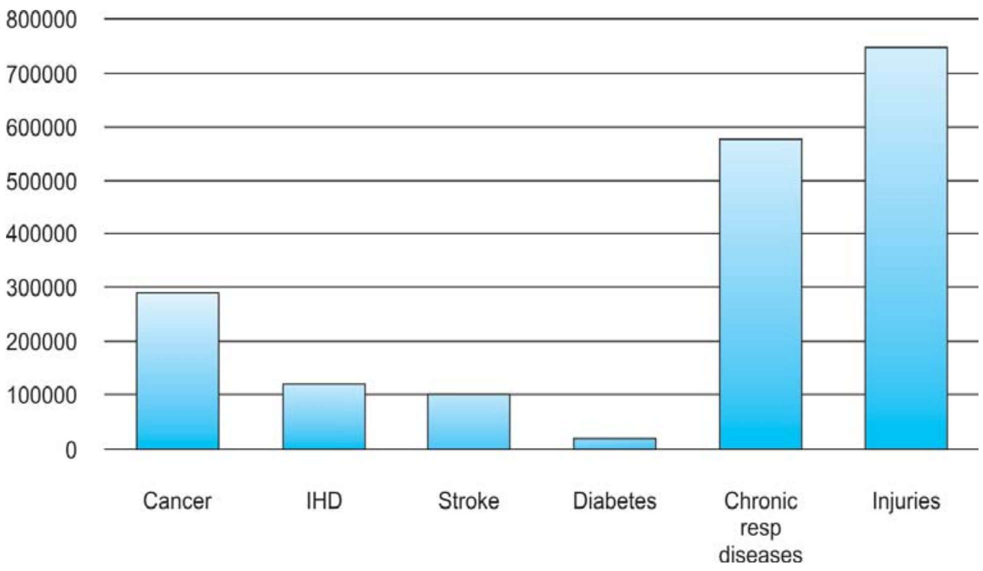


Fig. 77.5: Estimated mortality due to noncommunicable diseases in India (1998)[6]
(IHD: Ischemic heart disease)

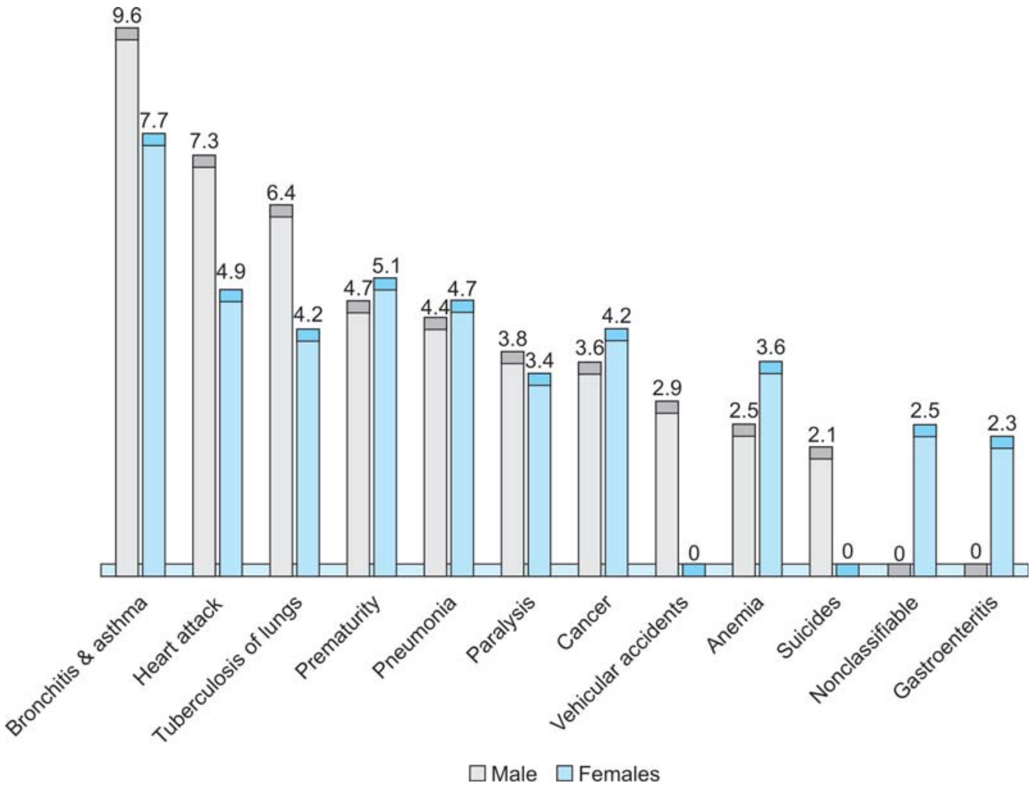
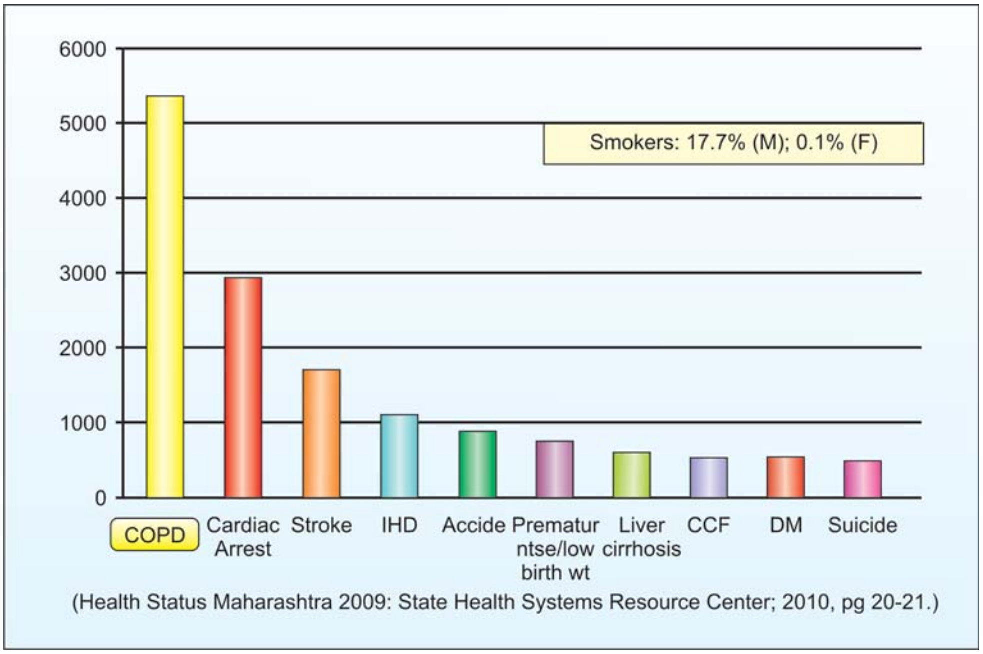


Fig. 77.6: Leading causes of mortality in rural India, 1994



(Health Status Maharashtra 2009: State Health Systems Resource Center; 2010, pg 20-21.)

Fig. 77.7: Top 10 causes of death in Maharashtra, 2008

practices, COPD continues to be used interchangeably with chronic bronchitis.[8] Though COPD has now been identified as a distinct clinical entity, confusion still remains in the minds of medical practitioners, especially at primary care level. The overlap between asthma and COPD is generally difficult to resolve and several patients are diagnosed and classified as "asthma," a term which a primary care physician finds easier to understand and explain to the patient.[8]

State-wise mortality data is currently available only for Maharashtra and according to a report published by the Maharashtra State Health Systems Resource Center in 2010,[9] COPD was found to be the leading cause of deaths in Maharashtra (Fig. 77.7). Mortality due to COPD was found to be almost twice that of coronary heart disease. The report was prepared after the analysis of the statistics from the respective bureaus of the public health department; Government of Maharashtra; Health Management Information System (HMIS), which provides updated data regarding public health initiatives; the Sample Registration System (SRS); the Survey of Cause of Death (SCD); National Family Health Surveys (NFHS) and also the district level health surveys. Whilst the authenticity and reliability of the data could be questioned, it cannot be denied that COPD is indeed one of the major causes of deaths in Maharashtra and it seems likely that the situation may not be too different in the other states in India.

PREVALENCE OF COPD

Global Prevalence of COPD

Prevalence of COPD varies from country to country and within the country from region to region due to the different levels of exposure to risk factors. The most common risk factors are tobacco smoking, industrial pollution, indoor air pollution in the form of usage of biomass fuel, etc. According to the WHO, 600 million people worldwide are believed to suffer from COPD.

Several studies have estimated the prevalence of COPD in the past, but the tools for diagnosis of COPD have been largely ill defined. On one hand, prevalence based on self-reported symptoms (chronic cough, sputum, etc.) most likely overestimated the true burden of COPD.[10] In fact, it is suggested that only half of the patients with the symptoms of chronic bronchitis actually have COPD. On the other hand, physician's diagnosis in the absence of spirometry usually underestimates true COPD.[11] Salvi and Barnes have summarized all the data available on the prevalence of COPD from various countries (Table 77.1).[12]

As is evident, there is a considerable variation in the prevalence of COPD across the globe. The variations in prevalence rates may not necessarily be only due to the actual difference in prevalence in various countries but also likely depends upon the fact that the diagnostic and

TABLE 77.1: Studies of chronic obstructive pulmonary disease (COPD) prevalence worldwide

	Study Center	*Participants*	*Age (years)*	*Method of Diagnosis*	*Prevalence of COPD*
Behrendt (2005)[13]	USA (Nationwide NHANES III)	13995	18-80	Prebronchodilator Spirometry (FEV$_1$/FVC <0.70)	6.6%
Shahab et al. (2006)[14]	England (Nationwide)	8215	≥35	Prebronchodilator Spirometry (FEV$_1$/FVC <0.70)	13.3%
Hardie et al. (2005)[15]	Bergen, Norway	1649	≥70	Respiratory Symptom Questionnaire	4.0%
Lamprecht et al. (2008)[16]	Salzburg, Austria	1258	≥40	Postbronchodilator Spirometry (FEV$_1$/FVC <0.70)	26.1%
Lindström et al. (2001)[17]	Norrbotten, Sweden; Lapland, Finland	13737	45-69	Symptoms; respiratory symptom questionnaire; self-reported physician	3.8% (Sweden) 3.2% (Finland)
Viegie et al. (2000)[18]	Po Delta, Italy	1727	>25	Spirometry: ERS (Prebronchodilator FEV$_1$/FVC <0.88 for men and <0.89 for women), BOLD (postbronchodilator FEV$_1$/FVC <0.70), ATS (Prebronchodilator FEV$_1$/FVC <0.75); clinical examination	11.0% (ERS); 18.3% (BOLD); 40.4% (ATS)
De Marco et al. (2004)[19]	Multinational (16 countries*; ECRHS)	20245	20-44	Prebronchodilator spirometry (FEV$_1$/FVC, 0.70)	2.5% (GOLD stage I); 1.1% (GOLD stage II/III
Liu et al. (2007)[20]	Guangdong province, China	3286	≥40	Postbronchodilator Spirometry (FEV$_1$/FVC <0.70); Physician; Respiratory symptoms questionnaire	9.4%; 12% (rural), 7.4% (urban)
Zhou et al. (2009)[21]	China (Nationwide CESCOPD)	20245	≥40	Postbronchodilator Spirometry (FEV$_1$/FVC <0.70)	5.2%
Ehrlich et al. (2004)[22]	South Africa	13826	>18	Respiratory symptoms questionnaire	2.6%; 2.3% (men), 2.8% women
Brashier B, Chest Research Foundation, Pune, personal communication	Pune, India (Slum in City)	12055	>45	Respiratory symptoms questionnaire	6.7%
Menzes et al. (2005)[23]	Brazil, Chile, Mexico, Uruguay, Venezuela (PLATINO)	5571	≥40	Postbronchodilator Spirometry (FEV$_1$/FVC <0.70)	15.8% (Brazil) 16.9% (Chile), 7.8% (Mexico), 19.7% (Uruguay), 12.1% (Venezuela)
Caballero et al (2008)[24]	Columbia (Five cities;[†] PREPOCOL)	5536	40	Postbronchodilator Spirometry (FEV$_1$/FVC <0.70); Physician; respiratory symptoms questionnaire	8.9% (Spirometry), 3.3% (Physician), 2.7% (questionnaire)

Tan et al. (2003)[25]	Asia-Pacific (12 Countries[‡])		≥30	Validate estimation model for prevalence of COPD	6.3% range from 3.5% (Hong Kong and Singapore) to 6.7% Vietnam
Kim et al. (2005)[26]	Korea (nationwide)	9243	>18	Postbronchodilator Spirometry (FEV$_1$/FVC, 0.70)	7.8%
Lindenberg et al. (2005)[27]	Norbotten, Sweden	666	20-69	Spirometry: BTS (Prebronchodilator FEV1/FVC <0.70, FEV$_1$, 0.80), ERS (Prebronchodilator FEV$_1$/FVC <0.88 for men and <0.89 for women), GOLD (Postbronchodilator FEV$_1$/FVC <0.70), ATS (Prebronchodilator FEV$_1$/FVC <0.75)	7.6% (BTS), 14.0% (ERS), 14.1% GOLD, 12.2% (ATS)
Fukuchi et al. (2004)[28]	Japan	2343	≥40	Prebronchodilator Spirometry (FEV$_1$/FVC <0.70)	10.9%
Ceveri et al. (2001)[29]	Multinational study (16 countries ECRHS)	17966	20-44	British Medical Research Council respiratory questionnaire; prebronchodilator spirometry (FEV$_1$/FVC, 0.70)	3.3%
Von Hertzen et al. (2000)[30]	Finland (nationwide)	7217	≥30	Respiratory symptoms questionnaire; clinical examination; Prebronchodilator Spirometry (FEV$_1$/FVC <0.70); Physician	14.1%

All studies were done in both men and women. **FEV$_1$/FVC:** ratio of forced expiratory volume in 1 second to forced vital capacity; …..= data not available or not studied; **ERS:** European Respiratory Society guidelines; **BOLD:** Burden of Obstructive Lung Disease criteria; **ATS:** American Thoracic Society guidelines; **GOLD:** Global Initiative for chronic Obstructive Lung Disease guidelines; **BTS:** British Thoracic Society guidelines.

[*] **ECHRS:** European Community Respiratory Health Survey; includes: Australia, Belgium, Denmark, France, Germany, Iceland, Ireland, Italy, Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, UK and USA.

[†] **Columbia 5 cities:** Barranquilla, Bogota, Bucaramanga, Cali, and Medelin

[‡] **Asia Pacific (12 Countries):** Australia, China, Hong Kong, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, and Vietnam.

research tools vary from study to study. The tools used to define COPD have included respiratory symptoms, self-reported COPD diagnosed by doctor and spirometry defined COPD (ratio between FEV$_1$ and FVC measured either before bronchodilator or after bronchodilator). Moreover, the cut-off value for the FEV$_1$/FVC ratio has also varied from study to study. Some studies have also used combinations of one or more of these tools.

There is considerable within study variation in the prevalence of COPD depending upon the criteria for defining COPD. For example, using the European Respiratory Society (ERS) definition of COPD (prebronchodilator FEV$_1$/FVC less than 0.88 for men and less than 0.89 for women) gives a prevalence of 11.0% which increases to 40%, if the American Thoracic Society (ATS) criteria is used to define COPD.[18]

Considering this wide variation in the study methodology and definitions of COPD, a worldwide study called Burden of Obstructive Lung Diseases (BOLD) has been initiated in 2002 which along with the Proyecto Latinoamericano de Investigacion en Obstrucción Pulmonar (PLATINO) study group has determined the prevalence of COPD using a standardized validated respiratory questionnaire and spirometry. A postbronchodilator FEV$_1$/FVC less than 70% on spirometry has been used to define COPD which is the Global initiative for Obstructive Lung Disease (GOLD) criteria for the diagnosis of COPD. BOLD and PLATINO together are currently developing a growing database of COPD prevalence worldwide.

The results of the BOLD study, which has been completed in 12 sites, including a population of 9,425, reported a prevalence of stage II or higher COPD of 10.1% overall (11.8% for men and 8.5% for women).[31] The prevalence increased with the age and pack years of smoking, but other less understood factors, such as

TABLE 77.2: Prevalence of COPD and its association with smoking in various population studies from India

	Population	*COPD prevalence (%)*		
		Men	*Women*	*M:F Ratio*
Wig (1964)	Rural Delhi	3.36	2.54	1.3
Sikand (1966)	Delhi	7.0	4.3	1.6
Viswanathan (1966)	Patna	2.12	1.33	1.6
Bhattacharya (1975)	Rural UP	6.67	4.48	1.6
Radha (1977)	New Delhi	8.1	4.6	1.8
Thiruvengadam (1977)	Madras	1.9	1.2	1.6
Viswanathan (1977)	Delhi Rural	4.7	3.5	1.3
	Urban	8.0	4.3	1.9
Charan (1977)	Rural Punjab	2.28	1.63	1.4
Malik (1986)	N. India Rural	9.4	4.9	1.9
	Urban	3.7	1.6	2.3
Jindal (1993)	N. India Rural	6.2	3.9	1.6
	Urban	4.2	1.6	2.6
Ray (1995)	South India	4.08	2.55	1.6

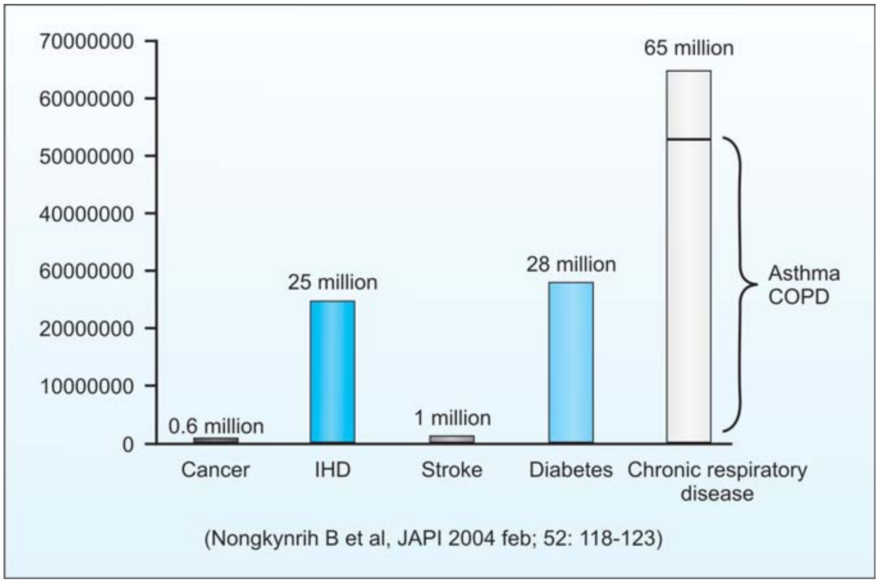
biomass heating and cooking exposures, occupational exposures and tuberculosis, also contributed to the location specific variations in the disease.[32]

COPD Prevalence in India

Jindal et al. performed an extensive review of all data published on COPD prevalence in India from 1964 to 1995 (Table 77.2).[33] This study provided the backbone for the estimation of morbidity and mortality of COPD in India and also helped to project the economic burden of COPD in India. As is evident, there is a wide variation in the prevalence of COPD in different parts of India, the highest being reported from North Indian rural population (9.4%). This wide variation could be explained by the wide variety in the exposure to risk factors.

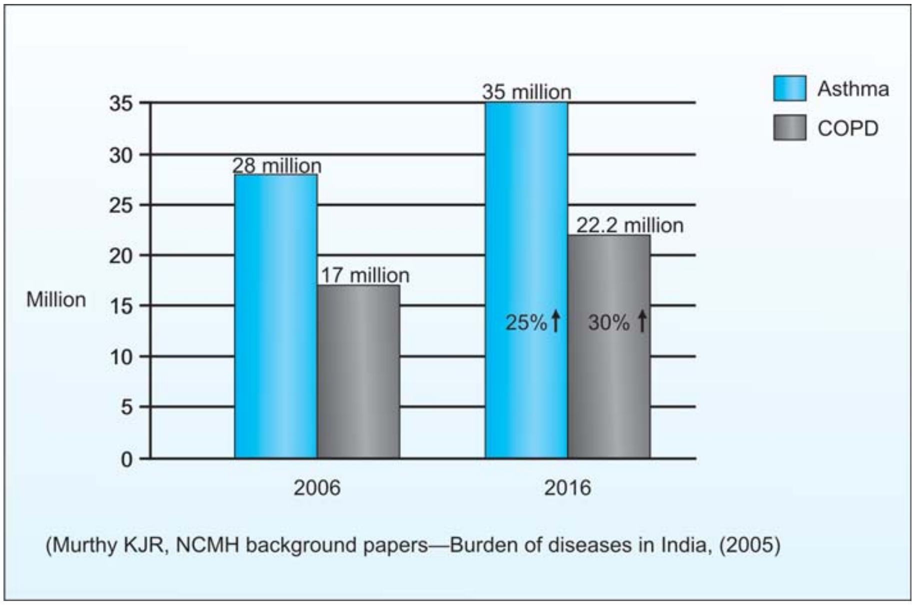
The National Commission on Macroeconomics and Health in its background papers on the burden of diseases estimated that there are about 14.9 million chronic cases of COPD in India in the age group of 30 years and above and these are projected to increase by nearly 50% by the year 2016. The estimated morbidity for noncommunicable diseases in India shows that the prevalence of chronic respiratory diseases is the highest amongst other common disease states (Fig. 77.8). Out of the 65 million cases of chronic respiratory diseases, about 17 million are due to COPD. The morbidity due to COPD is expected to increase to 22.2 million by the year 2016 (Fig. 77.9).[34]

In 2006, a large multicentric field survey was conducted in both the urban as well as rural populations at Bengaluru, Chandigarh, Delhi and Kanpur with the help of a structured and validated questionnaire. Prevalence of COPD amongst the 35,295 subjects investigated (age ≥35 years) was 4.1% with a male to female ratio of 1.56:1. Prevalence of COPD in smokers was 2.65 times higher than nonsmokers, and amongst the smokers, the prevalence was higher amongst *bidi* smokers as compared to cigarette smokers (8.2% and



(Nongkynrih B et al, JAPI 2004 feb; 52: 118-123)

Fig. 77.8: Estimated morbidity for noncommunicable diseases in India



(Murthy KJR, NCMH background papers—Burden of diseases in India, (2005)

Fig. 77.9: Estimated number of obstructive airways disease patients in India by 2016

5.9%, respectively). Exposure to Environmental Tobacco Smoke (ETS) was associated with a 40% increased odds of COPD which increased to 57% amongst those concomitantly exposed to biomass fuel.[35]

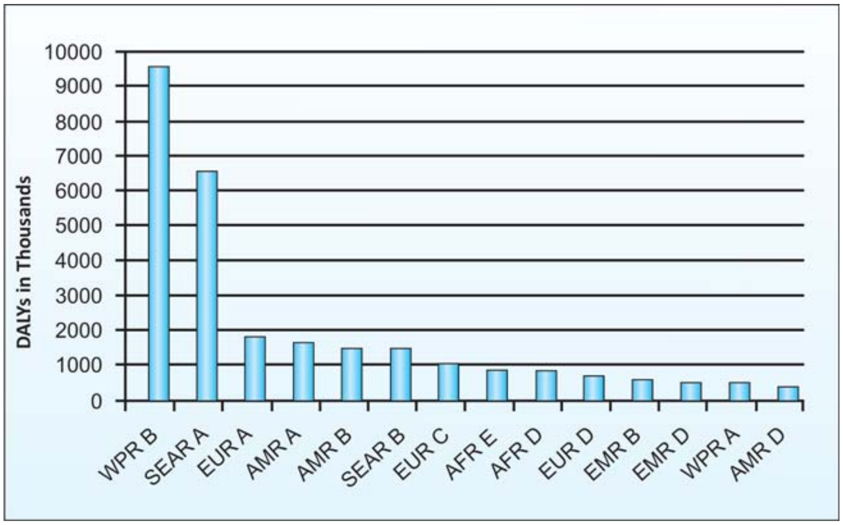
A questionnaire-based study amongst 12,000 slum dwellers from Pune city in Maharashtra revealed an overall prevalence rate of 6.5% (8.5% in males and 4.5% in females). Amongst those diagnosed with COPD, 69% were never smokers. The overall prevalence of questionnaire-diagnosed COPD amongst the never smoker males was 6.8% and females was 4.4%. In this study, absence of a separate kitchen for cooking was an independent risk factor associated with COPD prevalence in males (OR: 1.95, $p = 0.02$) while use of kerosene fuel for cooking increased the odds of COPD in females by around 2.5 times (OR = 2.48, $p = 0.01$).[36] In a recent study from rural population in Mysore, PA Mahesh et al. reported a prevalence of 7.1% (males = 11.1%, Females = 4.5%) using a structured questionnaire.[37]

DISABILITY-ADJUSTED LIFE YEARS DUE TO COPD

Mortality estimates give us the death rates due to a disease but the morbidity that is caused by the illness with respect to the Years Lived With Disability (YLD) which would otherwise have been years of good health and productivity for that individual and the Years of Life Lost (YLL) (premature mortality) which the patient would have otherwise lived for had the disease not occurred. The World Bank had commissioned a report for the estimation of the true burden of disease for more than 100 diseases and the report was published in 1996. The true burden of disease was calculated as Disability Adjusted Life Years (DALYs), which is a sum of the YLDs and the YLL. Disability adjusted life years for a specific condition are defined as the sum of years lost because of premature mortality (YLL) and years of life lived with disability (YLD) adjusted for the severity of the disability.[3] The DALYs due to COPD by WHO region are depicted in Fig. 77.10.

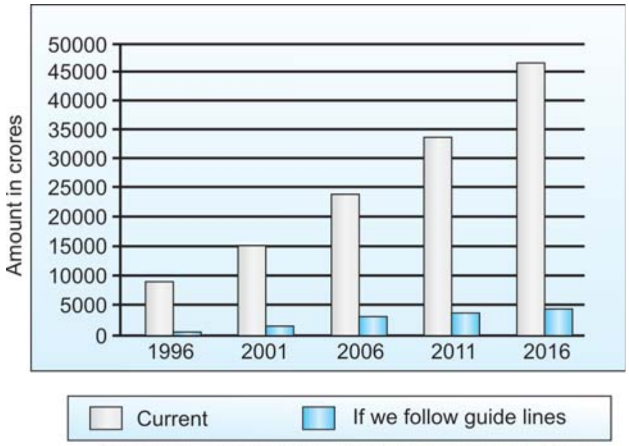
A considerable degree of morbidity is attributable to COPD. Worldwide, 1.9% of the DALYs were lost due to COPD. In 1990, COPD was the 12th leading cause of DALYs lost globally and was responsible for 2.1% of the total DALYs. According to future projections, COPD will be the fifth leading cause of DALYs lost worldwide in 2020, behind ischemic heart disease, major depression, traffic accidents and cerebrovascular diseases.[38]

A total of 27,756 thousand DALYs were lost globally in 2002 (Fig. 77.10) out of which maximum morbidity was seen in the Western Pacific Region B. In the South East Asian Region D, which mainly comprises India, 6,740 thousand DALYs were lost due to COPD in the year 2002.[3] In India chronic respiratory diseases are said to account for 3% of DALYs but this is likely to be an understatement. The current information available on COPD in India is bound to increase this figure tremendously.[8]



AFR = Africa; **AMR** = America; **EMR** = Eastern Mediterranean; **EUR** = Europe; **SEAR** = South East Asian Region; **WPR** = Western Pacific Region.
A: Very low child and adult mortality; **B:** Low child and adult mortality; **C:** Low child mortality and high adult mortality; **D:** High child and adult mortality; **E:** High child mortality and very high adult mortality. Figure created from data in reference 3.

Fig. 77.10: Estimated COPD DALYs by WHO region 2002



(Murthy KJR et al, NCMH background papers, 2005)

Fig. 77.11: Economic burden of COPD in India

ECONOMIC BURDEN OF COPD

Global Economic Burden of COPD

COPD is a costly disease with very high direct costs (value of health care resources devoted to diagnosis and medical management) and indirect costs (monetary consequences of disability, missed work, premature mortality and cost of attendants or family costs resulting from the illness).[38] In the European Union, the total direct costs of respiratory diseases is estimated to be about 6% of the total health care budget and COPD alone accounts for 56% of this budget amounting to about 38.6 billion Euros.[38] In the United States, the total economic cost of COPD morbidity and mortality has been estimated at \$23.9 billion in 1993. Of this, \$14.7 billion were spent on direct treatments for COPD-related illness and the remaining \$9.2 billion were for indirect costs.[39] Similar data from another US study suggest that 10% of persons with COPD account for less than 70% of all medical care costs.[39] The National Heart, Lung and Blood Institute (NHLBI) provides an estimate of the total (direct plus indirect) annual cost of COPD in the US to \$38.8 billion. More than half of this cost (\$21.8 billion) was due to direct expenditure.[40] The perpatient direct cost (in \$US 2005) was estimated to be in the range of \$2,700–\$5,900 annually.[40]

The presence of COPD also greatly increases the total cost of care of patients, especially when inpatient costs are considered. Presence of COPD related illness costs in the United States based on the 1987 Medical Expenditure Survey were 2.7 times the expenditures for patients without COPD (\$5,409 vs \$2001). The annual per capita expenditures for people with COPD were also 2.5 times the expenditures for people without COPD.[38]

The GOLD also states that in developing countries, direct medical costs may be less important than the impact of COPD on the workplace and home productivity. As the health care sector may not provide long-term supportive care services for severely disabled individuals, COPD may force two individuals to leave the work place—the affected individual and a family member who must now stay home to care for the disabled relative. Since human capital is often the most important national asset for developing countries, the indirect costs of COPD may represent a serious threat to their economies.

Economic Burden of COPD in India

According to National Commission on Macroeconomics and Health published data, the per capita expenditure on COPD was ` 42,664 in 2006 and is expected to increase to ` 62,630 in 2016. Figure 77.11 depicts the huge economic burden of COPD on India. India spent an estimated ` 25,209 crores for COPD (direct and indirect costs) in the year 2006 and this cost is expected to increase to ` 35,337.7 crores in the year 2011. A large part of this expenditure is because of delayed diagnosis and improper management.[34]

CONCLUSION

The incidence and prevalence of COPD is fast increasing, not only in the industrialized countries but also in developing countries due to the ever increasing smoking epidemic compounded by poor socioeconomic status in countries like India and China. It has been estimated that almost 50% of smokers may develop COPD.[41] In addition, nonsmoking COPD caused mainly due to exposure to smoke from biomass fuel, occupational exposure to dust and gases, poor socioeconomic status, etc. is fast emerging as an entity that is causing considerable morbidity and mortality amongst nonsmokers too.[13] The fact that the mortality rates due to COPD in India is the second highest in the world and the huge economic burden of the disease on the country indicates that India needs to take aggressive measures to prevent the development of COPD and calls for major policy changes to equip the health care system with facilities for early diagnosis and appropriate management of COPD.

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Risk Factors for Chronic Obstructive Pulmonary Disease

Sneha Limaye, Sundeep Salvi

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a chronic lung disease that is largely driven by environmental factors, although genetic susceptibility is also important. Risk for COPD is related to an interaction between genetic factors and many different environmental exposures, which could also be affected by comorbid diseases. Tobacco smoking is an age old established, major risk factor for COPD, but emerging evidence suggests that risk factors other than smoking are strongly associated with COPD.[1,2] These factors include exposure to indoor and outdoor air pollutants, workplace exposure to dust and fumes, history of repeated lower respiratory-tract infections during childhood, history of pulmonary tuberculosis, chronic asthma, intrauterine growth retardation, poor nourishment and poor socioeconomic status. The identification of risk factors is an important step toward developing strategies for prevention and treatment of any disease.

TOBACCO SMOKING

Tobacco smoking was first shown to be associated with the risk of developing COPD during 1950's.[3,4] When Fletcher and Peto reported that lung function decreased markedly in those smokers who had symptoms of chronic cough and/or breathlessness.[5] A subsequent larger and longer Framingham cohort offspring study confirmed these results.[6] All subsequent research then focused on smoking as the most important risk factor for COPD and several prevalence studies, in fact, have been done only amongst smokers. Currently, clinical trials in COPD recruit only smokers with at least 20 pack years of cigarette smoking exposure.

Tobacco smoking is highly prevalent in the developed countries, although the number of smokers is now declining slowly. On the other hand, the number of smokers in the developing countries is increasing rapidly. It is estimated that by 2030, tobacco consumption in any form will account for 10 million deaths per year, half of them aged 35–69 years. Almost 82% of world's smokers reside in the developing countries and nearly 17% of world's smoking population resides in India.[7] In India, an estimation of 65% of all men and 33% of all women use some or other form of tobacco. According to 55th round (1999–2000) of NSS in India, 54% of tobacco consumers consume *bidi*, 15% consume cigarette and 30% consume different tobacco chewing products. The prevalence of smoking in the Indian population is 28.5% in men and 2.1% in women.[8] There was, however, a wide range of the prevalence rate of smoking from the lowest of 13.9% in Punjab to the highest of 49.4% in Mizoram. *Bidi* was the most common form of smoking, more so in the rural areas. The different forms of tobacco smoking prevalent in India are cigarette, *bidi*, *hookah* and *chillum* smoking.[8]

In India and other Southeast Asian countries, *bidi* smoking is more common than cigarette smoking. *Bidis* are made up of tobacco wrapped in tendu leaf (Fig. 78.1). Although the amount of nicotine in a *bidi* is one-fourth that of a cigarette, the amount of tar is roughly five times greater. From COPD point of view, one *bidi* is as harmful as one cigarette. Due to the low combustibility of the tendu leaf wrapper, *bidi* smokers inhale more often and more deeply, thereby breathing greater amounts of tar.[9]

Fig. 78.1: *Bidis* are more popular form of smoking than cigarette

Cigarette smoke is a complex mixture of over 4,700 chemical compounds, generates high concentration of free radicals and oxidants like Reactive Oxygen Species (ROS), epoxides, peroxides and Nitric Oxides (NO).[10] Cigarette smoke contains two very different populations of free radicals, one in the tar and one in the gas phase. The tar phase contains several relatively stable free radicals, the principal radical being quinone/hydroquinone (Q/QH_2). The gas phase of cigarette smoke contains small oxygen and carbon-centered radicals that are more reactive than are the tar-phase radicals. One of the important mechanism through which tobacco smoke exerts its harmful effects on the lungs is the oxidative stress caused by reactive oxygen species.

Cigarette smoke contains 10^{17} oxidants per puff, of which 10^{14} are oxygen free radicals, which have the potential to produce an enormous oxidant burden on the lungs.[11] All tissues are vulnerable to oxidant damage, but by virtue of its location, the airspace epithelium is particularly vulnerable. Tobacco smoking increases the risk of COPD by 2–3 folds, although not all smokers develop COPD. Some of the earlier reports estimated that only 15% of smokers develop COPD. However, new evidence suggests that up to 50% of smokers develop COPD.[12] The risk of COPD also occurs amongst people who are exposed to second-hand smoke.[13,14]

INDOOR AIR POLLUTION AS A RISK FACTOR FOR COPD

It is estimated that about half of the global population (3 billion people) live in homes that use biomass fuel for cooking and heating purposes. Burning of biomass solid fuel (includes wood, twigs, crop residues and animal dung) emits very high levels of indoor air pollutants, both particulate matter as well as the gaseous pollutants (Figs 78.2A to C). Many of these homes are poorly ventilated, exposing these individuals to very high levels of indoor air pollutants.

Women, young girls and small children are exposed for the longest duration because they spend more time in close vicinity to the biomass smoke. During their lifetime, women are exposed for around 30–40 years, which is equivalent to 60,000 hours of exposure to biomass smoke or inhaling a total volume of 25 million liters of highly polluted indoor air.[15] The levels of indoor air pollutants, encountered in homes that use biomass fuel, are several orders higher than the levels in the most polluted urban cities in the world. These pollutants have the potential to produce intense oxidative stress in the lungs and the elastolytic effects of these pollutants have been found to be worse than those caused due to tobacco smoke. The exposure to biomass smoke induces the same amount of risk of developing COPD as tobacco smoke.

Figs 78.2A to C: Sources of different biomass fuels. (A) Dung cake. (B) Crop residues. (C) Firewood

As 3 billion people are exposed to biomass smoke worldwide as compared to 1.1 billion smokers, biomass smoke is likely to be the biggest risk factor of COPD.[15]

OUTDOOR AIR POLLUTION AND COPD

Ambient air pollution is a growing problem in most urban cities of the world. Over the last few decades, air pollution in most cities in the developed countries has decreased appreciably due to the advent of strict legislation and improvements in engine technology, but it continues to increase markedly in most of the cities of the developing countries. Both the gaseous and particulate matter components of urban ambient air pollutants have been shown to be associated with increasing respiratory morbidity and cardiovascular mortality.

One of the earliest studies that investigated an association between ambient air pollution and COPD was by Fairbairn[16] in 1958, who reported that postmen from England and Wales who worked in areas with higher outdoor air pollution levels, had a greater prevalence of COPD than those who worked in areas with lower ambient air pollution levels. A subsequent study from the United Kingdom showed that postmen who worked in more polluted cities had lower lung function values than those who worked in less polluted areas.[17] Similar observations were later reported in the general population.[18] More recently, living in areas closer to roads with heavy motor vehicular traffic have been shown to be associated with significant decrements in lung function,[19] and increased prevalence of COPD in women.[20]

Although there is a good evidence to suggest that the high levels of outdoor air pollutants increase COPD exacerbations and worsen preexisting COPD,[21] we do not have conclusive evidence to support the argument that outdoor air pollutants are responsible for causing new cases of COPD. Clearly, large, multinational, prospective epidemiological studies are needed to investigate this important question.

COPD ASSOCIATED WITH OCCUPATIONAL EXPOSURES

The association between occupational exposures and COPD has been observed for at least four decades. Earlier studies revealed that exposure to toxic gases at workplace,[22] grain dust in farms,[23] and to dust and fumes in factories,[24] were strongly associated with the risk of development of COPD. In 2003, the American Thoracic Society conducted a systematic epidemiological review of occupational factors associated with the development of COPD and reported that approximately 15% of COPD may be attributable to workplace exposure.[25] A more recent follow-up of the review has provided similar estimates.[26]

Farming as an occupation has been shown to be strongly associated with COPD. In their study of 1,258 adults of above the age of 40 years, Lamprecht et al.[27] investigated the association between farming and COPD prevalence [defined by a postbronchodilator Forced Expiratory Volume in One Second/ Forced Vital Capacity (FEV_1/FVC) ratio less than 0.70 on spirometry] and reported that the risk of COPD, attributable to farming, was 7.7% and that around 30% of the farmers had at least mild COPD. More recently, a study from Norway,[28] demonstrated that livestock farmers, compared to crop farmers, had a 40% greater risk of having COPD (95% CI: 10% to 70%) and that this correlated strongly with the levels of ammonia, hydrogen sulfide, inorganic dust and organic dusts measured by personal monitors at workplace.

Longitudinal studies have documented the association between COPD and occupational exposures in coal miners, hard rock miners, tunnel workers and concrete manufacturing workers. In heavily exposed workers, the effect of dust exposure may be even greater than that of cigarette smoking alone.[29] Construction workers exposed to fumes and mineral dust have been shown to have a significantly higher risk of death due to COPD.[30] Prolonged exposure to silica in occupations, such as the construction industry, brick manufacturing, gold mining and in iron and steel foundries (where average respirable dust levels reach up to 10000 $\mu g/m^3$), is also strongly associated with the development of COPD.[31] The burden of occupational COPD is likely to be high in countries of low and middle income, where occupational exposures to dust and fumes could be greater than in high-income nations, because of less stringent laws and lack of adequate facilities for reducing the exposures.

COPD ASSOCIATED WITH PULMONARY TUBERCULOSIS

Pulmonary tuberculosis (Fig. 78.3) has been shown to be associated with chronic airflow obstruction, particularly of the COPD phenotype, at the time of diagnosis,[32,33] during treatment,[34] and several years after the completion of treatment.[35] The amount of airflow obstruction is related to the extent of the disease determined

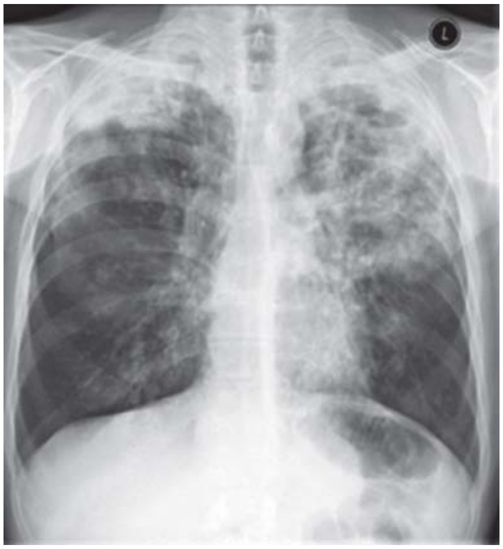

Fig. 78.3: Pulmonary tuberculosis as a risk factor for COPD

radiologically, the amount of sputum produced and the length of time after the diagnosis or completion of treatment.[36] Apart from the airway fibrosis that may follow tubercular infections, the immune response to mycobacteria may enhance the airway inflammation that is typical of COPD.

The prevalence of airflow obstruction in subjects with pulmonary tuberculosis has been shown to vary from 28 to 68% according to the study design, timing of assessment and medical or surgical treatment. In a nationwide household survey of 13,826 adults in South Africa, the strongest predictor of COPD, defined by self-reported symptoms of a chronic productive cough, was history of pulmonary tuberculosis. The odds ratios were 4.9 (95% CI 2.6–9.2) for men and 6.6 (95% CI 3.7–11.9) for women.[37] More interestingly, this risk was stronger than the odds ratios associated with tobacco smoking or exposure to biomass fuel smoke.

More recently, a study from five cities in Colombia (PREPOCOL Study)[38] that investigated the association between history of pulmonary tuberculosis and COPD (defined by postbronchodilator FEV_1/FVC ratio <0.70), reported a strong association with an odd ratio of 2.9 (95% CI 1.6–5.5). Further, this association was even stronger than that noted with tobacco smoking [OR: 2.6, (95% CI 1.9–3.5)].

The above studies from South Africa, Colombia, India and Latin America indicate that a history of pulmonary tuberculosis is a strong risk factor for COPD. More than 2 billion people, equal to one-third of the world's population, are infected with tubercle bacilli and an estimated 9.2 million new cases of tuberculosis are detected every year; 80% of them are present in 22 countries of the world.[39] Countries from Asia, Africa and Latin America have a particularly high burden of pulmonary tuberculosis. The cumulative burden of COPD associated with pulmonary tuberculosis is, therefore, likely to be much greater than previously believed, especially in the developing countries.[40]

CHRONIC ASTHMA AS A RISK FACTOR FOR COPD

Poorly treated chronic persistent asthma or poorly treated severe asthma can lead to changes in the lungs that are comparable to those caused by smoking.[41] In patients with severe asthma, the inflammation in the airways becomes more similar to the pattern seen in COPD, with an increase in the number of neutrophils and Interleukin-8, increased proteases, increased oxidative stress and a reduced responsiveness to corticosteroids.[42] This might reflect common mechanisms between COPD and asthma that are related to the intrinsic determinants of disease severity.

In a 5-year longitudinal study of 10,952 subjects, it was found that those with a new asthma diagnosis had lower initial values of lung function and an increased rate of decline in FEV_1 compared to nonasthmatic subjects.[43] Subsequent analyses from the same study after 15-years of follow-up showed that subjects with self-reported asthma still had a greater decline in FEV_1 over time than those who did not.[44] In a cohort of 3,099 adult subjects from Tucson, USA, that were followed-up for 20 years, it was seen that after adjusting for age, sex, smoking, Immunoglobulin E (IgE) and skin test reactivity, physician-confirmed active asthma was significantly associated with the subsequent risk of development of COPD.[45] Active asthmatics were 10 times more likely to acquire symptoms characteristic of chronic bronchitis and 17 times more likely to receive a diagnosis of emphysema by a physician. In this cohort, asthma was found to be the strongest risk factor for subsequent COPD [hazard ratio (HR) = 12.5; attributable risk (AR) = 18.5%], more than even tobacco smoking [hazard ratio (HR) = 2.9; attributable risk (AR) = 6.7%]. Primary care clinicians who practice long enough often report patients with acute bronchitis that morphs into chronic asthma that then develops into severe COPD.[46]

Poorly treated chronic persistent severe asthma may present with the features of COPD in the subsequent years. In many regions of the developing world as well as some parts of the developed world, asthma still remains poorly treated; it is likely that this may contribute significantly to the global burden of COPD.

TABLE 78.1: Genes implicated in COPD

Genes for which association studies have shown a significant relationship between polymorphisms and COPD	*Candidate genes for which there are no significant associations at present*
Alpha1-antitrypsin	Extracellular superoxide dismutase
Alpha1-antichymotrypsin	Secretory leucocyte leukocyte proteinase inhibitor
Cystic fibrosis transmembrane regulator	Cathepsin G
Vitamin D-binding protein	
Alpha 2-macroglobulin	
Cytochrome P450A1	
ABH secretor, Lewis and ABO blood groups	
HLA	
Immunoglobulin deficiency	
Haptoglobin	

COPD: Chronic obstructive pulmonary disease; HLA: Human leukocyte antigen.

GENETIC FACTORS

Although COPD is predominantly an environmental lung disease, it is clear that genetic susceptibility is also important. Recent studies have indicated that COPD can run in families, and for this several potential genes have been identified[47] (Table 78.1).

Though several genes have been implicated in COPD, work done to examine specific polymorphisms for the development of disease has been, at best, inconsistent, functional genetic variants influencing the development of COPD have not been yet definitively identified.

The best known genetic factor linked to COPD is deficiency of alpha 1-antitrypsin, a major circulating inhibitor of serine proteases, which arises in 1 to 3% of patients with COPD. Having low concentrations of this enzyme, particularly in combination with smoking or other pollutant exposures, increases the risk of developing panlobular emphysema. This rare recessive trait is most commonly seen in individuals of Northern European origin.

More recently, work is underway to study the role of antioxidant genes as potential candidates for increasing genetic susceptibility. There are several antioxidant genes, which play a major role in protecting the airways and lung parenchyma from environmental oxidative stress and a genetic defect in the production of these protective molecules may increase susceptibility to develop COPD.

SOCIOECONOMIC STATUS

Poor socioeconomic status is a risk factor independently associated with COPD and is likely to be indicative of other factors such as intrauterine growth retardation, poor nutrition (low intake of antioxidants), housing conditions, childhood respiratory tract infections, exposure to tobacco smoke, occupational risks, and biomass smoke and other indoor air pollutants. These factors might collectively contribute to the risk of COPD.[18] Socioeconomic status should therefore be treated as an independent risk factor for COPD.

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Pathophysiology of Chronic Obstructive Pulmonary Disease

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease syndrome characterized and defined by a single physiological parameter, limitation of expiratory airflow, which is accompanied by loss of lung elastic recoil, fibrosis, edema of the airways, intraluminal accumulation of secretions and bronchial smooth muscle contraction. Most often, these changes are slowly progressive over years. According to the current Global Initiative of Obstructive Lung Disease (GOLD) COPD is defined as a "disease characterized by chronic airflow limitation and a range of pathological changes in the lungs, some significant extrapulmonary effects and important comorbidities, which may contribute to the severity of disease in individual patient,"[1] and most interestingly with our improved understanding of pathogenic mechanisms, COPD now considered to be largely preventable and to a certain extent treatable.

Pathogenesis–Evolution of Concepts

All these changes in COPD are caused by a cascade of multiple complex inflammatory mechanisms occurring in the lung in response to chronic exposure to air pollutants, infections and various other risk factors. The first evidence of COPD dates back to 1679 where COPD (defined as emphysema at that time) was first described as voluminous lung or turgid lung occurring as result of trumpet blowing.[2] In 1814, Badham described this disease as associated with chronic cough and mucus hypersecretion and called this disease "Chronic bronchitis."[3] With the discovery of the stethoscope, Laennec gave a more vivid description of this disease as air entrapment in the lungs, which was caused not only by smoking, but also occurred in nonsmokers, especially those with familial predisposition, and suggested that the disease was very commonly prevalent in the general population.[2] Most of the earlier understanding of COPD was based on physiological and postmortem gross pathological observations. However, very little was known about the cellular and molecular changes of the disease, hence there was no optimal treatment available.

The first stride in our understanding of pathogenesis came in 1964 when Gross et al. first demonstrated the protease-antiprotease animal model for emphysema. He suggested that emphysema was a disease caused by over production of proteases enzyme in the lung parenchyma accompanied by reduced antiprotease activity that caused the alveolar wall destruction and development of emphysema.[4] Thereafter, over the next 50 years, understanding of the pathogenesis of COPD has advanced significantly, and new concepts still continue to emerge. Today it is clear that neutrophils, macrophages and T lymphocytes along with various inflammatory mediators and proteases are the primary culprits in the pathogenesis of COPD. New concepts of protease/antiprotease imbalance, steroid tolerance, amplified oxidative stress, autoimmune character of COPD, disease of accelerated aging of the lung and more recently systemic inflammation have emerged, which are instrumental in altering the management in COPD patients and have given novel insights for new drug discoveries for this chronic disease.

Pathophysiological Changes

The pathology of COPD is characterized by certain morphological and cellular changes occurring in the airways and lung parenchyma due to ongoing chronic inflammatory processes. Pathological changes, such as subepithelial infiltration of mononuclear cells (macrophages, CD8+ T lymphocytes), mucous gland hypertrophy and inflammation, subepithelial infiltration of eosinophils (during exacerbations of COPD), subepithelial infiltration of neutrophils, goblet cell hyperplasia, smooth muscle hypertrophy, wall fibrosis and destruction of the alveolar attachments, tend to occur in both proximal and peripheral airways of the lungs. Further, the inflammation of COPD also causes lung parenchymal changes, such as, destruction and enlargement restricted to the respiratory bronchioli and the central portion of the acinus (centriacinar emphysema), destruction and enlargement uniformly involving the whole acinus (panacinar emphysema) and infiltration of CD8$^+$ T lymphocytes (Fig. 79.1).

The basic pathophysiologic consequences of COPD inflammation consists of increased resistance to airflow, loss of elastic recoil and decreased expiratory flow rate. The alveolar walls frequently break because of the increased resistance of air flows and increased apoptosis of the alveolar epithelial cells. Consequently, more effort is required for the air to be exhaled, which happens mostly due to narrowed airway and pressure changes in the thorax. These physiological changes cause earlier closure of small airways resulting in more air trapping in the lungs. Further, hyperinflated lungs flatten the curvature of the diaphragm and enlarge the rib cage. The altered configuration of the chest cavity places the respiratory muscles, including the diaphragm, at a mechanical disadvantage and impairs their force-generating capacity. This results in increase in the metabolic work of breathing, and the sensation of dyspnea heightens (Fig. 79.1). All these changes occur due to inflammatory cells and mediators, which are increased in COPD.

Role of Neutrophils in COPD

The neutrophil has been highly acclaimed as a key effector cell in the recalcitrant pathogenesis of COPD. Its role was first identified in 1963, when it was recognized that the deficiency of an endogenous inhibitor of serine proteases, alpha-1-antitrypsin was an important cause of early onset severe asthma.[5] This coincidental observation led to the proteinase/antiproteinase theory of the pathogenesis of emphysema that is now accepted widely as a key mechanism of the disease development.[6-10] The presence of neutrophils has been inversely correlated with prebronchodilator and postbronchodilator FEV$_1$, with the strongest correlation in patients without bronchodilator reversibility.[11,12] Moreover, neutrophilic inflammation has been primarily implicated in steroid nonresponsiveness in COPD.[13,14]

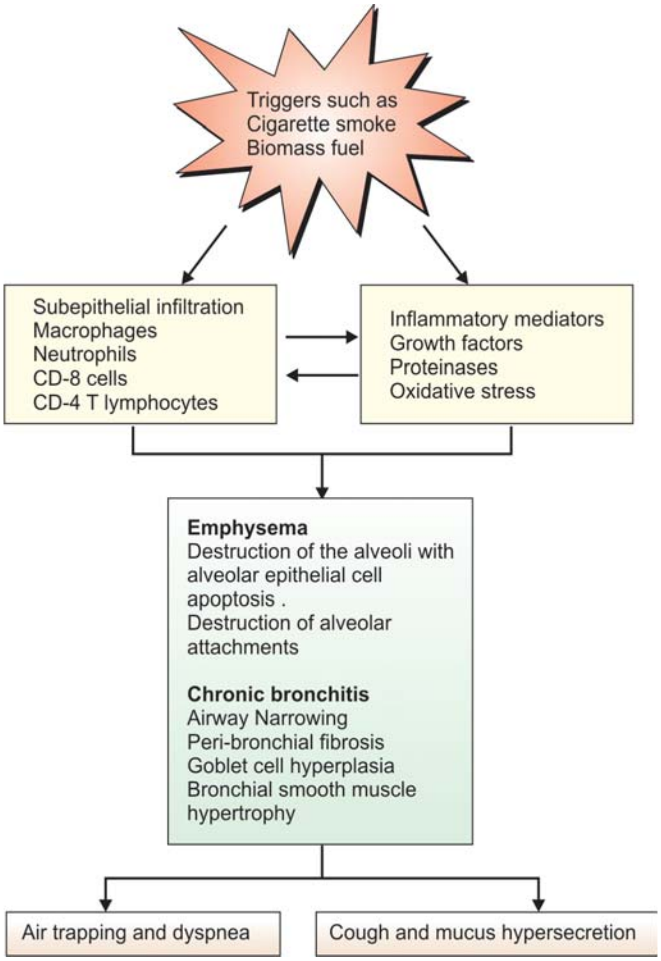
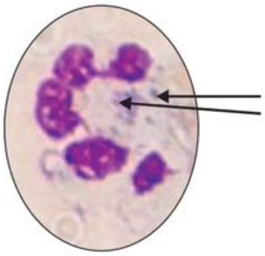

Triggers such as
Cigarette smoke
Biomass fuel
Subepithelial infiltration
Macrophages
Neutrophils
CD-8 cells
CD-4 T lymphocytes
Inflammatory mediators
Growth factors
Proteinases
Oxidative stress
Emphysema
Destruction of the alveoli with alveolar epithelial cell apoptosis .
Destruction of alveolar attachments
Chronic bronchitis
Airway Narrowing
Peri-bronchial fibrosis
Goblet cell hyperplasia
Bronchial smooth muscle hypertrophy
Air trapping and dyspnea
Cough and mucus hypersecretion

Fig. 79.1: Pathological changes occurring in COPD

This polymorphonuclear leukocyte originates from the bone marrow and passes through a series of developmental stages, including promyeloblasts and myeloblasts before attaining its fully differentiated form. It is at these stages when all the destructive proteinases secreted by the neutrophils develop and stay in a dormant state as azurophilic granules till the cells are further activated (Fig. 79.2).[15] The mature neutrophils survive in the systemic circulation for approximately 12 hours before undergoing apoptosis.[15] The neutrophils easily flow through the systemic vasculature except the



Azurophilic Granules containing:

- Myeloperoxidase,
- Bactericidal/permeability increasing protein (BPI)
- Defensins
- Serine proteases, e.g. proteinases 3
- Neutrophil elastase
- Cathepsin G, cathepsin B
- MMPs, e.g. MMP 9, MMP1, MMP3, MMP 12

Fig. 79.2: Neutrophil

pulmonary capillary bed, where it has to negotiate its shape and size to traverse through the much narrower pulmonary capillaries. Radiolabeled studies indicate that the journey of neutrophil across the pulmonary capillary bed is sluggish when compared to Red Blood Cells (RBCs), and the neutrophils need to deform themselves to traverse the full pulmonary capillary until the postcapillary venule.[16,17] This causes a large amount of neutrophils to remain naturally sequestrated in the lungs, where they are believed to provide active defense mechanisms against the environmental pollutants and pathogens.[17] This sequestration in the pulmonary capillaries allows time for the neutrophils to interact with capillary endothelium resulting in their transmigration across the pulmonary capillary membrane to the interstitium and airspaces of the lungs when triggered by inflammatory mediators and infections such as those seen in COPD (Figs 79.3 and 79.4).[17]

In order to enter the lungs, the neutrophils first adhere to the endothelial surface of the pulmonary capillaries through adhesion molecules and then migrate into the lungs where they survive for one to two days. The Cell Adhesion Molecules (CAMs) serve as ligands for leucocyte cell receptors, mediating the adhesion of neutrophils to the endothelium prior to their subsequent extravasation into inflamed tissue of lung.[18,19] In COPD, there is an increased migration of neutrophils into the lungs. This may occur due to enhanced neutrophil recruitment and/or delayed tissue clearance. Neutrophil accumulation in tissues is a dynamic process that is governed by both rate of neutrophil recruitment from the bloodstream and their rate of clearance from the lung tissue by lymphatics (Fig. 79.3).

Studies have described abnormalities in the circulating neutrophils of patients with COPD that can facilitate their recruitment to the lungs. The cigarette smoke, which is the major risk factor of COPD attenuates the property of deformity of neutrophils, which is required by them to negotiate their streamline pathway into the pulmonary vasculature.[19-21] The exact mechanism for such physiological consequences is not yet known; however, in vitro studies have shown that chronic tobacco smoke exposure can alter the kinetics of proteins such as filamentous actin (F-actin), which constitutes the major cytoskeleton and contractile apparatus of neutrophils.[21] This neutrophil stiffness impedes their already compromised flow in the lung capillaries. As a result their contact with the capillary endothelium is prolonged, which enhances their transmigration into the lungs even without adhesion molecules. Furthermore, in COPD there is also increased expression of adhesion molecules in both the endothelium as well as neutrophils cell surface, which enhances their migration into the lungs. It has been suggested that the initial phase of inflammation in COPD appears to be triggered by the expression of leukocyte-endothelial adhesion molecules in the lungs. Increased levels have been shown of various cellular adhesion molecules such as Intercellular Cellular Adhesion Molecule-1 (ICAM-1), endothelial adhesion molecules (E Selectin) which are all increased in the Bronchoalveolar Lavage (BAL) and systemic circulation of COPD subjects (Fig. 79.3).[22-30]

The inflammatory cells including neutrophils, release various cytokines and chemoattractants such as Interlukin-8 (IL-8),[31] LTB_4,[32] Matrix Metallopeptidase-9 (MMP-9)[33] and neutrophil elastase,[8,9,10] which provide a suitable milieu for the relentless migration of neutrophils and other inflammatory cells into the lungs and keep the intractable inflammation of COPD ongoing even after the risk factors or triggers are removed.

Once the activated neutrophils enter the lung parenchyma, they start releasing a battery of serine proteinase from the dormant azurophilic granules, which contributes to the destruction of the lung elastic tissue, ultimately leading to pathological changes such as chronic bronchitis and emphysema. There is also evidence to suggest that the neutrophils from the COPD subjects have greater chemotactic responses and greater ability to digest the surrounding tissue than the neutrophils of normal subjects indicating fundamental differences in the neutrophils of COPD.[34]

The four major neutrophilic proteases, which damage lung elastic tissues are neutrophil elastase, proteinase-3, cathepsin G and cathepsin B.[8,9,10,35] These enzymes have been shown to produce emphysematous and chronic bronchitis changes in various experimental models of COPD. The primary role of these proteolytic enzymes is to generate a pathway for the movement of leukocytes into the tissue and in this process they unsparingly degenerate the elastic connective tissue of the lung

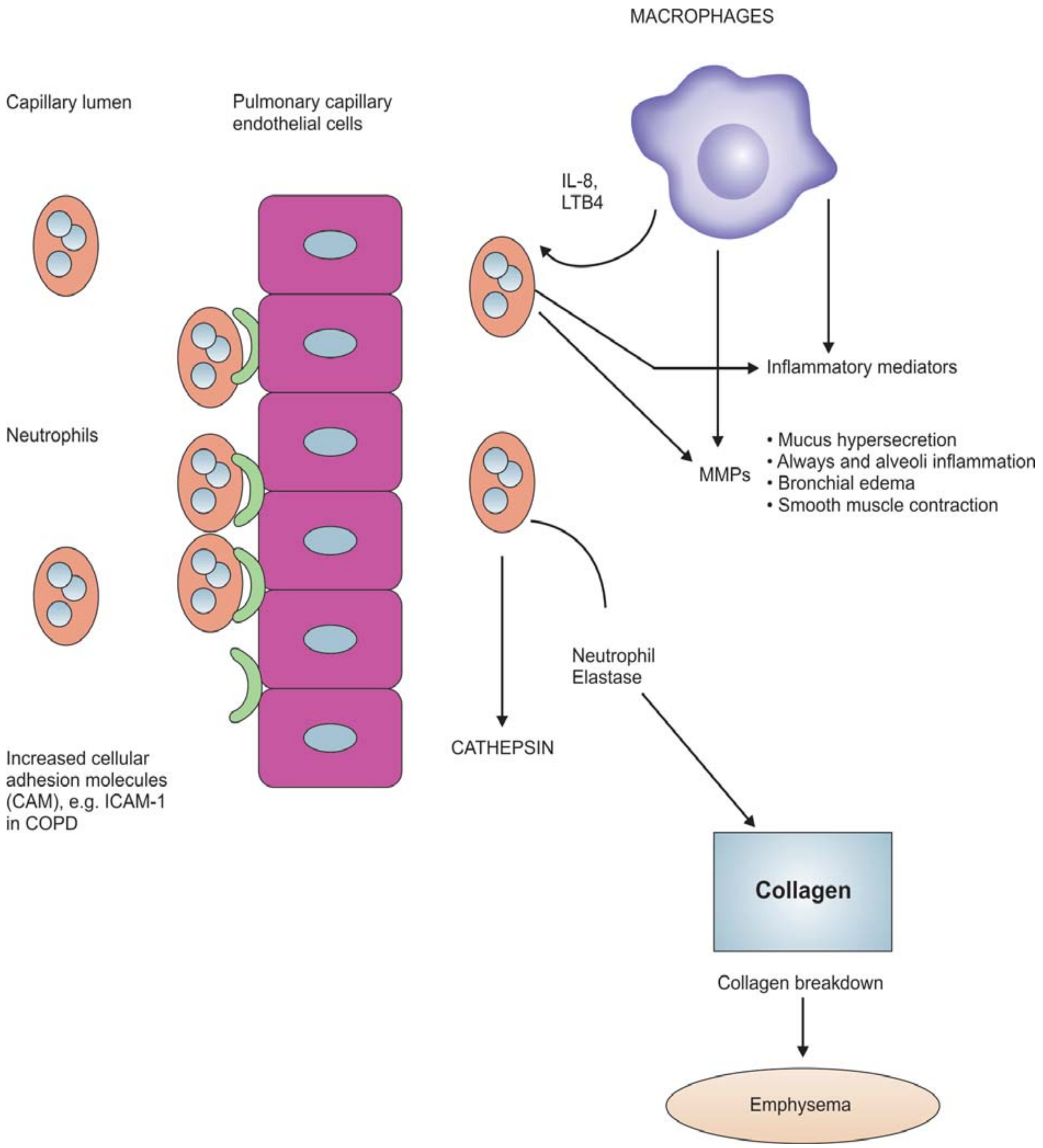

MACROPHAGES
Capillary lumen
Pulmonary capillary endothelial cells
IL-8,
LTB4
Inflammatory mediators
Neutrophils
MMPs
• Mucus hypersecretion
• Always and alveoli inflammation
• Bronchial edema
• Smooth muscle contraction
Neutrophil Elastase
CATHEPSIN
Increased cellular adhesion molecules (CAM), e.g. ICAM-1 in COPD
Collagen
Collagen breakdown
Emphysema

Fig. 79.3: Mechanisms of neutrophils migration from the pulmonary capillaries into the lungs. These mechanisms are amplified in COPD

parenchyma leading to emphysema. This happens despite the activation of natural repair process of reaccumulation of elastin.[22-30] As neutrophils move in close proximity to connective tissue, they degrade these structures, which can be reduced, but not prevented by another protein called alpha-1-antitrypsin (α-1-AT). Alpha-1-antitrypsin is an endogenous inhibitor of neutrophil elastase, and its deficiency is accompanied by severe emphysema seen in COPD, which develops in younger age. Approximately 1% of all COPD are due to alpha-1-antitrypsin deficiency. The normal levels of alpha-1-antitrypsin in the plasma are 1.5–3.5 g/l and

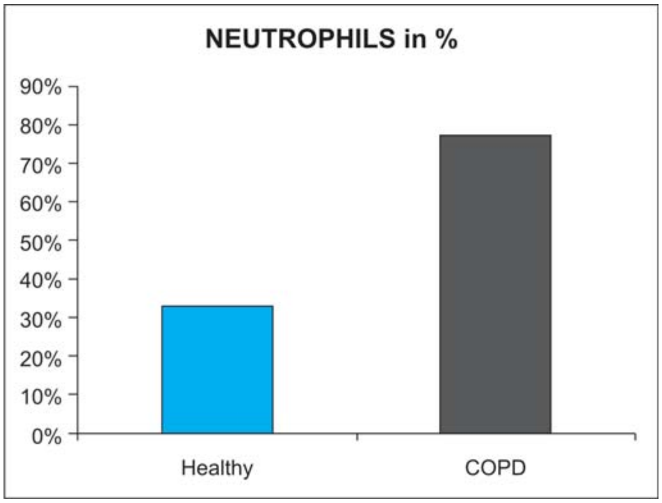


Fig. 79.4: Percentage of neutrophils in bronchoalveolar lavage of COPD versus healthy subjects (Adapted from Rato Djukanovic et al; Atlas of induced sputum. An Aid for research and Diagnosis: Parthenon Publishing; 2004; Chapter 5, pp. 71)

levels below 40 to 60% of this range are strongly associated with the development of emphysema. There is also evidence to suggest that neutrophil elastase activates matrix metalloproteinases (MMPs), which digest collagen and elastin.[36]

Neutrophil proteases also cause changes in the bronchi to produce the features of chronic bronchitis; it damages the airway epithelium,[37] causes mucus gland hyperplasia,[38] reduce the ciliary beating,[35] increases mucus secretion[39] and compromises the immunity of the airways by cleaving the C3bi opsonophagocytic receptors[39] and causes Immunoglobulin degradation, giving rise to chronic bacterial colonization of the airways.

In the healthy lung tissue there are inhibitors, which counteract the proteases activities for the enzymes released from inflammatory cells, and these include Secretory Leukoprotease Inhibitor (SLPI),[40,41] and in normal circumstances a balance is maintained between proteases and antiproteases levels in the lung. It has been proposed that in COPD the concentration of elastase released from the azurophil granule is so elevated that it cannot be totally inhibited by the normal surrounding concentrations of inhibitors. There has been growing interest in aiming to restoring this balance in the lungs of COPD with the help of several different intervention strategies that seem to have promising prospects for future therapy in COPD management.[41]

Role of Macrophages in COPD

Macrophages are cells, which are ubiquitously present in the lungs and serve as an important defense mechanism against particulate matter and pathogens that invade the lower respiratory tract. These cells are derived from peripheral blood monocytes, which migrate into the lungs where they mature into macrophages. The environmental toxins and noxious particles, which are inhaled into the lungs are usually cleared by these cells, thus preventing the lungs from being exposed to the harmful affects of these substances. Macrophages also engulf the antigens and present them to various other immune cells via different immunological mechanisms.[36] Sputum and BAL studies have shown that during chronic inflammatory conditions, such as COPD and exposure to cigarette smoke there is a 5 to 10 fold increase in the numbers of macrophages in the lungs, which are more concentrated in the centriacinar zones where emphysema is most marked, where they are likely to play a role in initiation, modulation and eventually termination of inflammatory response that characterize COPD.[42-45] Macrophage may tend to survive much longer as long as 2 years in some smokers. Macrophages are also important source of many inflammatory mediators and growth factors, which play an important role in the pathology of COPD and repair of damaged tissue.[36]

There is a positive association between macrophage numbers in the alveolar walls and the presence of mild-to-moderate emphysema as well as the degree of small airways obstruction seen in patients with COPD.[45] The slow progression and chronicity of COPD parallels the chronic increase in the numbers macrophages that is seen at sites of tissue damage/injury and supports the concept that macrophages are, at least in part, responsible for the pathologic consequences.[36] Some animal studies have also shown that chronic exposure to cigarette smoke can induce increased expression of collagen digesting enzymes in the macrophages.[46,47] Notably, the stubborn character of COPD inflammation and its poor response to steroids is majorly attributed to the evidence that the alveolar macrophages in COPD appear to be resistant to the anti-inflammatory effects of corticosteriods and this is linked to reduced activity and expression of histone deacetylase-2, a nuclear enzyme that switches off inflammatory genes activated through the transcription factor Nuclear Factor-kappa B (NF-κB).[48,49]

It is unclear whether increased numbers of macrophages in COPD are because of sequestration to facilitate lung repair or whether the normal transmigration process has failed. In usual circumstances the major role of a macrophage is to migrate to the site of the pathogen and phagocytosize it. These are then further removed from the lungs by mucociliary system and pulmonary lymphatics. But, in COPD these mechanisms seem to be impaired and hence macrophage clearance does not match pulmonary macrophage accumulation, reflecting continuous elevated sequestration triggered by the affects of cigarette smoke. The presence of macrophages in the lungs could also be attributed to the constant repair, which is needed to counteract the ongoing destruction of the lung tissue by various inflammatory mediators and protienases in COPD.

The macrophages in COPD have dysfunctional phagocytosis and lytic mechanisms, they macrophages ineffectively remove noxious substances from the lungs, which further triggers the migration of more macrophages from the peripheral blood into the organ. Further this means there may be the inadequate clearance of neutrophils by macrophage apoptosis and the release of neutrophil proteinases during necrotic neutrophil cell death. This can have devastating consequences. Moreover, dysfunction in macrophages makes a COPD subject more susceptible to invading triggers and microorganisms with subsequent increase in the frequency of exacerbations, which aggravates the pathophysiology of the disease.[50,51] The bacterial colonization of the respiratory tract and frequent exacerbations of COPD have been primarily attributed to the defective phagocytosis of the macrophages seen in COPD. The evidence indicates that alveolar macrophages from COPD patients phagocytose fewer apoptotic epithelial cells and pathogenetic bacteria, such as *Escherichia coli, Streptococcus pneumoniae and Haemophilus influenzae* compared to both nonsmokers and smokers without COPD.[52-58]

Alveolar macrophages from COPD patients have an increased baseline and stimulated secretion of inflammatory proteins, including certain cytokines and chemokines such as IL-8, IL-6, IL-10 TNF-α, LTB_4, etc. and reactive oxygen species, which account for all of the pathophysiological features of COPD. These mediators in turn, stimulate the recruitment of other inflammatory cells such as neutrophils and CD8 Lymphocytes into the lungs.[59,60] The macrophage also has enormous proteolytic potential, involving many classes of enzymes with broad ranges of substrate specificity. The secretion of proteinases by other inflammatory cells, as well as resident structural cells into the same extracellular environment may provide a potent proteinase cocktail that overwhelms the native inhibitors. If such proteinase activity remains unopposed, it is likely that the connective tissue matrix is continually abraded in the vicinity of these inflammatory cells. Macrophages also engulf the neutrophil elastase released from the neutrophils and stores them for further degradation of the matrix.[61,62]

The major interest in the macrophages in the pathogenesis of COPD is essentially due to their ability to release series of proteinases, particularly MMPs (Fig. 79.5) and series of elastinolytic cysteine proteinases, such as cathepsin K, L and S, which have potential elastolytic properties.[33,36,63] Matrix metalloproteinases are zinc- and calcium-dependent proteinases, which are known to degrade the matrix particularly the broad range of connective tissue that has an important role in tissue development and remodeling of the damaged tissue. Although released from macrophages, they are activated by serine proteinases released from neutrophils. These proteinases also inactivate Tissue Inhibitors of MMPs (TIMPs), leading to elevated MMP activity. This in turn enables the autoactivation of other latent MMPs progressing to the cascade of ongoing proteases destruction.[43,64]

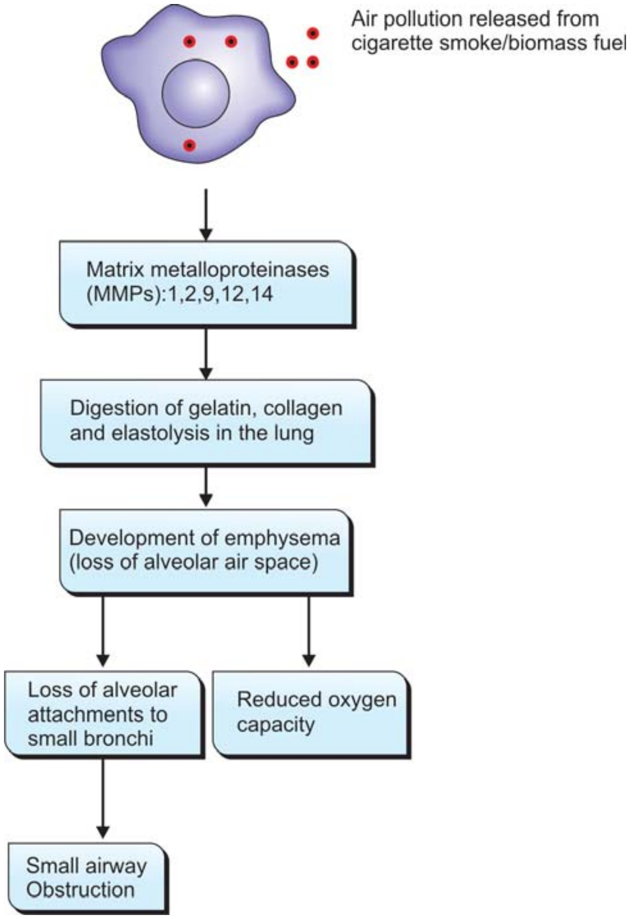

Air pollution released from cigarette smoke/biomass fuel
Matrix metalloproteinases (MMPs):1,2,9,12,14
Digestion of gelatin, collagen and elastolysis in the lung
Development of emphysema (loss of alveolar air space)
Loss of alveolar attachments to small bronchi
Reduced oxygen capacity
Small airway Obstruction

Fig. 79.5: Role of macrophages in tissue destruction seen in apoptosis through MMPs

Alveolar macrophages have also been shown to release Neutrophil Elastase (NE) over a period of time *in vitro*. Although, NE is not synthesized in macrophage, it is internalized into the cell by receptor-mediated processes. Macrophages, therefore, may epitomize a store for neutrophil elastase. Although, this property is very similar to ravaging NE, but unlike NE, which is rapidly released from azurophilic granules of neutrophils, the MMPs are more strictly regulated to cellular environment and their expressions are modified by cytokines and various growth factors.[36] Some of the major MMPs found in the inflamed lung environment of COPD patients are MMP-2, MMP-9, MMP-12 and MMP-14. The MMP-2 and MMP-9 have very strong gelatin digesting and elastolytic properties respectively, while MMP12 is implicated in the earlier stages of COPD (Fig. 79.5). [33,45,65-69]

Role of T Lymphocytes in COPD

The first evidence of the role of T lymphocytes in the pathogenesis COPD was demonstrated in 1995, wherein the correlation between the number of T lymphocytes in the lung and extent of emphysema was first revealed.[69,70] It was also realized that the inflammation of COPD was not only limited to the innate immune mechanisms, but also involved adaptive immunity with the infiltration of $CD8^+$ and $CD4^+$ cells not only in the alveolar wall and small airways, but also in the adventia of pulmonary vasculature, indicating the importance of these cells in the development of pulmonary hypertension related to COPD. Subsequent studies have further shown that although both the $CD4^+$ and $CD8^+$ cells are increased in the airways and the lung parenchyma of the patients with COPD, it is the $CD8^+$ cells which are more predominant and more likely involved in the pathophysiology of COPD.[71,72]

The mucosal layers of the airways contain local lymphoid follicles that consists of a core B lymphocytes surrounded by T cells and it has been suggested that the antigens are presented to the T cells in these lymphoid nodes resulting in clonal expansion of $CD4^+$ cells and to larger extent $CD8^+$ cells.[73] The $CD8^+$ and $CD4^+$ cells are fully activated in the lungs of COPD with the increased expression of inflammatory mediators such as CXCR3 with parallel strong epithelial expression of its ligand Interferon Gamma (IFN-γ) Inducible Protein 10 (IP-10), which is a powerful chemoattractant of the CD8 lymphocytes.[74,75] IFN-γ has been implicated in driving and maintaining T cell responses and promotes an immune inflammation with neutrophils and macrophages. The IFN-γ stimulated $CD8^+$ cells release further destructive enzymes, such as perforin and granzyme B, which have the ability to induce apoptosis of the alveolar epithelial cells.[76-78] The $CD8^+$ lymphocytes also produce battery of other cytokines such as IFN-γ, IL2, IP-10, monokine induced by IFN-γ (CXCL9), IFN-γ inducible T cell alfa chemoattractant (CXCL11) and IL-4, which are known to stimulate other inflammatory cells and mediators in COPD (Fig. 79.6).[70,75,77]

Intriguingly, an antigenic mechanism is required to stimulate the T cell inflammatory response. This inflammatory response appears in mild COPD and increases markedly with increasing disease severity and persists even after the triggers, such as air pollution or tobacco smoke, are removed. This self perpetuation of the adaptive immune system confers further understanding as it may explain the persistence of inflammation in the lungs of COPD patient. It is possible that the inflammatory and oxidative stress injury can

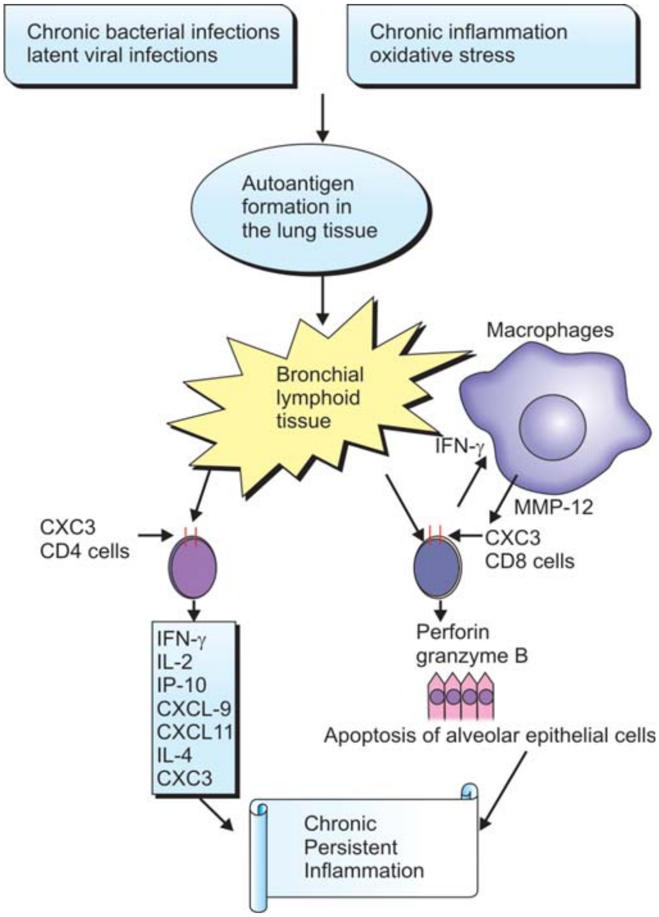

Chronic bacterial infections
latent viral infections
Chronic inflammation
oxidative stress
Autoantigen formation in the lung tissue
Bronchial lymphoid tissue
Macrophages
IFN-γ
MMP-12
CXC3
CD4 cells
CXC3
CD8 cells
IFN-γ
IL-2
IP-10
CXCL-9
CXCL11
IL-4
CXC3
Perforin
granzyme B
Apoptosis of alveolar epithelial cells
Chronic Persistent Inflammation

Fig. 79.6: Role of lymphocytes in COPD inflammation

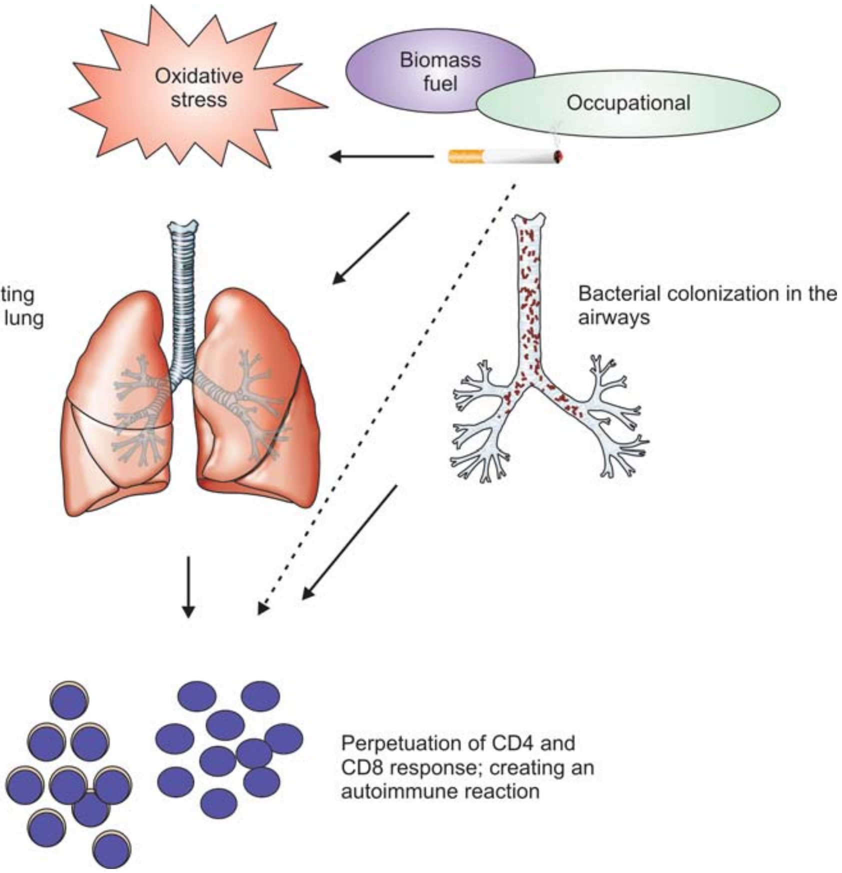

Oxidative stress
Biomass fuel
Occupational
Oxidative stress and cigarette smoke creating autoantigen from the lung tissue
Bacterial colonization in the airways
Perpetuation of CD4 and CD8 response; creating an autoimmune reaction

Fig. 79.7: Autoimmune mechanisms in COPD

create endogenous autoantigens in the lungs augmenting continued CD4/CD8 response in the lungs.[70] There are also antigens in the tobacco smoke, which may also induce the response. Another possibility is that this chronic immune response is actuated, or at least continued, by chronic infectious processes of the respiratory tract often seen in the patients with severe disease, in which there is increased colonization of the lower airways. These infections could either costimulate or mimic as an antigen and provide a persisting antigenic stimulus that maintain the inflammatory processes.[79-82] The association between recurrent childhood viral infections and the development of COPD in adult life, indicate that viruses and bacteria recruit lymphocytes into the lungs as a part of the adaptive immunity (Fig. 79.7).

Interestingly, in the chronic cigarette smokers who do not develop COPD, the autoantigens generated by the oxidative stress and toxins may also induce the lymphocytic inflammation. But this induction is controlled by the subset of another $CD4^+$ cells, collectively known as regulatory T cells, which are capable of suppressing autoreactive lymphocytes through the secretion of inhibitory mediators such as IL-10 or direct cell–to-cell contact.[83] In COPD, there is a greater increase in $CD8^+$ cells than the T regulatory cells and there is also evidence that the number of these cells may be reduced, thereby further enhancing the autoimmune processes.[83] Furthermore, inflammatory ligands of CXCR3, which have been shown to be increased in the lymphocytes of COPD lungs have also shown to increase the expression of MMP-12 in the alveolar macrophages, thereby providing a direct link between T cells and alveolar destruction.[84]

The mounting evidence implicating T cells as important components of COPD inflammation is overwhelming. The understanding that the COPD inflammation is most likely driven by antigen has tremendous therapeutic interest. Currently, there is search of molecules that could inhibit receptors, such as CXCR3 and block the trafficking of Th1 and Tc1 cells into the lungs.[70]

Role of Inflammatory Mediators in COPD

The composition of inflammatory mediators involved in COPD pathogenesis has varied and include cytokines such as TNFα, IL-6 and IL-5; chemokines such as GRO alfa, MCP-1, MIG (IP-10), LTB4 and IL-8; oxidation products such as 8-isoprostane; hormones such as leptin; and enzymes such as MMPs, serine proteinases and neutrophil elastases and many more.[85-91] Amongst these IL-8 is primarily released by stimulated macrophages, epithelial cells, endothelial cells and neutrophils and is one of the most abundant inflammatory mediators present in COPD. It also increased during COPD exacerbations rendering it to be an important inflammatory mediator involved in accelerated decline in the lung volumes.[92-96] The systemic IL-8 has also shown to be related to increase peripheral muscle weakness in COPD, which is one of the most common systemic manifestations of the pulmonary disorder.[97] IL-8 has shown to increase the mRNA abundance of mucin genes in *in vitro* experiments. Upregulation of airway mucin genes by inflammatory/immune response mediators is one of the major contributors to mucin overproduction in COPD.[98,99]

The secretion of IL-8 is augmented by the triggering of IL-8 genes in macrophages, epithelial cells, endothelial cells and neutrophils in the lungs by stimulants such as cigarette smoke, air pollutants, free oxidant radicals and M3 receptor agonists.[100] The secreted IL-8 binds with receptors such as CXCR 1 and CXCR2, and also the toll receptors, present on the target cells.[101-104] The primary function of IL-8 is to induce cellular chemotaxis of neutrophils. However, in addition IL-8 also induces series of other cellular-physiological responses required for its migration and its target function phagocytosis like increase of intracellular Ca^{2+}, exocytosis of proteinases and generation of free oxidant radicals, degranulation of neutrophils and release of neutrophil elastase. IL-8 is also known to activate macrophages,[105] CD-8 lymphocytes, endothelial cells[106] and mast cells.

These diverse properties of IL-8 have made it an important target for COPD therapy. Notably, a recent preliminary clinical trial has shown that treating COPD subjects with the monoclonal antibody against lL-8 can improve dyspnea in COPD patients, but it fails to improve lung functions.[107] This means that targeting IL-8 perhaps may not be enough to control COPD inflammatory ravage. Moreover, therapies such as these could also affect the activity of neutrophils, which are important defense cells required for innate immunity that could lead to the development of infections in the respiratory tract.

TNF-α is another inflammatory mediator with an important role in COPD pathogenesis. Sputum and BAL samples from the COPD subject have shown to increase in the presence of TNF-α in the airways and lung parenchyma. The increased number of macrophages in COPD are a potential significant source of TNF-α.[89] The physiological outcomes of COPD inflammation, such as increasing airflow obstruction, hypercapnia[108] and hypoxemia[109] are shown to be associated with an enhanced TNF-α response in COPD. TNF-α enhances neutrophil chemotaxis and migration by inducing the expression of chemokine IL-8 and by up-regulation of endothelial adhesion molecule.[94,95] It also induces apoptosis in the macrophages[110] and is the major systemic inflammatory mediator that causes the weight loss and nutritional depletion seen in COPD.[91,111]

Increased levels of TNF-α have also been detected in the sputum of subjects with exacerbations of COPD.[112] The increased number of macrophages in COPD is a potential significant source of TNF-α. The levels of TNF-α increase during exacerbations and exercise.[112,113] TNF-α has been also shown to be associated with increased leptin levels in the blood, which is a cytokine that regulates nutrition, especially during COPD exacerbations indicating TNF-α may lead to changes in nutritional parameters and body weight in the course of the disease.[91] Further, genetic studies have also indicated that the range of COPD phenotypes may be driven by specific underlying genetic polymorphism occurring in the TNF-α gene.[114]

With such a diversified role in the pathogenesis of COPD, the assumption of negating the affects of TNF-α with conventional TNF-α antagonist seems to be a thought provoking strategy to manage COPD. However in a randomized, double-blind, placebo controlled, phase II clinical trial, infliximab did not show any significant clinical benefit in COPD patients,[115] indicating, that targeting one specific inflammatory mediator may not be enough to control COPD inflammation.

Leukotriene B_4 (LTB_4) is another inflammatory mediator that has been implicated as the major chemoattractant responsible for neutrophil recruitment and activation in COPD. LTB_4 seems to be the prominent chemotactic factor in patients with the most severe COPD and during acute exacerbations. Its major source is probably the alveolar macrophage and it is assumed that the recruitment of neutrophils could further amplify the effect.[87] The elastase could stimulate the macrophages to release more LTB_4, resulting in further neutrophils recruitment.[87] In addition, LTB_4 also recruits CD8 T cells to the sites of inflammation.[116] LTB_4 receptors are further up-regulated on the macrophages and neutrophils of COPD patients. Antagonism of LTB_4 receptors is currently being considered as a mode for treating COPD.[117]

IL-6 is an inflammatory mediator, which has been frequently associated with systemic comorbidities in COPD.[118,119] This cytokine has been found in great abundance in both systemic circulation and airways of COPD subjects and its enhanced expression has been related to the symptoms of breathlessness, skeletal muscle weakness, insulin resistance, pulmonary hypertension, cardiovascular morbidity and most significantly exacerbations. [118,119] IL-6 has shown to increase fibrinogen levels and thrombocytes in systemic circulation of the COPD subjects, which increases the risk of ischemic heart disease and myocardial infarction in these patients.[119] Remarkably, myocardial infarction is the primary cause of mortality in the COPD patients and IL-6 can be attributed to this. Pulmonary hypertension that occurs secondary to COPD may also be accounted to IL-6. This interleukin has been shown to induce pulmonary artery remodeling in all severities of COPD primarily due to hypoxic stimuli, which is known to cause presser affects on pulmonary vasculature and induces an over expression of the IL-6 genes. IL-6 further potentates pulmonary pressure response to hypoxia and promotes micro-arteriole thrombosis in the lung.[120]

Muscarinic Receptors

Muscarinic receptors have also been shown to play an important role in the pathophysiology of various airway inflammatory diseases, including COPD. Airway smooth muscle expresses abundant muscarinic M_2 and M_3 receptors, roughly in a 4:1 ratio.[121] M_2 receptor is an inhibitory receptor, while M_3 is a primary receptor subtype responsible for bronchial and tracheal smooth muscle contraction. In COPD, the cholinergic activity and muscarinic responses are enhanced and this is due to increased activity of M_3 receptor, although, their numbers do not increase in the airways.[121-125]

The M_3 receptors constrict smooth muscles primarily by modulating calcium kinetics in the muscle cell. Stimulation of M_3 receptors activates phospholipase-C (PLC) Inositol 1,4, 5-trisphosphate (IP_3)[121] and CD 38 - cyclic ADP ribose (cADPr) pathways to induce the movement of calcium out of sarcoplasmic reticulum into cystol for the activation of myosin-actin contractile apparatus.[126-130] M_3 receptor stimulation also enhances the sensitivity of calcium ion in the cell by inhibiting myosin light chain phosphatase (MLCP) through pathways such as phosphoinositide-derived diacylglycerol (DAG)-protein kinase C (PKC)-CPI-17 and RhoA-Rho kinase pathway.[131-144] An increased expression in these molecules has been shown in the presence of inflammatory mediators such as those seen in COPD and cigarette smokers.

In addition, there is a vagal neuronal mechanism, which is modulated in COPD. The inflammation and environmental insults damage the epithelial cells of the airways and expose the ubiquitously present C-afferent nerve fibers lying in the subepithelial region. These fibers when stimulated, due to noxious stimuli and inflammation, transmit messages to the central nervous system, which reacts by increasing the acetylcholine vagal transmission to the bronchi. The acetylcholine acts on both the active muscarinic receptors, such as M_1 and M_3, and inhibitory receptor M_2.[145-152] But, due to underlying inflammation the inhibitory affects of M_2 receptors are dysfunctional in COPD, leaving only the M_3 and M_1 receptors to act on the airway smooth muscles. This results in bronchoconstriction, mucus hypersecretion and cough.[153-157] The cholinergic-receptor stimulation has shown to act synergistically with growth factors to activate mucus cell activation and goblet cell hypertrophy, which is a pathological hallmark of various airway inflammatory diseases such as COPD.[158-161] This indicates that blocking these receptors could have far reaching bronchodilatory effects than the other bronchodilators acting through different mechanisms. Clinical experience with antimuscarinic receptors has indeed supported this argument.

Muscarinic receptors are also known to cause mesenchymal cell proliferation, differentiation and pulmonary vascular remodeling. More recently the increased expression of the M_3 receptor has been identified on macrophages, neutrophils and lymphocytes of COPD patients.[162-165] There is also an evidence of increased acetylcholine induced neutrophilic chemotactic activity in COPD (Fig. 79.8).[166,167] Very recently it has been shown that M_3 receptors augment cigarette smoke induced IL-8 secretion from the smooth muscle cells, and that selective muscarinic antagonists abrogate these effects.[168,169] Thus, anticholinergic therapy can potentially achieve far reaching significant controller effects in COPD that extends its capacity as medication to promote bronchodilatation.

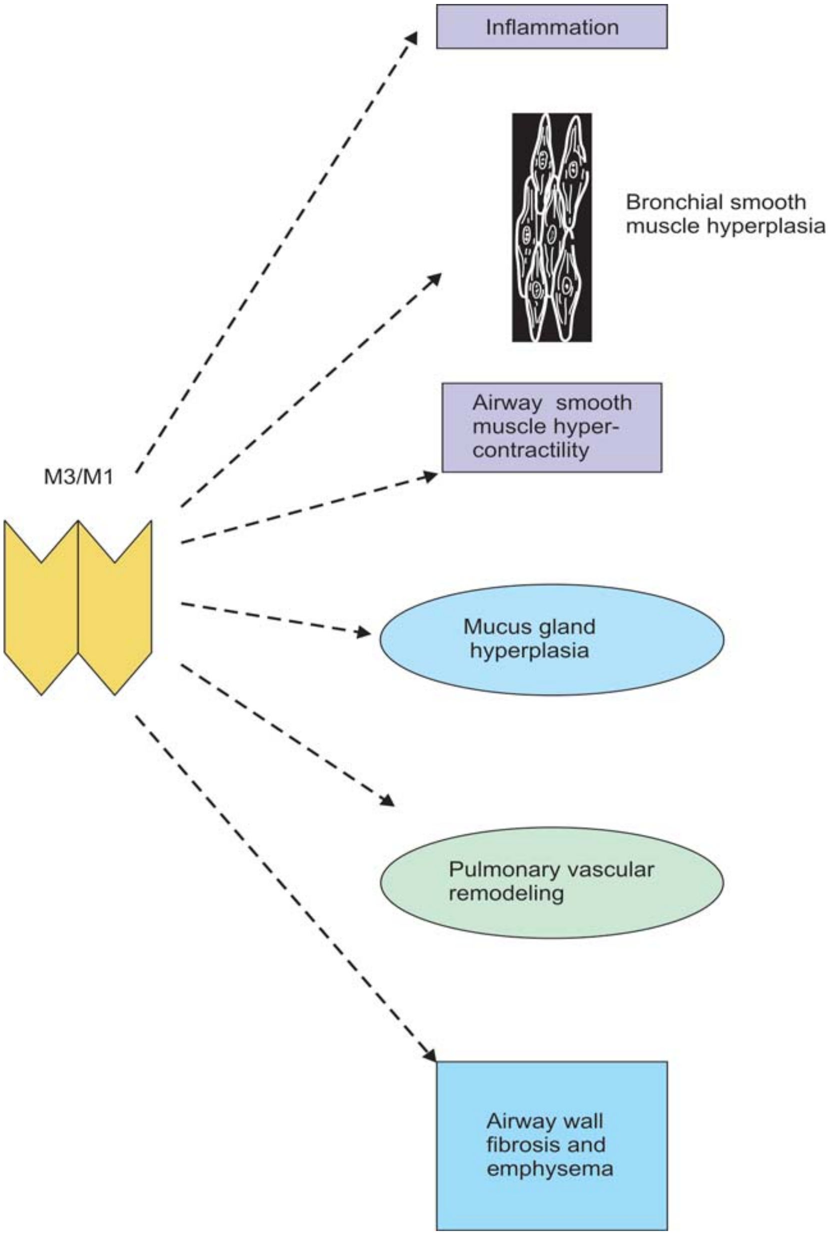

Inflammation
Bronchial smooth muscle hyperplasia
Airway smooth muscle hyper-contractility
M3/M1
Mucus gland hyperplasia
Pulmonary vascular remodeling
Airway wall fibrosis and emphysema

Fig. 79.8: Role of muscarinic receptors in pathogenesis of COPD

Role of Oxidative Stress in COPD

There is now overwhelming evidence for the presence of increased oxidative stress in patients with COPD. Oxidative stress has a very significant role in every stage of the pathogenesis in COPD. Increased oxidative stress in the airspaces can initiate a number of early inflammatory events in the lungs. The free oxidant radicals in the lungs and systemic circulation arise from the sources of air pollutants such as cigarette smoke and biomass fuel, and also inflammatory cells such as neutrophils and macrophages.[170]

Amongst the complex mixture of over 4,700 chemical compounds present in the cigarette smoke, free radicals and other oxidants account for the major deleterious effects on the respiratory system. It has been estimated that cigarette smoke contains approximately 10^{15} oxygen radicals per puff, primarily of the alkyl and peroxyl types.[170] The other important compounds present in cigarette smoke include nitrous oxide and semiquinone, which are also capable of producing reactive oxygen species such as superoxide anion (O_2^-), peroxynitrite, alkyl peroxynitrites and hydrogen peroxides.[171] On the other hand, the oxidant burden of biomass fuel has not been yet demonstrated, but considering inhaling the smoke released from burning biomass without the intervention of filter could be a much higher source of reactive oxygen compounds than cigarette smoke.

The epithelial lining fluid and mucus are the first line of defense in the lungs against inhaled oxidants by quenching the short-lived radicals in the cigarette smoke.[172] However, cigarette smoke condensate, which forms in the epithelial lining fluid, may continue to produce reactive oxygen species for a considerable period in patients with COPD, as part its pathogenesis.[173,174] Reactive oxygen species are also released from activated inflammatory leukocytes, such as neutrophils and macrophages,[42,175-181] which are known to present in increased numbers in the lungs of cigarette smokers. The inflammatory mediators released by these cells permanently switch on the oxidative stress mechanisms, providing a continuous source of free oxidant radicals, which not only confine to the lungs, but also spill into the systemic circulation and affect other body organs with particular predilection to the heart and skeletal muscles.[20]

A series of physiological and pathological changes present in COPD have been attributed to oxidative stress, which include the oxidative inactivation of antiproteases and surfactants, mucus hypersecretion, membrane lipid peroxidation, alveolar epithelial injury, remodeling of extracellular matrix and apoptosis. Reactive Oxygen Species (ROS) have been shown to reduce the synthesis of elastin and collagen and also fragmenting these skeletal proteins. ROS affects the structure of matrix proteins such as hyaluronate and proteoglycans and reduces the viscosity of the extracellular matrix for easy movement of inflammatory cells. Moreover, oxidative stress reacts with the membrane phospholipids present in the airway epithelial cells and activates the arachidonic acid in the cell membranes to release prostaglandins and leukotrienes, which are potent inflammatory agents. Injury to the epithelium may be an important early event following exposure to cigarette smoke, and is shown by an increase in airspace epithelial permeability and this has been shown to be strongly associated with increased amount of free oxidant radicals in the airways.[170]

Oxidative stress also activates other cellular systems that increase the production of inflammatory mediators such as IL-8, IL-1 and TNF-α. It also enhances the aging process by down regulating various anti-aging molecules such as Nrf2, sirtuin, histone deacetylase (HDAC) and oxidative protein, and also activates processes that are implicated in cell senescence and Deoxyribonucleic Acid (DNA) damage. Furthermore steroid resistance of COPD inflammation has been implicated to be caused by increased oxidative stress.[182] Oxidative stress reduces steroid responsiveness via a reduction in HDAC2 activity and expression (Fig. 79.9).[182]

Airways are always exposed to various ambient pollutants, which are inhaled during respiration, that generate oxidative stress inside the airways. The airways are protected from this ongoing oxidative stress by a series of antioxidants, which are found ubiquitously in the respiratory tract lining fluid throughout the respiratory tract. These antioxidants generally present in the fluid lining the airways are cysteine residues such as mucin and glutathione, uric acid, albumin, vitamin E and vitamin C.[183-188] The reactive oxidant species enhance the secretions of mucin[189] and glutathione in the respiratory lining fluid to counteract the oxidant load, but in diseases like COPD, this increase may not be sufficient to deal with excessive oxidant burden seen in this disease either due to is depletion of the antioxidants or reduced production.[170] Therefore, an improvement in the antioxidant capacity in COPD patients is an interesting therapeutic approach. Currently there is no effective antioxidant therapy, which can effectively thwart the oxidative stress in the lungs of COPD patient. However, N-acetyl-cysteine (NAC), a precursor of glutathione, which is a very powerful and ubiquitously distributed antioxidant has met with varying success with more positive results in higher doses.[182]

Other interesting antioxidants, such as dietary polyphenol (curcumin-diferuloylmethane, a principal component of turmeric); resveratrol (a flavonoid found in red wine); green tea (theophylline and epigallocatechin-3-gallate); ergothioneine (xanthine and peroxynitrite inhibitor); quercetin; erdosteine and carbocysteine lysine salt; spin traps such as α-phenyl-N-tert-butyl nitrone; a catalytic antioxidant (ECSOD mimetic); manganese (III) meso-tetrakis (N,N′-diethyl-1,3-imidazolium-2-yl) porphyrin (AEOL 10150 and AEOL 10113); and a superoxide dismutase mimetic M40419 have also been reported to inhibit cigarette smoke-induced inflammatory responses *in vivo*.[182] Since a variety of oxidants, free radicals and aldehydes are implicated in the pathogenesis of COPD, it is possible that the therapeutic administration of multiple antioxidants will likely be effective in the treatment of COPD.

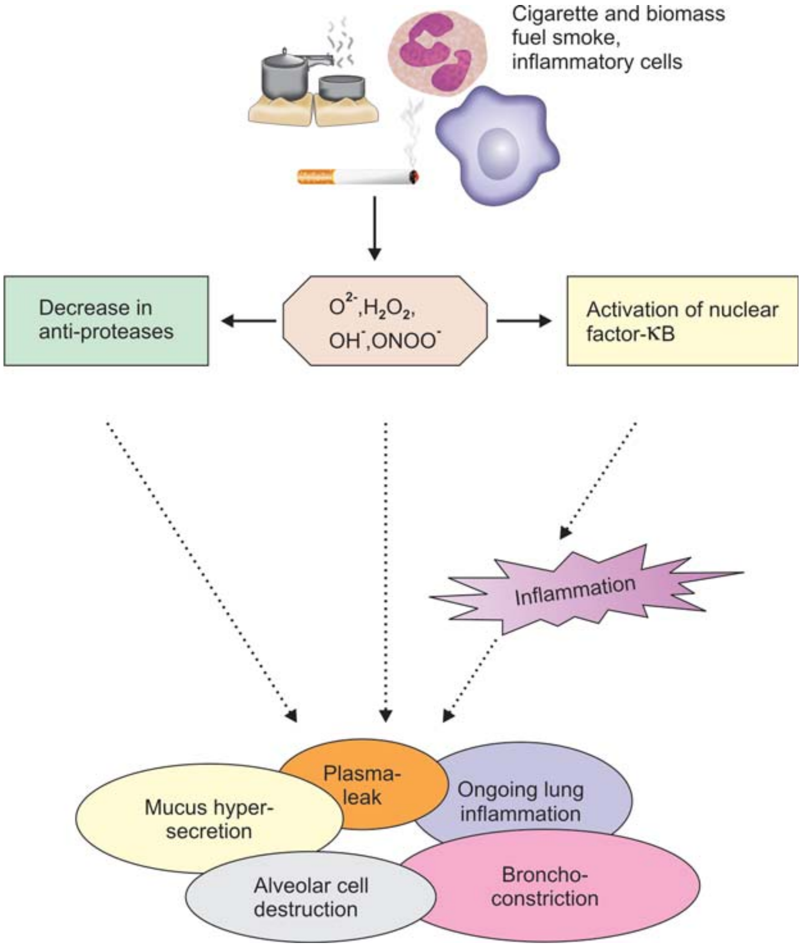

Cigarette and biomass fuel smoke, inflammatory cells
Decrease in anti-proteases
O2-,H2O2, OH-,ONOO-
Activation of nuclear factor-κB
Inflammation
Plasma-leak
Mucus hyper-secretion
Ongoing lung inflammation
Alveolar cell destruction
Broncho-constriction

Fig. 79.9: Role of oxidative stress in pathogenesis of COPD

COPD: A Disease of Accelerated Aging[182]

The link between aging and the pathogenesis of COPD has been elucidated in numerous studies. Senescence is a complex outcome of both intrinsic and environmental factors, especially oxidative stress, and therefore, the role of pollutants, such as cigarette smoke and indoor air pollution are key factors linking aging lung to COPD. Although, at the molecular level there are numerous similarities between aging and COPD, the molecular mechanisms have not yet been fully explored.

As the age increases, there is a indolent decline in lung function with airways showing physiological airway obstruction ($FEV_1/FVC<70\%$) along with emphysema even in the normal healthy elderly population who may have never smoked in their life. These observations indicate that the number of neutrophils in the lower respiratory tract of healthy elderly individuals is likely increased, and there is increased release of neutrophil elastase, which could contribute to the loss of elastic recoil and of elastin fibers in the aging lung, which in turn would reduce interdependence between the airways and parenchymal structures, thus contributing to the deterioration of lung function.[182] Intriguingly, in COPD all these changes occur, but at much earlier age. Glucocorticoid sensitivity is reduced during aging as well as in COPD.[190-192]

The oxidative stress also drives proinflammatory transcription factors such as NFêB to switch on multiple inflammatory genes responsible for the expression of various inflammatory mediators and forms an important aspect of normative aging process. This mechanism is accelerated in COPD, especially in the lungs, adding to the body of evidence that COPD is a disease of accelerated aging of the lungs.

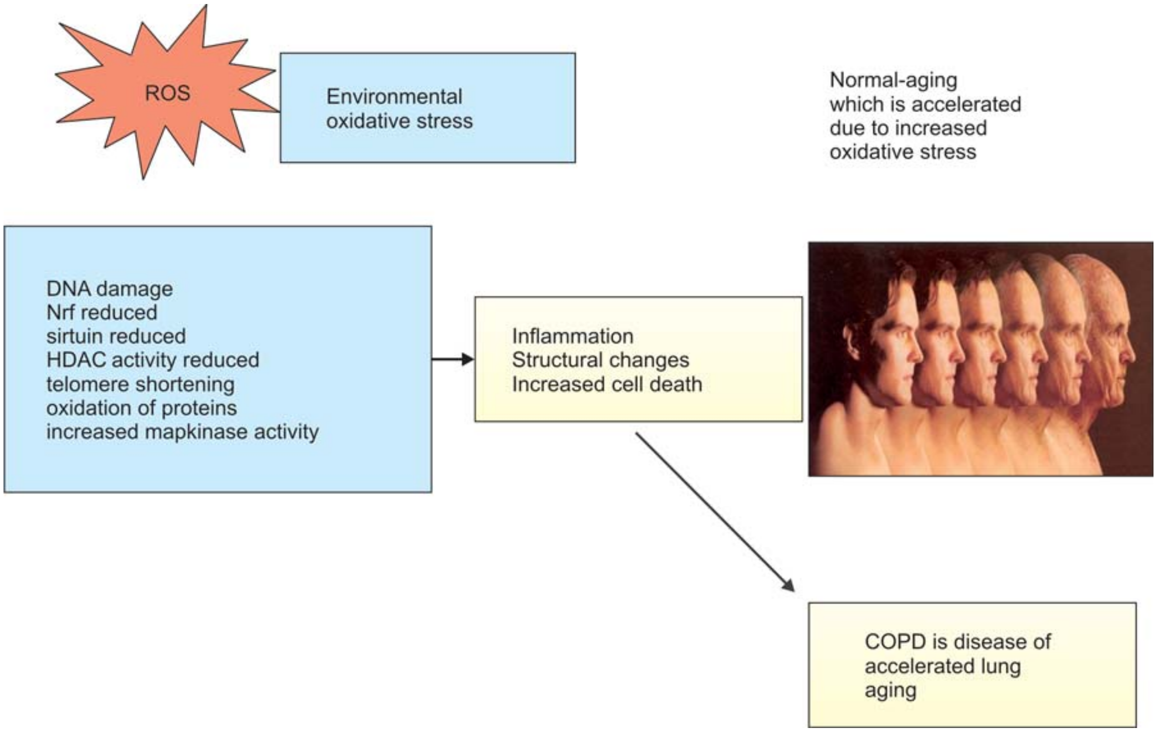

ROS
Environmental oxidative stress
Normal-aging which is accelerated due to increased oxidative stress
DNA damage
Nrf reduced
sirtuin reduced
HDAC activity reduced
telomere shortening
oxidation of proteins
increased mapkinase activity
Inflammation
Structural changes
Increased cell death
COPD is disease of accelerated lung aging

Fig. 79.10: Role of oxidative stress and accelerated aging process in COPD

The molecular transitions, which are responsible for aging, are such that the growing oxidative stress due to accumulating free reactive oxygen species alters the genetic machinery by damaging the DNA and shortening the telomere. A telomere is a region of DNA at the end of a chromosome, which protects the end of the chromosome from deterioration and shortening with each round of cell division. This mechanism limits the proliferation of human cells to a finite number of cell divisions by inducing replicative senescence, differentiation or apoptosis. Eventually, the cells with shorter telomeres can no longer replicate and taken over time the signs of aging start showing up. Oxidative stress, not only greatly accelerates telomere shortening in cells, but also causes somatic mutations in DNA, thereby causing the DNA damage, and COPD is a disease in which oxidative stress is amplified by several folds. Telomere length has been demonstrated to be significantly shorter in patients with emphysema than in asymptomatic nonsmokers in alveolar type II cells and endothelial cells, peripheral blood mononuclear cells and fibroblast (Fig. 79.10).[182]

Deficiency of several anti-aging molecules such as sirtuins, klotho, Senescence Marker Protein-30 (SMP30), HDAC and Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2); the molecules responsible for DNA repair, such as DNA-dependent protein kinase (DNA-PK) and Ku86 (or Ku80), have shown to cause emphysematous changes in the lungs and various other senility related changes in animal models. Increasing oxidative stress, a regular outcome of aging, decreases these molecules in various organs exposing them to aging changes. Currently these molecules form very important therapeutic targets for research in various chronic diseases associated with aging such as COPD.[193-199]

COPD is a Disease of Systemic Inflammation

Chronic obstructive pulmonary disease has classically been considered to be an intrathoracic condition characterized by poorly reversible airway obstruction. However, COPD has been recently recognized as a multicomponent disorder, associated with systemic inflammation and extrapulmonary manifestations. It has now been well documented that the inflammation that develops in the patient, does not confine to the lungs, but spills into the systemic circulation through the pulmonary vessels and predisposes almost every organ system in the body with particular predilection to the heart, as the heart is the first organ that receives all the blood from the pulmonary vasculature.[200-212]

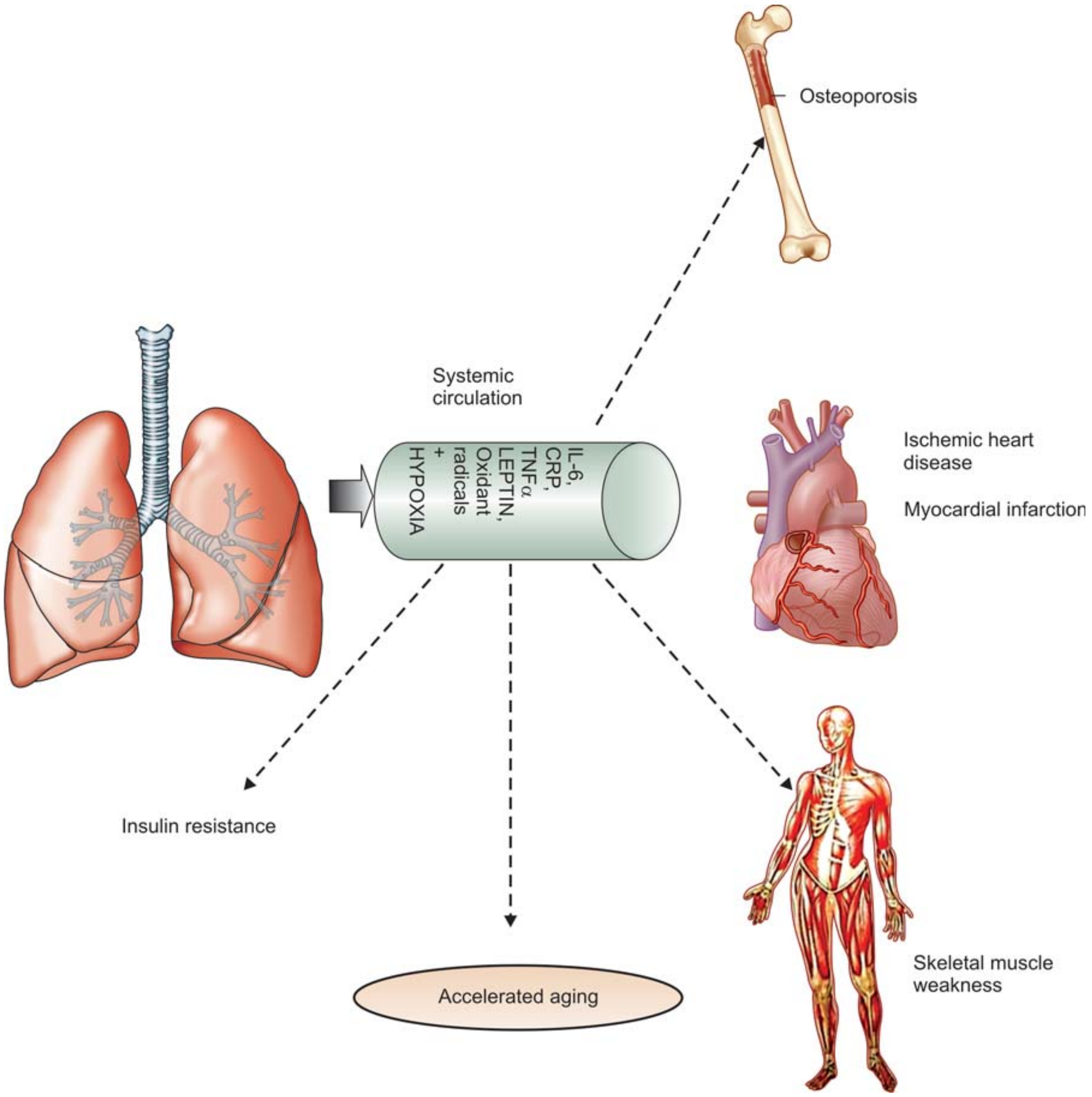

Osteoporosis
Systemic circulation
IL-6,
CRP,
TNFα
LEPTIN,
Oxidant
radicals
+
HYPOXIA
Ischemic heart disease
Myocardial infarction
Insulin resistance
Accelerated aging
Skeletal muscle weakness

Fig. 79.11: Systemic effects of COPD inflammation

There is always a persistent, low-grade systemic inflammatory response present in part of COPD patients. Various studies have shown enhanced levels of acute phase proteins like C-Reactive Protein (CRP)[213,214] and proinflammatory cytokines such as TNF-α[215] and IL-6[216,217] in many COPD patients. Moreover, there has been a consistent strong association between reduced lung function and systemic inflammation. Even increased polymorphisms have been shown in the inflammatory genes and there is increasing interest in identifying a haplotype of inflammatory genes, which predisposes to systemic manifestation of COPD.[218]

These inflammatory makers along with persistent hypoxia increase the basal metabolism in the body leading to catabolic changes such as reduced muscle mass, wasting of skeletal muscles and diaphragmatic weakness. Notably, interventions such as regular exercise and physiotherapy have been shown to reduce systemic inflammation. Further the systemic inflammation also increases oxidative stress in various other organs. COPD is associated with chronic heart failure in more than 20% of patients and myocardial infarction is by large the commonest cause of mortality in all grades of severity COPD. Up to 70% of COPD have underlying osteoporosis.[202,203] There has also been a strong association between depression and COPD. There is emerging evidence indicating insulin resistance in some COPD patients due to systemic inflammation and recently an association with diabetes and COPD has been demonstrated. COPD has also been related to metabolic syndrome as it predisposes patients to increased cardiovascular morbidity and diabetes mellitus (Fig. 79.11).[200]

There is increasing interest in reducing systemic inflammation with medications like low-dose statins,[219] antioxidants[220] and steroids[221] for the chronic management of COPD. Some retrospective observations indicate that such concomitant medications have the potential to increase survival and morbidity in COPD patients.

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Pulmonary Function Testing in Chronic Obstructive Pulmonary Disease

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HISTORY AND EVOLUTION

The role of Pulmonary Function Testing (PFT) in diagnosis and management of Chronic Obstructive Pulmonary Disease (COPD) has evolved over time. While accurate descriptions of the diseases grouped together under COPD predate any formal definitions,[1] the recognition of progressive respiratory symptoms and illnesses arising after exposure to noxious stimuli, especially cigarette smoke came much later in the mid 20th century. These illnesses were formerly known by multiple labels, of which two, namely chronic bronchitis and emphysema, were officially endorsed by the American Thoracic Society in 1962.

"Chronic bronchitis" was defined as a cough productive of sputum for at least three months of two consecutive years. Emphysema was defined in anatomic terms of enlarged alveolar spaces due to the destruction of alveolar walls. Neither definition encompassed any physiologic considerations. The term "COPD" encompassing both chronic bronchitis and emphysema is considered to have originated soon after.[1] In this era, the definition of COPD was mostly in clinical or structural terms and the disease was well established by the time a diagnosis was made. While the scientific and technical basis of PFTs, including all current methods was already well established by this time due to seminal work by stalwarts of the field, such as DuBois, Hyatt and Mead, the full recognition of the clinical utility of these tests in COPD came much later.

The 1959 Ciba symposium on "terminology, definitions and classification of chronic pulmonary emphysema and related conditions" presciently stated that the standardized collection of functional, clinical and pathological data may lead to the development of specific diagnostic criterion.[2] Forced expiratory tests of "ventilatory function," identical to modern spirometry and tests of "alveolar-capillary and circulatory function," such as arterial blood gases and cardiopulmonary exercise testing, were recommended as essential tests. Tests of lung compliance and resistance by the use of an esophageal balloon and a whole body plethysmograph (body box) were recommended as supplemental tests, amongst others such as gas diffusion and nitrogen washout. Over the next few decades, alterations in such measures of physiologic function were correlated to clinicopathological data and it became possible to reliably distinguish between the common lung diseases.

With the emergence of computed tomography as a preferred test to study structural lung diseases, such as emphysema, pulmonary fibrosis, etc. relatively simple and widely available tests like spirometry that primarily measure expiratory airflow limitation in Obstructive Airway Disease (OAD), supplanted more complex methods. Over time, this has led to new definitions of COPD in which previous distinctions are done away with and the disease is simply defined in functional terms, as predicted in the 1959 Ciba symposium. The most recent guidelines from Global Obstructive Lung Disease (GOLD) initiative of World Health Organization/ National Heart Lung and Blood Institute state that COPD is a disease state characterized by airflow limitation that is not fully reversible.[3] The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. The GOLD initiative revolutionized the definition of COPD by entirely basing the diagnosis of COPD upon the measurement of airflow limitation. It also emphasized the need to educate primary care and general practitioners, and to promote objective criterion.

Today, pulmonary function testing to evaluate airflow limitation is by definition necessary to diagnose COPD and also contributes immensely to its management. The various approaches and their relative merits are summarized in the following sections. To conform to the GOLD definition of COPD, pulmonary function testing needs to be done initially to look for airflow limitation, followed by the response to bronchodilators to look for reversibility and finally, multiple times thereafter to call the obstruction as persistent or progressive, these being key features of COPD. However, this does not mean that the GOLD definition is all inclusive and there is scope to incorporate factors such as dyspnea, which correlates well with subjective disability and Quality of Life (QoL); as well as other assessment of functional capacity like the six-minute walk test.

THE CLINICAL NEED FOR PULMONARY FUNCTION TESTS

Early Diagnosis

The need for pulmonary function testing in diagnosing COPD is not just a question of semantics and academic distinctions. Chronic obstructive pulmonary disease has a relatively silent stage where measurable airflow limitation exists despite a paucity of symptoms. In this phase, smoking cessation, the most effective intervention, can arrest the progression of COPD. Therapeutic options in advanced stages are poor and cannot reverse the disease. In a large study conducted in the United States,[4] it was seen that most patients with spirometric abnormalities diagnostic of COPD or other obstructive disease never had their conditions diagnosed, nor were they receiving systematic therapy. Similar studies in the United Kingdom[5] and Canada[6] show strikingly similar figures with about 67% of patients who visited primary care for any reason having undiagnosed obstructive disease.[6] Importantly, poor lung function was strongly associated with adverse outcomes, which could have been avoided or delayed by early diagnosis and treatment. Thus, clinicians must become aware of the fact that obstructive airway disease is no longer an exclusively clinical diagnosis and there is an unmet need for better detection early, because the true prevalence of COPD is much higher than it seems. It can be very conservatively estimated that in our own practices, in the absence of lung function testing, about half of the COPD cases might be missed.

Management

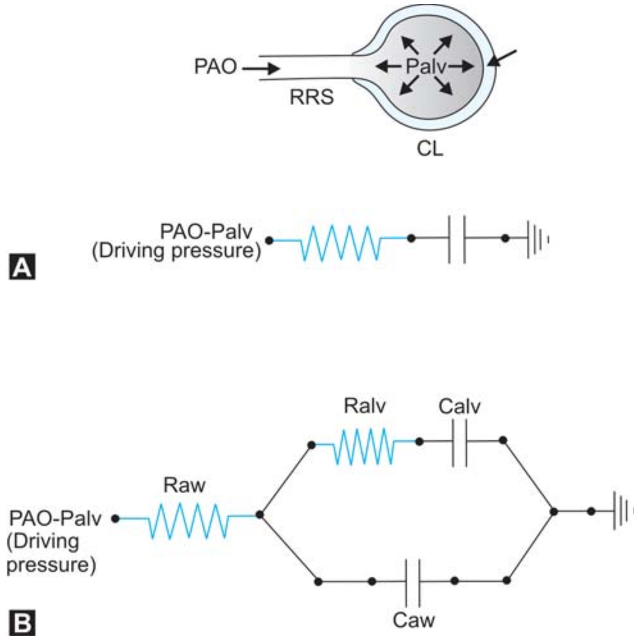
Optimal management of lung diseases, including COPD, requires objective assessment of lung function in addition to the subjective assessments of well-being. In addition to guide bronchodilator therapy, subsets of COPD patients identifiable by functional testing, may benefit from treatment with inhaled corticosteroids.[7] Some of these may have an asthmatic component characterized by partial reversibility to bronchodilators and increased exhaled nitric oxide. Other important uses for pulmonary function testing in routine practice include preoperative risk assessment and determination of suitability for pulmonary surgeries.[8,9]

PHYSIOLOGICAL PRINCIPLES

It may be pertinent to briefly review the physiology of the respiratory defect in COPD before discussing the findings and interpretation of the investigations. Airflow limitation, which defines COPD, refers to a reduced maximal expiratory flow of air despite normal respiratory effort. While a full review of the mechanical properties of the lung relating to the flow of air during breathing are beyond the scope of this chapter, a brief introduction is provided in a simple mechanical model of the lung.[10,11] It can be seen that expiratory flow of air can be diminished by increased resistance of the conducting airway, reduced driving pressure, or both (Figs 80.1A and B). Key concepts of how these mechanisms relate to COPD are discussed further.

Airway Resistance in COPD

The major mechanisms of increased resistance in COPD are narrowing, dynamic closure and occlusion of airways. Narrowing of airways is due to a multitude of causes such as thickened and inflammed mucosa, hypertrophied smooth muscle, and loss of expansile stretching effects of lung parenchyma. Airway closure is a physiological mechanism by which further exhalation at lower limits of lung volumes (Residual Volume, RV) is prevented by apposition of airway walls. This is exaggerated in narrowed and inflammed COPD airways, sometimes to the extent that it can be seen at tidal volumes of breathing. This pathological increase in RV is compensated by hyperinflation, which is the compensatory mechanism of the lung to “pull open” the



Figs 80.1A and B: A simplified model of the lung showing airflow to the alveoli as a function of airway resistance, driving pressure and lung compliance.
PAO: Pressure at the airway opening; Palv: Alveolar Pressure; PPL: Pleural Pressure.

airways. This has adverse mechanical consequences leading to increased work of breathing and ineffectiveness of respiratory muscles, as discussed in the next section.

The third mechanism of airflow limitation is the occlusion of the airways, most commonly by mucus plugs. This is distinct from the increased mucus production in the large airways, which while causing cough, does not cause airway occlusion. Here, it is important to realize that the bronchial tree is a parallel arrangement of resistances and hence, the increase in resistance is much greater with a homogenous narrowing, even of a smaller degree than a localized complete obstruction. This is determined by the law of parallel resistances, $1/R = 1/R_1 + 1/R_2 + \ldots + 1/R_n$; such that homogeneous reduction of all airway diameters by half would lead to 16-fold increase in reductions (fourth power) while equivalent complete obstruction in terms of area, would lead to only four-fold increase in resistance. This translates conceptually to the fact that the total resistance in a parallel arrangement is lower than the lowest resistance, hence the lesser rise in resistance with a segmental collapse or a localized obstruction than with a total obstruction in a portion of the airways. Another fact to consider is that in normal lungs the cross-sectional area increases markedly while moving through the progressively higher generations of airways (Weibel's Trumpet Model).[12] Thus the small airways with their maximal contribution to area contribute least to the resistance of the airways. Since, these are the initial sites of pathology, techniques that permit detection of small airway disease hold promise in COPD diagnosis.

Expiratory Driving Pressures in COPD

In addition to obstruction, especially with emphysema as the predominant pathology, there is destruction of the lung tissue leading to a decrease in elasticity and loss of the supporting structures around airways and the alveolar walls. The loss of elastic recoil leads to reduced driving pressures for any given volume during expiratory flow, and higher volumes for a given transpulmonary pressure than the normal lung. The static expiratory pressure-volume curves (Fig. 80.2) show this as a marked deviation from the normal slope of the pressure volume relationship with a higher Total Lung Capacity Ratio (TLC), Functional Residual Capacity (FRC) and RV. All the above changes in COPD are attended by mechanical consequences, such as flattening of the diaphragm and abnormal inspiratory muscle action angles on the ribcage. These are the primary causes for the feeling of breathlessness in COPD patients. The loss of parenchymal support also implies that airways are more prone to collapse.

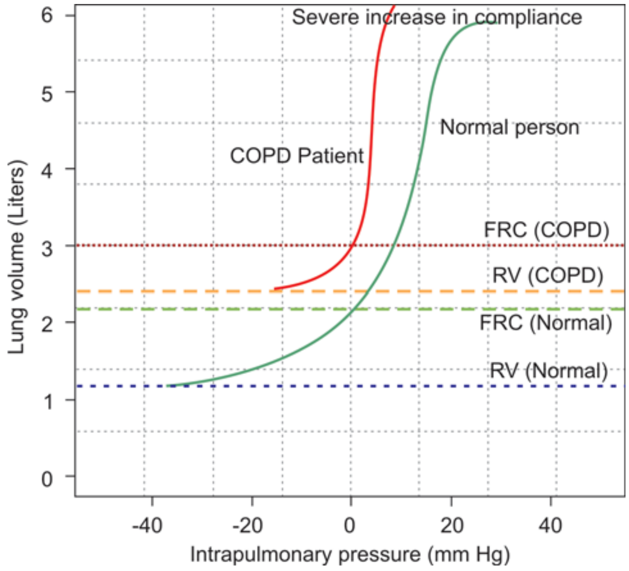


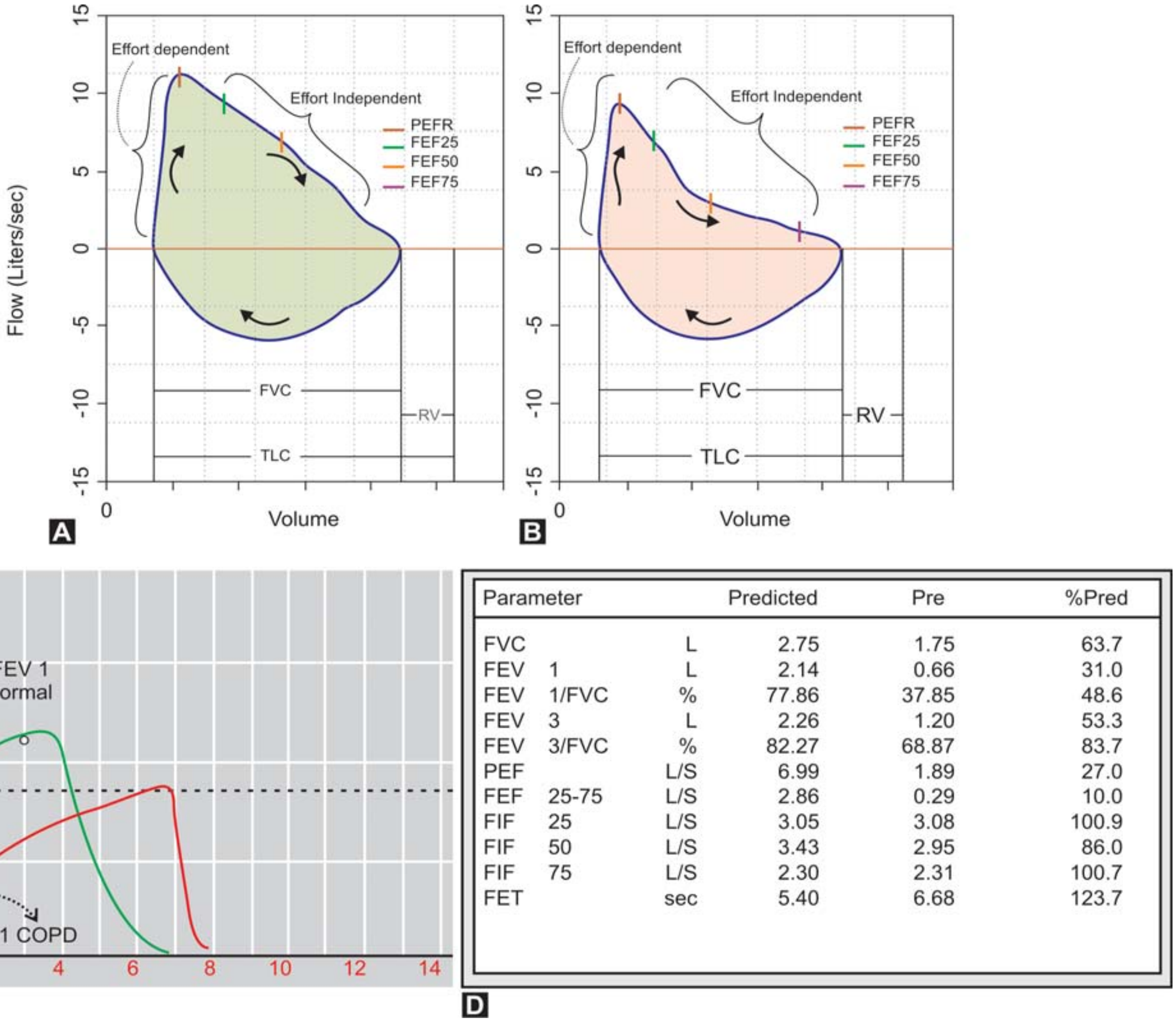
Fig. 80.2: Pressure-volume curve for the respiratory system of a healthy subject and a COPD patient. The TLC, RV and FRC, all are increased in COPD.

The reduced driving pressures, hyperinflation and increased propensity to collapse are characteristic of COPD in contrast to increased airway resistance which is also seen in asthma. Together, these result in expiratory airflow limitation as discussed below.

Expiratory Airflow Limitation: Principles and Pitfalls

During forced exhalation, there is an effort-dependent phase, where the driving pressure is dependent upon the effort followed by an effort independent phase where the elastic recoil of the lung determines the driving pressure. It is important to note that in the effort independent phase, the resistive segment is not the entire airway but only the region proximal to the pressure equalization point. This point is referred to as the choke point, simplistically shown as collapse of the airway, but more accurately the point where local flow velocity reaches the local speed of wave propagation. Figure 80.3 shows the common indices related to expiratory flow limitation during a forced exhalation maneuver. Notably, these correlate to the resistance of airways to airflow, but are only an indirect approximation since they are influenced by: Effort; lung recoil; location of choke point; and resistance of a variable segment defined by the location of choke point(s).

Other methods to indirectly assess airflow limitation include direct measurements of the resistance of the airways [Whole Body Plethysmography (WBP), body box] or the respiratory system [Impulse Oscillometry System (IOS) or Forced Oscillation Technique (FOT)].[13] These are substantially different from spirometry, which directly measures expiratory airflow limitation during a



Parameter			Predicted	Pre	%Pred
FVC		L	2.75	1.75	63.7
FEV	1	L	2.14	0.66	31.0
FEV	1/FVC	%	77.86	37.85	48.6
FEV	3	L	2.26	1.20	53.3
FEV	3/FVC	%	82.27	68.87	83.7
PEF		L/S	6.99	1.89	27.0
FEF	25-75	L/S	2.86	0.29	10.0
FIF	25	L/S	3.05	3.08	100.9
FIF	50	L/S	3.43	2.95	86.0
FIF	75	L/S	2.30	2.31	100.7
FET		sec	5.40	6.68	123.7

Figs 80.3A to D: Common indices of expiratory airflow limitation (during a forced inhalation maneuver)

forced exhalation maneuver. In WBP, the relationship of measured changes in airflow (dV') to calculated changes in alveolar pressure (dPalv) during breathing is used to estimate either airway resistance (Raw) or specific airway resistance [SRaw; SRaw = Thoracic gas volume (TGV) x Raw]. Since alveolar pressure changes cannot be directly measured, the patient breathes in a closed body box such that, using Boyle's law, they can be estimated (dPalv = PdV/V, where P is BTPS corrected atmospheric pressure and V is TGV). In contrast, IOS or FOT rely upon the additional airflow (V') induced by applied pressure signal (P).

The use of suitable impulses (IOS) or pseudorandom noise (PRN-FOT), allows determination of respiratory system impedance [Zrs and its frequency dependence (Zrs{f} = P{f}/V'{f}/)]. Zrs being a complex parameter is further split into a resistive component (Rrs) and a reactive component (Xrs). The reactive component comprises of inertive behavior of air that resists acceleration and an opposing elastic behavior of lung (mostly parenchyma) that stores energy during volume expansion. Importantly, the elastic component is not the inverse of static compliance but reflects nondissipative energy storing properties of the lungs. Diseased stiff lungs that have a low compliance have reduced ability to store and return energy. In many ways, this is analogous to an electrical circuit. Advanced readers with interest in IOS can find more detailed information elsewhere.[14]

CLINICAL APPLICATIONS

Spirometry

Spirometry remains the cornerstone of diagnosis in COPD, but care must be exercised in following the procedure to the highest applicable standards.[15-19] Since, it measures flow limitation during a forced expiratory maneuver, the key aspects are adequacy of the maneuver, accurate measurement of flow, appropriate use of normal reference values, and last but not least—repetition. Quality assurance guidelines based on the standards defined by GOLD, are presented below, divided into test preparation, performance and evaluation.

Preparation

- Spirometers should be calibrated on a regular basis, preferably weekly for machines that measure volume (bellows) and daily for machines that measure flow (differential pressure pneumotachograph, turbine, ultrasonic). Calibration is done by using a gas syringe that pushes known volume of air through the device at a representative flow rate. Some technologies, such as pneumotachographs, require more careful attention to calibration than others. Changes in ambient temperature may require recalibration.
- The personnel conducting the test should be thoroughly trained for conducting spirometry. Since spirometers have individual quirks based on the technology used for volume/flow detection, the training must be relevant to the actual instrument in use. Except in rare circumstances, most modern spirometers provide equivalent data and are often pre-certified to comply with international guidelines. While a full discussion on choosing spirometers is beyond the scope of the current test, there is no such thing as "the best spirometer" and the choice depends upon the intended application.
- Spirometers that provide visualization of the flow-volume loop should be used. Else, the equipment should have the capability to recognize a "bad-test," such as an inadequate expiration and prompt the possible reason for the error. It is preferable to use spirometers that conform to digital data standards that are portable across systems for easy collation of data.

Performance

- Accurate and reproducible spirometry requires careful attention to the detail. The exhalation should be forceful, fast and complete. The posture of the individual should be straight to maximize the force developed by the chest and abdominal wall muscles.
- At least three reproducible volume-time curves are necessary and at least two out of the three Forced Expiratory Volume in One Second (FEV_1) values should be within 5% or 100 ml of each other (whichever is greater). The best measurement is selected for comparison against the predicted values.
- The expiratory volume-time curves should be smooth and free from irregularities. This is particularly troublesome in individuals with cough which creates irregular flows during the test. Ironically, the maneuver itself has a tendency to precipitate cough and airway closure in persons with airway disease.
- The exhalation should begin from a full inspiration and should continue until it reaches a plateau. This might take anywhere between 6 and 15 seconds or even longer in severely diseased individuals.
- FEV_1/ Forced Vital Capacity (FVC) ratio should be selected from the technically acceptable curve with the largest sum of FVC and FEV_1.

- The above-mentioned procedure is repeated after a bronchodilator has been given to characterize the reversibility of the obstruction.

Evaluation

- The results are compared with the predicted normal values of FEV$_1$ and FVC for that particular age, sex, height and race.
- The ratio of FEV$_1$ to FVC is termed as Forced Expiratory Ratio (FER). The postbronchodilator FER of less tha 0.7, along with FEV$_1$ less than 80% predicted value confirms airflow limitation that is not fully reversible.
- The predicted values should be appropriate for the population under study. In India, we should use local reference values rather than standard western standards that often come with the equipment.[20] However, the lack of such predictive values in the elderly creates a risk of over-diagnosing COPD due to the fall in normal lung function with age. GOLD mentions this as one of the urgent step to be taken for proper diagnosis.
- The measurements should be serially repeated over time to assess the progression of airflow limitation. Typically COPD is defined as a progressive disorder without reversibility of airflow limitation.

Typical shapes of flow volume loops from spirometry tests (Fig. 80.4) can help to identify the pattern and site of airway obstruction.

Spirometric Classification of Severity

In this chapter, we conform to the GOLD guidelines update 2009 for diagnosing and classifying COPD.[3] While these guidelines seem to result in the increased risk of false negatives in young and false positive in elderly subjects, compared to alternative recommendations from American Thoracic Society and European Respiratory Societies; they serve as important global standards. The spirometric classification stages the disease into four stages on the basis of severity. The initial diagnosis relies on the postbronchodilator spirometric cut-point of FEV$_1$/FVC as less than 0.7. These cut-off points are chosen for the sake of simplicity and have not been validated clinically, but support for taking FEV1/FVC less than 0.7 as a diagnostic criterion comes from a study on a random sample which shows that in healthy people of all ages, the ratio was more than 0.7. This is the primary disagreement between GOLD criterion and the ATS/ERS recommendations that support use of population specific Lower Limit of Normal (LLN) criterion that may vary with age, sex or even ethnicity. Consequently, the stages based upon these ratios are somewhat empirical (Table 80.1). Nonetheless, for practical application, GOLD has made some effort to integrate spirometric classification with clinical picture although the synthesis is somewhat artificial because of imperfect relationship between the two.

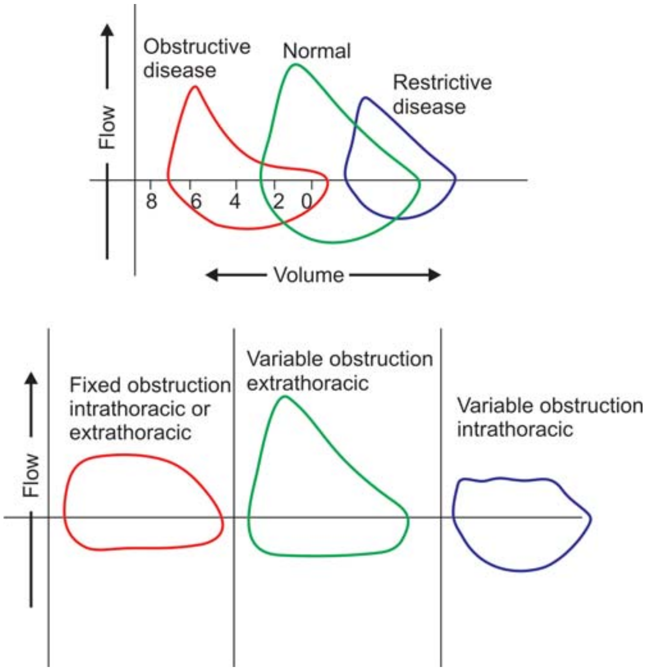


Fig. 80.4: Flow volume loops in some clinical situations as labeled. Extrathoracic obstructions affect inspiration, intrathoracic affect expiration and fixed such as tracheal stenosis affect both.

TABLE 80.1: Summary of GOLD criterion for staging of severity of COPD

Stage I	Mild	FEV1/FVC < 0.7 FEV1 ≥ 80% predicted
Stage II	Moderate	FEV1/FVC < 0.7 50% ≤ FEV1 < 80% predicted
Stage III	Severe	FEV1/FVC < 0.7 30% ≤ FEV1 < 50% predicted
Stage IV	Very Severe	FEV1/FVC < 0.7 FEV1 < 30% predicted or < 50% predicted plus chronic respiratory failure

(Respiratory failure: arterial partial pressure of Oxygen (PaO$_2$) <8 kPA (60 mm Hg) with or without arterial partial pressure of CO$_2$ (PaCO$_2$) greater than 6.7 kPa (50 mm Hg) while breathing at sea level)

Stage I: *Mild COPD* — characterized by mild airflow limitation (FEV1/FVC <0.7; FEV1 >80% predicted). Symptoms of chronic cough and sputum may be present, but not always. The individual is usually unaware that his or her lung function is abnormal because of limitation starting with small airway involvement.

Stage II: *Moderate COPD* — characterized by worsening airflow limitation (FEV1/FVC <0.7; 50% < FVC < 80% predicted), with shortness of breath typically developing on exertion and cough and sputum sometimes also present. This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or an exacerbation of their disease.

Stage III: *Severe COPD* – characterized by further worsening of airflow limitation (FEV_1/FVC <0.7; 30% < FEV_1 < 50% predicted), greater shortness of breath, reduced exercise capability, fatigue, repeated exacerbations that almost always affect the patients' quality of life.

Stage IV: *Very Severe COPD* – characterized by severe airflow limitation (FEV_1/FVC <0.7; FEV_1 <30% predicted or <50% predicted plus chronic respiratory failure). Respiratory failure might lead to signs of right heart failure such as elevated Jugular Venous Pressure (JVP), pitting edema at ankles and cor pulmonale due to effects on the right heart. Patients may also have Stage IV (Very Severe COPD) even with FEV_1 more than 30 % predicted if any of these complications are present. At this stage, the quality of life is appreciably impaired and exacerbations may be life threatening.

Since degree of airflow limitation correlates only modestly with the symptomatic disability, GOLD emphasizes that the spirometric classification is an educational tool and a pragmatic approach towards the initial management of the patient. It also suggests that the symptomatic impact of the disease should be taken into account because cough and sputum may precede the airflow limitation by years and hence may be important indicators for identifying the individuals at risk for developing COPD. Importantly, in the 2008 update, the previous category labeled as Stage 0, aimed at identifying "at risk individuals" who were defined as "chronic cough and sputum without spirometric abnormality" has been dropped. This is because these individuals do not necessarily progress on to Stage I. Nevertheless, the message that chronic cough and sputum are not normal is unchanged as before. Also, contrary to the earlier hopes of bronchodilator reversibility testing being a predictor of progression in COPD; unlike asthma, this test is now more or less abandoned except for a few indications. No clear relationship has been found between bronchodilator reversibility and disease progression. This was further complicated by increased probability of subjects with low initial FEV_1 being categorized as reversible, even with absolute increase in FEV_1 (200 ml) criterion being included. The test is presently indicated only for atypical COPD patients with history of childhood asthma or nigh-time awakening with cough and wheeze. The protocol for the same can be found in GOLD guidelines.

Limitations

There is a clear scope to improve upon the current spirometry based guidelines because of its limitations at the two ends of the disease spectrum, namely early disease and advanced disease. Small airway disease, which is an early marker of obstructive airway diseases such as COPD and asthma, is hard to detect by spirometry. This has been shown in clinical trials,[21,22] and is understandable in physiological terms because spirometry starts with a full inhalation to total lung capacity and operates over high lung volumes for most of the FEV_1 portion, thereby masking small airway disease. While indices related to the later part of the curve operating at low lung volumes, such as FEF25, are more sensitive to small airway disease, technical variability often precludes reliable use of these parameters. Very recent studies in COPD subjects report that more accurate quantification of small airway disease by Impulse Oscillometry correlates very well with the symptomatic disability and St George's Questionnaire measures.[23] This is discussed further in the next section.

Conventional spirometry also fails to live up to the expectations in severe disease. When a patient with severe COPD makes a maximal expiratory effort, he succeeds only in causing significant thoracic gas compression because the thoracic cage contracts, yet the gas cannot leave because of severely diminished airflow. This gas compression leads to distortion of the volume-flow relationship, inaccuracy of the FV loop and exaggerated estimates of flow limitation. In fact, if such patients were to make a sub-maximal effort, they would generate better airflow. This is a well-recognized problem that has been addressed by the late Dr Joseph Rodarte's group.[24] Another important problem inherent to the current guidelines is that, they paradoxically use failure of therapeutic (bronchodilator) response for the diagnosis of COPD, yet propose to guide the therapy with the same test. However, in absence of other widely available alternatives, this represents a best possible solution focused at identifying declines in lung function and taking corrective measures.

MEASURING SMALL AIRWAY DISEASE: IMPULSE OSCILLOMETRY

As discussed in the above section on spirometry and in the introductory section in physiology, a major limitation of spirometry is that it neither truly measures resistance nor is sensitive to small airway disease which may identify early COPD. Early detection offers an opportunity for early intervention and perhaps delayed progression. Impulse oscillometry, a forced oscillation based technique appears to be particularly promising in this regard[25,26] and is discussed in detail below.

Forced Oscillation Technique

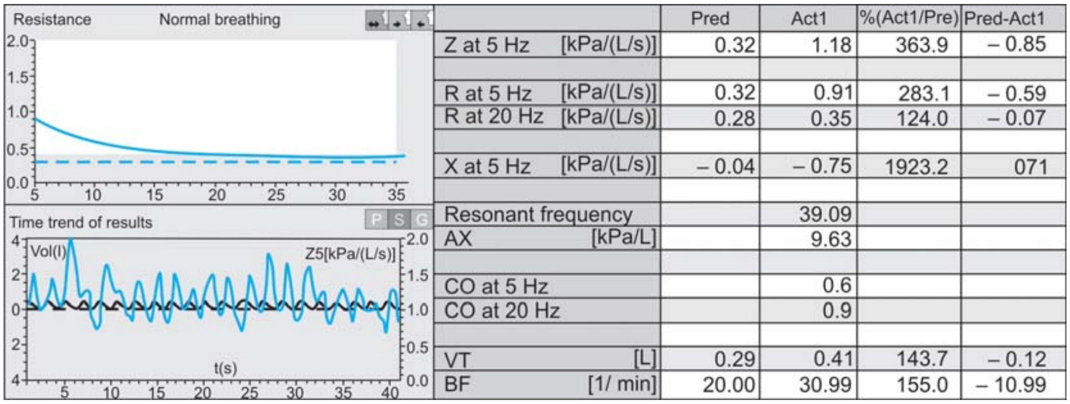
Forced Oscillation Technique (FOT) is advancement in the direction of measuring pulmonary function by allowing measurements of central and peripheral respiratory resistance, without the need for performing any maneuvers. This allows the testing to be performed in subjects incapable of performing the maneuver and excludes the possibility of introducing changes in airway physiology that are attributable to the maneuver itself. As an example, investigators have observed that a forced expiration itself causes bronchoconstriction in individuals who have a tendency to develop bronchospasm. Therefore, the first measurement, which most often is not the best, affects the following measurements being performed in the same test. It has been noted previously that the deep inhalation that precedes the forced expiration, limits the ability to detect modest peripheral airway obstruction.[27]

The principle of the technique has been discussed in the section on physiology. Briefly, it uses superimposing or "forcing" external pressure signals upon the tidal volume breathing of the individual. The flow changes introduced by these small pressure changes are then utilized to calculate the "impedance of the respiratory system," as discussed earlier. The term resistance is replaced with impedance here because the pressure being applied is not constant but consists of mono- or multi-frequency sinusoidal pressure signals. In other words, it is analogous to an Alternating Current (AC) electrical circuit rather than a Direct Current (DC) one. An AC circuit has an "in phase" (real) component of impedance known as resistance and an "out of phase" (imaginary) component of impedance called reactance. Reactance can be further partitioned into the "energy storing and returning" component analogous to capacitance and an inertial component called inertance analogous to inductance in the electrical circuit theory. It is worth mentioning that the clinical use of the technique does not require much technical understanding, although an understanding of both is recommended for research related use.

A pure sinusoidal pressure wave is the basis for the monofrequency forced oscillation technique, whereas multifrequency pressure waves are utilized in multifrequency Pseudo Random Noise FOT. Impulse Oscillometry (IOS) is a further advance that utilizes time-discrete pressure impulses (signals) rather than continuous signals, providing excellent temporal and spatial resolution. These signals are sufficiently different from the spontaneous respiratory patterns of people and do not require any special instructions to the patient in terms of breathing pattern. Impedance is a function of the forcing frequency and must be interpreted in this context. At low frequency (5 Hz), the pressure wave is able to influence flow in the entire lung, including the peripheral airways; while at higher frequencies (e.g. 20 Hz), it primarily influences the upper and central airways. Therefore, resistance at 5 Hz (R5), which is the real part of impedance, denotes the resistance of the total respiratory tree; while R20 corresponds to the upper and central airways. It can be seen that R5-R20 is a measure of peripheral airway resistance. Thus, IOS has a distinct advantage of giving differentiated spectral values of impedance at different frequencies. These parameters are quite well studied and interpreted, although there is a much wider scope to the analysis of these measurements than is presently being employed.

Performance of the Test

The test is performed during normal tidal breathing. This makes it particularly attractive at extremes of age and in those where comprehension or circumstances, e.g. mental illness, post-surgical state, prevent performance of maneuvers. Specifically in IOS, a short reading of about 30 seconds with tidal volume breathing and impulses delivered at 0.02 second interval is recommended. Specific questions may be addressed by changing the impulse rate and the length of recording. The individual sits straight and relaxed while breathing in a relaxed manner. Swallowing movements or glottic closure is best avoided as they can cause artefacts in the reading. To avoid the dissipation of pressure at the cheeks, it is recommended to have hands kept on them, while the nose is closed off by using a nose clip.



	Pred	Act1	%(Act1/Pre)	Pred-Act1
Z at 5 Hz [kPa/(L/s)]	0.32	1.18	363.9	– 0.85
R at 5 Hz [kPa/(L/s)]	0.32	0.91	283.1	– 0.59
R at 20 Hz [kPa/(L/s)]	0.28	0.35	124.0	– 0.07
X at 5 Hz [kPa/(L/s)]	– 0.04	– 0.75	1923.2	071
Resonant frequency		39.09		
AX [kPa/L]		9.63		
CO at 5 Hz		0.6		
CO at 20 Hz		0.9		
VT [L]	0.29	0.41	143.7	– 0.12
BF [1/ min]	20.00	30.99	155.0	– 10.99

Fig. 80.5: Representative IOS traces from normal (above) and COPD (below) subjects. Note the frequency dependence of R in COPD such that R5 >R20 as well as an absolute increase in R suggestive of peripheral and generalized airway obstruction respectively. Note the increase in R5 relative to R20 in COPD patient. Also note increase in total impedance at 5 HZ (Z5) during expiration in COPD.

TABLE 80.2: IOS Parameters and typical reference values

IOS Parameters	*Typical Values**
Z5 (Total impedance at 5Hz)	0.33
R5 (Resistance at 5 Hz)	0.31
R20 (Resistance at 20 Hz)	0.30
X5 (Reactance at 5 Hz)	–0.07
Fres (Resonant Frequency)	9.11
AX (Area under the reactance curve)	1.4

*These values are for a normal Indian male, 165 cm tall, 65 kg weight. More than 50% elevation is considered abnormal.

Interpretation

A summary of the measured indices is shown in Table 80.2.

Healthy lungs typically show R and Z values not more than 50% higher than the standard reference values calculated from age, sex, height and weight. Such equations are not yet published for India, but will be released soon. Our initial experience suggests that normal Indian values for these are somewhat higher than for western populations, especially in small-statured women, presumably due to smaller lungs. In health, R is minimally frequency dependent (Fig. 80.5) with R5-R20 being very low. Resonant frequency in adult subjects is typically less than 12 Hz. While a number of diseased patterns are described relating to peripheral airway obstruction, central airway obstruction and extrathroracic obstruction, a full discussion is beyond the scope of this chapter. In COPD, the pattern is typically of small airway obstruction, where R is increased beyond normal and R5 >R20. Almost invariably an increase in Fres and Ax is also seen. A volume dependence of R and Z can be seen such that they increase during expiration. IOS is extremely sensitive to small airway disease and correlates better with the symptomatic disability and St. George's Questionnaire measures than spirometry.[22]

Limitations

Impulse oscillometry is not useful for the diagnosis of restrictive lung disease, since its emphasis is on resistances, not volumes. While Fres is increased in restrictive lung disease, that is a non-specific sign. It should be noted that an IOS system is technically equipped for spirometry since it measures flow, which like spirometers is integrated to measure volumes. Thus, IOS is a highly promising approach in COPD. Continuing education of health practitioners about newer techniques and application of these at a larger scale might be a good initiative in defining COPD in a better way.

OTHER TESTS

Body Plethysmography

Whole body plethysmography, more commonly known as body box because the patient sits inside a closed box, allows determination of airway resistances and Thoracic Gas Volumes (TGV).[28] For any small instantaneous change in thoracic volume of the breathing subject, there is a corresponding opposite change in the box gas volume, which is detected as a box pressure change. Coupled with measurements of airflow at the mouth of the subject, this permits determination of Specific Airway

Resistance (sRaw). While techniques permitting measurements during natural breathing exist, commonly used commercial implementations require the patient to breathe in a fast and shallow pattern, similar to panting. This minimizes the glottic resistance and temperature artefacts, permitting estimation of sRaw from the slope of the trace between changes in box pressure versus airflow at the subject's mouth.

Specific airway resistance is an accurate and sensitive index of airway obstruction, being relatively independent of lung volumes and therefore insensitive to hyperinflation induced airway dilation. Interruption of airflow during panting by a shutter permits estimation of TGV from the trace between mouth pressure and box pressure. This can be readily understood as an application of Boyle's law to a closed (by shutter) thoracic gas compartment for which change in pressures during expansion and contraction is known, i.e. $PV = \text{constant} = (P+dp)(V+dV)$; $V=P(dV/dp)$ where P is atmospheric pressure and V is FRC, dP is pressure change at mouth during shutter occlusion, dV is change in thoracic volume obtained from box pressure signal. Knowledge of true FRC permits calculation of other lung volumes such as TLC, RV, etc. Lung volumes estimated by body plethysmography reflect the total compressible gas during breathing even if communication to airways is reduced or absent. Thus, volume measurements by plethysmography are superior to gas dilution methods in COPD, because of insensitivity to airway occlusion and closure that would otherwise cause systematic underestimates.

Spirometry can also be performed in the body box setup. Body box spirometry is free of compression artifacts mentioned previously and is more reliable than conventional spirometry in patients with severe COPD; however, it is technically more demanding. In addition to the regular calibration of airflow similar to spirometry, the equipment also needs to be calibrated daily for ambient conditions (room temperature, atmospheric pressure and humidity), box calibration (leak test result should typically be between 4 and 7s) and volume calibration. Regular calibration of volume and assessment of the dynamic responsiveness of the system to oscillating signals is particularly recommended. This is usually accomplished by alternately injecting and removing known volumes into the sealed body box by a piston or pump. Very importantly, the calibration factor requires adjustment for the air displaced when a subject is seated inside the box. This is a part of the standard analysis and the users only have to input correct values for the subject's weight. Importantly, patients must be adequately instructed for performance of suitable panting such that the traces obtained are reproducible and near-linear in the central regions of the trace. When used appropriately, the body box is a very sensitive pulmonary function test that can accurately measure the various components of COPD and distinguish between predominant emphysema and predominant bronchitis.

Peak Expiratory Flow Rate (PEFR)

Contrary to asthma, where peak expiratory flow has a distinct role in the management, it has a limited role in COPD management because the peak flow might be relatively well preserved, despite the FEV_1/FVC ratio being low. Therefore, there is a weak correlation between the two, limiting its use in management of COPD.[29]

Helium Diffusion

Equilibration of known quantity of an inert gas that is neither consumed nor absorbed with the lungs followed by measurement of the concentration postequilibration permits determination of the unknown equilibration volume, i.e. lung volume. While this is a commonly used test in many conditions, it tends to systematically underestimate lung volume in COPD patients because equilibration can be slow and incomplete.[30]

Transfer Factor (TLCO and KCO)

This is a quantitative test for the quality of oxygen transfer across the lungs. It is based on measurement of the relative transfers of Carbon Monoxide (CO) and helium, when inhaled as a mixture. Helium is an inert gas and the concentration in the expired air is lesser than inspired air because of dilution with the resident gas in the lungs. On the other hand, CO is a surrogate for Oxygen, since it additionally crosses the alveolar membrane and binds tightly to hemoglobin. Knowing the inhaled concentrations of these two gases, one can calculate the transfer factor expressed either as CO transfer factor (TLCO) or transfer factor per unit lung volume accessed (diffusion coefficient) to correct for nontransfer across the areas of lung which could not be accessed (e.g. pleural effusion). This is also known as Carbon Monoxide Transfer Coefficient (KCO). KCO tends to be high in airway disease, such as asthma, except when severe. Emphysema causes a fall in KCO because of loss in the area available for gas transfer by creating large airspaces and destruction of alveolar-capillary membrane. Hence, in an individual known to have COPD, KCO is a marker for the extent of emphysematous change in the lung. The utility of this test is limited by its nondiscriminatory power as KCO also decreases in conditions where restrictive or vascular changes are present in the lung.[29]

Fraction Exhaled Nitric Oxide (FENO)

Although there is limited experience with this test in COPD patients, this might be useful in distinguishing cases where asthma seems to be a possible component of airflow limitation. This is because asthma, particularly of the "Atopic" variety is characterized by higher levels of nitric oxide exhaled in the breath. This is correlated with the amount of eosinophilic inflammation in the airways and excellent reviews are available explaining the molecular mechanisms and the sites for generation of NO in airways.[31] The reader is encouraged to refer to these for further application.

THE FUTURE

Anticipated future trends in pulmonary function testing are described as follows: [32]

- Standardization with more physicians embracing the benefits of following common international guidelines; this seems inevitable
- Focus on early detection: It is increasingly recognized that onset of COPD predates onset of diagnostic changes in spirometry by many years. We hope that new guidelines will address this lacuna and move away from sole emphasis on airflow limitation.
- Convergence and portability of technology: Miniaturization of technology has already significantly reduced the size of PFT equipment. This coupled with uniform standards, has permitted new-generation devices with high user friendliness to penetrate the nonspecialist market.
- Innovative web-based applications, such as tele-PFT, e-learning and Internet-based distance education, are also likely to result in a paradigm shift in coming years.

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Systemic Manifestations and Comorbidities

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD), a syndrome of progressive airflow limitation caused by an abnormal inflammatory reaction of the airways and lung parenchyma, is now considered a systemic disease with widespread extrapulmonary manifestation.[1-6] The comorbid conditions, in association with pulmonary manifestations, pose additional problems of management. There is a resultant increase in the overall morbidity, mortality, health care burden and costs. In view of the recognition of the multisystem involvement and manifestations, the disease in future may be well classified and discussed amongst systemic than the pulmonary diseases.

PATHOGENESIS

The mechanisms of systemic manifestations are not completely understood. The pathogenetic process initiated in COPD is likely to have a variety of effects on target tissues. The pathologic changes in the lungs, such as peribronchial fibrosis, airway narrowing, destruction of alveolar walls and loss of elastic recoil lead to airflow limitation. An imbalance between oxidants and antioxidants plays an important role in the pathogenesis of COPD. Reactive oxygen species generated by neutrophils are removed by blood antioxidants and antioxidant enzymes. Thus, the ability to prevent the injurious effects of oxidative stress depends on the antioxidant capacity of the blood and the tissues. There is a marked oxidant-antioxidant imbalance in smokers and during acute exacerbations of COPD.[7] The increased oxidative burden is also likely to cause changes in fibrinolysis contributing to atherosclerosis.

The following mechanisms have been postulated to explain the pathogenesis of COPD:

Mediators and Cytokine Spillover from Lungs

There is an increase in the circulating levels of a variety of cytokine mediators such as Interleukin (IL)-1 beta, IL-6 and Tumor Necrosis Factor (TNF)-alpha and Interferon (IF)-gamma and leptin in patients with COPD.[8-18] Migration and activation of inflammatory cells is regulated by cytokines and chemokines, secreted by epithelial cells, endothelial cells, smooth muscle cells, fibroblasts and inflammatory cells. The systemic effects, however, are not directly attributed to the changes in the lungs. Possibly they are caused by low-grade systemic inflammation due to the presence of numerous inflammatory mediators and cytokines released from the lungs into the systemic circulation, i.e. lung to plasma spill-over.[2,11-13]

A large number of cytokines, chemoattractants and other mediators have been identified. Neutrophil granulocytes are the key players and the most important chemoattractants seem to be IL-8 and Leukotriene B4 (LTB4).[14]

Attempts have been made to study their role through analyses of exhaled air condensates. Inflammatory cytokines have been isolated from sputum exhaled breath condensate and Bronchoalveolar Lavage (BAL) fluid from COPD patients.[15] However, unlike in asthma, the findings in COPD have not been very helpful. Inflammatory markers in the blood [e.g. IL-6, C-Reactive Proteins (CRPs) and fibrinogen] have been also studied.[12]

Systemic inflammatory markers in COPD were assessed in the large Bergen COPD Cohort Study on 409 patients and 231 healthy subjects aged 40–75 years.[12] Plasma levels of CRP, Soluble Tumor Necrosis Factor (sTNFR)-1, osteoprotegerin neutrophil activating peptide-2, CXCL16 and chemoattractant protein-4 were determined by ELISA tests. COPD patients had significantly lower levels of osteoprotegerin and higher levels of CRP. Soluble tumor necrosis factor-1 was significantly associated with important comorbidities such as hypertension and depression. It was thus concluded that the presence of these circulating inflammatory mediators was an important phenotypic feature of COPD.

Peripheral Blood Inflammatory and Other Cells

The evidence from other cross-sectional studies show no clear association between lung and systemic inflammation, which suggest that the systemic inflammatory response is not caused by the “spill-over” or overflow of inflammatory mediators from the pulmonary circulation, but by the systemic peripheral, inflammatory cells such as the neutrophils and lymphocytes.[18,19] There are several other cells including the macrophages and the mononuclear cells, which are attracted by mediators such as CCL2 and CCL3. Involvement of T-lymphocytes especially the cytotoxic $CD8^+$ cells has been also postulated.

The presence of hypoxia in severe COPD may also be responsible for an increased production of cytokines which activate TNF-alpha and soluble TNF-R.[20] It is also possible that the inflammatory mediators are produced by the muscle cells or other extrapulmonary cells located in the endothelium and fatty tissue.[21]

While it is likely that different systemic manifestations are explained by different mechanisms, the concept of inflammation as responsible for multisystem involvement has been clearly established. The understanding of these pathogenetic mechanism is expected to change the clinical practice and pharmacotherapy of COPD.[22-26]

SYSTEMIC MANIFESTATIONS

There are a large number of systemic features and comorbidities seen in COPD (Table 81.1). Interestingly some of the general clinical features, such as weakness, weight loss, anxiety, depression and others earlier considered as “vague” or nonspecific in nature, are now identified as more definitive and significant manifestations of nonpulmonary system involvement and they are described as follows:

TABLE 81.1: Important systemic manifestations of COPD

1. General:	Wasting and weight loss, Nutritional anomalies, anemia
2. Musculoskeletal:	Skeletal muscle dysfunction Osteoporosis Reduction in exercise tolerance and performance
3. Cardiovascular:	Pulmonary vascular disease/ Chronic cor pulmonale, ischemic heart disease— acute cardiac events Cardiac failure Stroke
4. Endocrinal:	Diabetes Metabolic syndrome Dysfunction of pituitary, thyroid, gonads and adrenals
5. Neuropsychiatric:	Depression Disordered sleep Anxiety Cognitive function decline

Wasting and Weight Loss

Muscle wasting and weight loss are common manifestations of COPD. The Body Cell Mass (BCM) is the actively metabolizing and contracting tissue. The alterations in BCM, recognized clinically by weight loss, essentially pertain to loss in Fat-Free Mass (FFM) in COPD. Loss of FFM adversely affects muscle aerobic capacity and exercise capacity.[27,28] Weight loss appears to arise from an increased basal metabolic rate occurring due to an increased work of breathing. Inhaled salbutamol, altered amino acid composition and tissue hypoxia may result in an increased metabolic rate.[29-31]

Acidosis, infection, alteration in body composition and changes in intermediate metabolism or inadequate caloric intake, especially during acute exacerbations of the disease, are associated with an increased breakdown of cell proteins, especially in muscles. An important relationship is likely with acute exacerbations.[32] There is preferential loss of skeletal muscles, especially in the lower extremities in patients with COPD. The muscle wasting is increasingly noticed in quadriceps muscles. Physical inactivity leads to quadriceps muscle weakness in patients with advanced COPD. Quadriceps muscle weakness is related to low circulating levels of testosterone in men with COPD.[33] Histologic study of biopsy specimens obtained from the quadriceps of patients with COPD has shown a loss of aerobic type I fibers and a reduction in oxidative enzymes.[34,35] It has been hypothesized that inflammatory cytokines may contribute to muscle wasting through the inhibition of myogenic differentiation.[36]

The mechanisms underlying weight loss and muscle wasting are incompletely understood, but likely to involve an imbalance in an ongoing process of protein degradation and replacement. It may include alteration in the relative levels or activities of endocrine hormones such as insulin, growth hormone, testosterone and glucocorticosteroids.[37]

Skeletal Muscle Dysfunction

The patients with COPD exhibit skeletal muscle dysfunction characterized by muscles atrophy and diminished strength.[38] It also results in marked reduction in exercise capacity.[39] Among the muscles, diaphragm is put into constant work and it has to work against an increased load. Other skeletal muscles are utilized less due to inactivity.[40]

Skeletal muscle dysfunction is likely to occur from sedentary lifestyle, tissue hypoxia and systemic inflammation.[39] Systemic inflammation, causing muscle dysfunction, is the result of the effects of cytokines such as TNF-alpha, IL-6 and IL-8, and oxidative and nitroactive stress.[41] They are likely to cause protein inactivation and degradation leading to dysfunction, atrophy and apoptosis.[42] It must be noted that an increased inflammation in the lung does not correlate with increased levels of circulating inflammatory markers.

The circulating neutrophils appear to be activated in patients with COPD and they show enhanced chemotaxis and extracellular proteolysis.[43] They produce greater amount of reactive oxygen species.[44] Besides low-grade systemic inflammation, nutritional depletion, corticosteroid medication, chronic inactivity, age, hypoxemia, smoking, oxidative and nitrosamine stresses, protein degradation and changes in vascular density are some other factors contributing to muscle dysfunction in COPD.[45]

Weight loss and skeletal muscle dysfunction cause limitation in the activities and the exercise capacity of the patient with COPD and indirectly on the quality of life. There is worsening of exercise tolerance and performance, increased health care utilization and increased mortality.[46,47] Muscle weakness is recognized to contribute independently to poor health status. Some of these manifestations, i.e. body mass index, degree of air flow obstruction, dyspnea and exercise capacity (the BODE index), have been used as measures of disease severity and mortality risk in COPD.[48-50]

Cardiovascular Problems

Cardiovascular system has a complex interaction with the respiratory system.[51] Pulmonary vascular abnormalities are common in the presence of a chronic lung disease such as the COPD. Pulmonary hypertension, right ventricular dysfunction and chronic cor pulmonale have been recognized since long.[52-54] It is now known that structural changes in pulmonary arteries can occur early in COPD before the onset of hypoxemia.[55] Systemic inflammation, atherosclerotic coronary heart disease and cardiovascular deaths are known as important complications of COPD.

Cardiac failure was seen in 10% to 46% of patients of COPD, while 40% of patients with cardiac failure showed some evidence of COPD, about half of whom were not earlier recognized.[56] There is enough data from epidemiological and other studies to show that atherosclerosis and coronary artery disease are associated with decline in Forced Expiratory Volume in One Second (FEV_1). The risk for cardiovascular death was 75% greater for patients who had a lower FEV_1.[57] Cardiovascular death was also shown to increase by 28% and hospitalization for cardiovascular causes by 42% for every 10% decline in FEV_1.[58] Arrhythmias in COPD are common, but rarely fatal. The right ventricular arrhythmias are more often seen in the presence of chronic cor pulmonale.

The occurrence of both COPD and coronary artery disease is possibly due to the shared risk factors, such as tobacco smoking, as well as to the similar pathogenic mechanisms, i.e. systemic inflammation.[59]

Endocrinal Disorders

A number of endocrine functional disorders have been described in COPD.[60] Derangements of pituitary and thyroid function, gonads and adrenals have been seen in some studies. Diabetes along with other manifestations of metabolic syndrome has been described especially in the presence of cardiovascular disease.[2,56,59,61]

Several mechanisms have been proposed to cause endocrine dysfunction — hypoxemia, hypercapnia, systemic inflammation and glucocorticoid administration for airway obstruction. The presence of endocrine imbalance increases the overall morbidity and cardiovascular risks. The decreased protein anabolism and increased catabolism affect the body mass and also accounts for muscle dysfunction. Altered renin-angiotensin-aldosterone function affects the blood flow, fluid balance and the renal function. Other systemic effects of endocrinal disorders include the disturbances of control in breathing, worsening of respiratory mechanics and impairment of cardiac function.[60]

Neuropsychiatric Derangements

Depression and anxiety are more common in COPD than in healthy age-matched controls.[62,63] Disordered sleep is commonly ascribed to hypoxemia, hypercapnia and diminished ventilatory responses.[64,65] It is further aggravated by the concomitant presence of nocturnal respiratory symptoms, anxiety and depression. Obstructive sleep apnea is present in about 10 to 15% patients of COPD ("overlap syndrome").[65] The other sleep disturbances seen in more than half of the COPD patients include the diminished arousal responses, longer latency in falling asleep, more frequent awakenings or generalized insomnia.[66] The severity of sleep disturbances increase with the severity of disease.

Impairment of intellectual function is also common.[67] The cognitive decline, along with other neuropsychiatric problems, is attributed to the presence of hypoxemia and has shown to improve with long-term oxygen therapy in some small studies.[68] More work requires to be done on the subject.

Osteoporosis

Osteopenia and osteoporosis were reported in 68% of patients with COPD.[69] Osteoporosis may lead to generalised bony pains, compression fracture of the spine and compromised lung function due to kyphosis and thoracic vertebral compression. Corticosteroid therapy, including inhaled steroids, is generally considered responsible for osteoporosis; although in one study, compression fractures were reported in 49% of patients who had COPD and had never received steroids.[70]

THERAPEUTIC CONSIDERATIONS

The recognition of systemic features has made the greatest impact on clinical course, complications and therapy of COPD. The variable host response and subsequent clinical phenotyping has made it possible to develop a targeted treatment with the help of a multisystem approach.[71] Some of the treatment failures are possibly due to the phenotype heterogeneity of COPD and its different systemic manifestations. The future treatments with statins, angiotensin-converting enzyme inhibitors and anti-inflammatory drugs, targeting the comorbid conditions, may help to change the natural history of COPD and improve the mortality.[24-26] There are several novel anti-inflammatory drugs such as the phosphodiesterase-4 inhibitor and other inhibitors of nuclear factor—κB and p38 mitogen-activated protein which may prove beneficial. Antioxidants may also help to control comorbidities.

Lastly, it is shown that the elderly patients, who are at an increased risk of almost all the comorbidities of COPD discussed earlier, may benefit from the treatment of concomitant comorbidities. Further, development of anti-aging molecules, such as sirtuin agonists, can be helpful and may also reduce the risk of lung cancer.[25] It should however not be overlooked that aging alone is not an exclusion criterion for pulmonary rehabilitation and other treatment of COPD.[72] Assessment and appropriate treatments of COPD and the comorbid conditions has been shown to provide similar benefits of management.

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Role of Infections in Chronic Obstructive Pulmonary Disease

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of mortality worldwide, anticipated to become the third by the year 2020.[1,2] The role of infections in COPD is poorly understood and highly underestimated. Infections not only play a pivotal role in initiation and progression of COPD, but also affect the clinical course of COPD. Historically, bacteria have been considered as the main infectious cause of COPD exacerbations.[3] However, a growing body of evidence, has implicated viral respiratory infections in the exacerbations of COPD.[4,5] Recent studies have shown the role of both viruses and bacteria in the initiation and progression of COPD.

DO BACTERIA CAUSE/INITIATE COPD?

Bacterial Airway Colonization: Initiation of COPD Inflammation

In a normal healthy subject, the respiratory tract is almost always sterile. In a stable chronic bronchitis patient, the sputum produced is usually mucoid and scant. Even during these quiescent periods, cultures of sputum have yielded presence of potentially pathogenic bacteria in around 25 to 50% of cases.[6] Organisms including nontypeable *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pneumoniae* have been found to be the predominant bacteria in early studies. Once these bacteria colonize the lower airway, they can directly cause airway inflammation and impair mucociliary clearance, thereby perpetuating a vicious circle of impairing local defenses.[7]

TABLE 82.1: Role of bacterial infections in COPD

- Chronic childhood lower respiratory tract infection impairs lung growth
- Chronic colonization induces a chronic inflammatory response
- Chronic infection alters the host response to cigarette smoke
- Acute exacerbations of chronic bronchitis
- Bacterial antigen induced hypersensitivity and bronchial hyperreactivity

Several putative roles of bacterial infection in the etiology, pathogenesis and the clinical course of COPD have been identified (Table 82.1).[6,7]

Childhood Infection and Adult Lung Function

Several studies have shown a lower Forced Expiratory Volume in One Second (FEV_1) and often a lower Forced Vital Capacity (FVC) among adults who experience recurrent lower respiratory tract infection during childhood.[7,8] This association has been observed even after controlling for confounding factors such as tobacco smoke and other exposures. The defect in lung function is consistent with “smaller lungs,” suggesting impaired lung growth. The extent of decrease in FEV_1 is unlikely to cause symptomatic pulmonary disease on its own, but make the individual further susceptible to the effects of additional injurious agents such as tobacco smoke and other environmental insults. The impact of childhood bacterial lower respiratory tract infection on the prevalence of COPD is likely to be greater in developing countries where there is a high incidence and inadequate treatment of these infections.[8]

Bacterial Colonization Central to Progression of COPD: Vicious Circle Hypothesis

In the absence of any underlying lung disease, the tracheobronchial tree is sterile. However, in patients with COPD, tobacco smoke and other environmental insults cause damage to the airway epithelium and impair mucociliary clearance of the tracheobronchial tree. Chronic colonization with potential respiratory pathogens, predominantly nontypeable *H. influenzae* (NTHI), *S. pneumoniae* and *M. (Branhamella) catarrhalis*.[9,10] Once the bacterial pathogens have gained a foothold in the lower respiratory tract due to impaired mucociliary clearance, they persist in the airway mucosa as bacterial colonizers and further impair the mucociliary clearance by releasing a whole host of bacterial products which cause airway epithelial injury (Fig. 82.1).[11]

Bacterial Infection and Mucociliary Clearance in COPD: A Role in Initiation of COPD Inflammation

The tracheobronchial ciliary escalator is of paramount importance in maintaining the sterility of the lower respiratory tract by transporting bacteria trapped in mucus towards the pharynx.[12]

Disruption of this ciliary activity is therefore likely to play an important role in the establishment of a chronic colonization in the tracheobronchial tree. Rapid inhibition of ciliary beat frequency has been seen with *Nontypeable Haemophilus influenzae* (NTHi) and *Pseudomonas aeruginosa,* but not with *Staphylococcus aureus.*[13] On direct microscopic examination, ciliary dyskinesia and ciliostasis is also seen. Human neutrophil elastase, released by activated neutrophils, further inhibits ciliary activity and damages respiratory epithelium.[13,14] Bacterial products released in the airways act as a potent stimulus for neutrophil migration into the airways, elastases released from these chemotactic neutrophils act synergistically with bacterial products and cause airway epithelial injury and further inhibition of tracheobronchial ciliary function.

Bacterial Infection and Airway Epithelial Injury

An important component of the vicious circle hypothesis is the potentially damaging effects of bacteria and bacterial products on airway epithelial lining cells. In an *in vitro* tissue culture model of nasal turbinate epithelium, Read et al.[15] have demonstrated that NTHI is capable of causing airway epithelial injury. They studied infected airway epithelia after 30 minutes, 14 hours and 24 hours of incubation with a NTHI strain. At 30 minutes, the airway epithelium and cilia were intact and the bacteria were found associated with the overlying mucous layer. At 14 hours, patchy injury developed to the airway epithelium, with bacterial cells now associating with these damaged epithelial cells but not with intact epithelium. At 24 hours, detached epithelial cells with adherent bacteria were seen. Such epithelial injury in the large airways would contribute to bacterial persistence and in the small airways contribute to the respiratory bronchiolitis that causes progressive airway obstruction. This study demonstrated that bacteria that colonize and infect the lower respiratory tract in COPD are capable of fostering in the tracheobronchial tree—an environment in which they can persist, supporting the central tenet of the vicious circle hypothesis (Fig. 82.1).

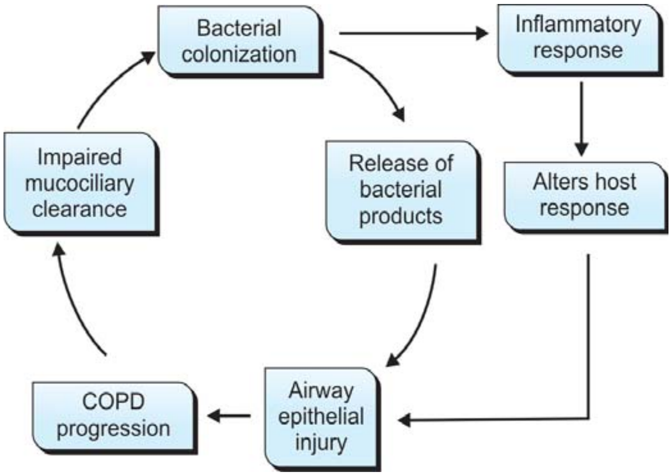

Fig. 82.1: Bacterial colonization contributing to COPD progression

Bacterial Infection and Airway Inflammation

The presence of bacteria in the lower airways in patients with stable COPD has been labeled as *colonization*. Recently, more attention is being directed towards the possible effects of bacterial products and their chronic inflammatory response on the elastase-antielastase balance in the lung. This abnormal bacterial colonization of the tracheobronchial tree is not only confined to the large airways but has been shown to extend to the peripheral airways also by bronchoscopic protected specimen brushings culture.[16] Interestingly, it was observed that even during colonization, bacteria in these airways were likely to be in a constant state of turnover, releasing extracellular products, undergoing lyses and releasing a variety of proteins, Lipooligosaccharides (LOS) and peptidoglycans. These LOS are a potent source of inflammatory stimulus, which have been shown to be associated with the development of emphysema in animal models.[17] In the large airways, such inflammation would contribute to excess mucus production while in the smaller airways, it would contribute to the development of respiratory bronchiolitis and progressive airway obstruction.

The Role of infections: COPD Exacerbations

Periods of acute worsening of COPD, termed "exacerbations," greatly affect the quality of life and health of patients and place a greater burden on the health services.[18] Chronic obstructive pulmonary disease is characterized by exacerbations, which are caused mainly by infections of the tracheobronchial tree or by inhalation of toxic gases. During an exacerbation, the underlying airway inflammation is augmented and there is a sustained worsening of patient's condition from the stable state. Chronic obstructive pulmonary disease exacerbations are a major cause of hospital admissions, frequent exacerbations and are associated with increased mortality and impaired health-related quality of life.[19] Previous studies have reported that patients who experience frequent exacerbations present with an accelerated rate of lung function decline.[20,21] Increased frequency of exacerbations also increases the disease severity. Management of exacerbations should aim at a prompt diagnosis, effective and optimum treatment that would reduce exacerbation frequency.

Historically, bacteria have been considered to be the main infectious cause of exacerbations. A growing body of evidence, however, implicates viral respiratory tract infections as an important risk factor associated with COPD exacerbations.[3,5] Though bacteria plays a very important role in colonization and progression of COPD, acute viral infections are usually the first and primary infectious agents during an acute infective exacerbation.

Pathogenesis of Viral Exacerbations

Despite the epidemiologic evidence linking respiratory virus infection to exacerbations of COPD, the exact cellular and molecular mechanisms by which viruses cause exacerbations remain largely undetermined.[3] Several studies have looked into the key issues that drive virus-induced exacerbations of airway diseases.[22] There is now an increasing body of evidence from experimental rhinovirus infections that respiratory viruses that typically cause. Upper Respiratory Infections (URIs) can, infact, infect the lower airways.[22-24] Recent research suggests that many respiratory viruses, including the major group of rhinovirus, attach to airway epithelial cells through Intercellular Adhesion Molecule-1 (ICAM-1). It has been shown that the expression of ICAM-1 is increased on the epithelial cells of bronchi in patients with COPD. Moreover, induction of ICAM-1 expression has been shown to promote the recruitment and activation of inflammatory cells. Viral infection of epithelial cells lead to the destruction of epithelial lining of the airways, the extent of epithelial destruction varies according to virus type. For example, influenza virus typically causes extensive airway epithelial necrosis, whereas infection with rhinovirus results only in patchy damage.

Viral infection of epithelial cells also initiates and regulates the release of proinflammatory cytokines and chemokines such as Tumor Necrosis Factor-Alpha (TNF-á), Interleukin-8 (IL-8), Epithelial-Derived Neutrophil Attractant (ENA-78), Leukotriene B4 (LTB4), CCL5 (RANTES) and endothelin-1.[25-27] The released IL-8, ENA-78 and LTB4 attract neutrophils, which stimulate mucus production and result in increased production of purulent sputum,[27] whereas CCL5 (RANTES) attracts eosinophils, lymphocytes, macrophages and activated T cells, resulting in apoptosis of virus-infected cells.[28] This results in airway inflammation, airway remodeling, tissue destruction and loss of lung function. Endothelin-1 causes bronchoconstriction and vasoconstriction, resulting in airflow obstruction and impaired gas exchange. Interleukin-6 which is also released from epithelial cells during exacerbations induces systemic inflammation which results in cachexia, muscle wasting, depression and vascular events that can characterize severe, complicated exacerbations of COPD.[29,30]

Viral infections, however, often coexist with bacterial pathogens in patients with COPD during exacerbations. Therefore, for severe exacerbations marked by increased dyspnea, increased sputum production and increased purulence, the consideration of the possible role of bacteria and the use of antibacterial agents is indicated.

Management of Viral Exacerbations

In specific circumstances, antiviral agents may be useful for the treatment of COPD exacerbations. The use of oseltamivir, an antiviral drug, in COPD exacerbations appears appropriate only during the presence of an influenza epidemic. The novel capsid-binding inhibitor, pleconaril and the 3C protease inhibitor, rupintrivir, modestly reduce symptoms during human rhinovirus-induced colds. The efficacy of these compounds in patients with virus-induced COPD exacerbations, however, has not yet been fully examined. Anti-inflammatory therapy may have a therapeutic role in

COPD exacerbations[25] and several potential anti-inflammatory treatments are now in clinical development.[31] Future therapies could range from selective inhibitors of key virus-induced signaling pathways in epithelial cells to the antagonists of specific chemokines that may play a key role in pathogenesis.

Intercellular Adhesion Molecule-1 has been specifically described as a potential target to block as a means of preventing rhinovirus infection.[31] Another drug that requires mention is Nitric Oxide (NO). Nitric oxide exerts direct antiviral activity against several viruses associated with exacerbations, also inhibits virus-induced generation of several cytokines from epithelial cells.[32] Traditional methods of preventing the transmission and acquisition of respiratory viruses should be advocated to treat virus-induced exacerbations. Immunization with standard influenza virus vaccine is associated with reduced hospitalization rates, fewer outpatient visits, less severe illness, lower mortality related to pneumonia and influenza in older persons[33-35] and a reduced risk of influenza-related illness in persons with COPD.[36]

Acute Bacterial Exacerbations

Bacteria have been isolated from the sputum in approximately 60% of Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB) cases. The most common isolated organisms include *H. influenzae, Haemophilus parainfluenzae, S. pneumoniae* and *M. catarrhalis.*[6,19-21] The contributions of these four organisms can depend on the severity of underlying airway disease. A number of studies have found more virulent organisms in the airways of severe chronic bronchitis patients with acute exacerbations including *S. aureus, Pseudomonas* species and members of the *Enterobacteriaceae* family.

Bacterial exacerbation is the acquisition of new strains of bacterial pathogens from the environment that are able to establish an infection in the tracheobronchial tree because of the compromised innate lung defenses. These pathogens interact with airway cells, elicit an inflammatory response which underlies the pathophysiology and symptoms characteristic of an exacerbation. An immune response that can be mucosal, systemic or both, develops to the infecting bacterial strain. This immune response contains the infectious process, could eradicate the infecting pathogen and prevent reinfection with the same strain.[37] However, because of the antigenic diversity among bacterial strains, the immunity tends to be strain-specific rather than widely protective.

Other mechanisms contributing to acute bacterial exacerbations include an increase in bacterial load and an interaction with other etiologies such as viruses, which also could contribute to bacterial exacerbations. In general, during ABECB, many of the same bacteria that are found in the airways during clinically stable periods are present, but at higher colony counts.[20] The higher counts lead to an airway bacterial load which crosses the clinical threshold to present with an exacerbation. The role of atypical pathogens such as the *Mycoplasma* and the *Chlamydia* species seems to follow three separate mechanisms in ABECB:

1. Infection with *Chlamydia pneumoniae* infection at an early age can make airways more susceptible to the effects of irritants, such as cigarette smoke, and can increase the risk of chronic bronchitis later in life.
2. Both these species can cause ABECB themselves.
3. Atypical organisms and viruses can cause a primary infection that can lead to severe lower airway inflammation, enabling a secondary increase in bacterial proliferation that can lead to an exacerbation.[5,6,20]

The exact role of bacterial infections in causing COPD exacerbations is however not completely understood because of the following commonly encountered reasons:

- Bacteria are known to colonize the lower airways in COPD patients, even in the absence of symptoms of an exacerbation
- Patients with COPD are highly heterogeneous. As a result, bacteria may vary from patient to patient, likely to play different roles in different individuals
- The information obtained from the cultures of expectorated sputum samples is limited since the samples do not reliably reflect conditions in the lower airways
- Even if bacteria play a role in exacerbations, they probably account for only half of all the infectious episodes in COPD patients
- The three bacteria most strongly implicated in causing exacerbations (nontypeable *H. influenzae, M. catarrhalis* and *S. pneumoniae*) are exclusively human pathogens, limiting the use of animals models to illustrate the role of these bacteria during an exacerbation.

Understanding the Pathogenesis of Acute Exacerbations of COPD (AECOPD)

The pathologic lesions of chronic bronchitis (AECB) involve morphologic changes in both the large and small airways. In patients with chronic bronchitis, these airways contain a marked presence of inflammatory cells with a predominance of monocytes, lymphocytes and CD8+ cells and neutrophils in the airway lumen. In the large airways, inflammation leads to metaplasia of both the columnar and goblet cells that line the epithelium. In addition, there is an increase in the size of the mucus-secreting glands in smooth muscle, connective tissue in the bronchial wall and degeneration of the airway cartilage.[6,37]

There is emerging evidence that ABECBs are associated with increased airway inflammation. There appears to be a clear association between the degree of inflammation and the severity and frequency of the exacerbations. Bronchoalveolar lavage specimens, taken during ABECB, show increase in the absolute number and percentage of neutrophils. Levels of IL-8, LTB4 and Myeloperoxidase (MPO), all have been found to be increased during AECB.

Diagnosis and Management of Acute Bacterial Exacerbation

The clinical diagnosis of ABECB traditionally uses some combination of the original three Anthonisen criteria: Increased cough, dyspnea or increased sputum purulence from baseline. There are no characteristic laboratory and radiographic tests that can confirm the diagnosis of ABECB. Some clinicians have proposed major and minor criteria; the major criteria consist of the original Anthonisen criteria and the minor criteria consist of wheezing, sore throat, cough and symptoms of the common cold, including nasal congestion or discharge. They define an ABECB as the presence of at least two major symptoms or one major symptom and one minor symptom for at least two consecutive days.[18,30]

There are no characteristic physical findings. Some have suggested that severe exacerbations may be associated with body temperatures greater than 38.5°C, although this is highly controversial. Chest radiographs are not helpful in making the diagnosis, but they can indicate pneumonia or other diagnoses, such as congestive heart failure. The exception to this is a patient presenting to the emergency department or being hospitalized where routing chest X-rays may reveal abnormalities that lead to changes in management (16 to 21% of cases). Sputum Gram stain and culture have a limited role in diagnosing ABECB due to the frequent colonization of airways in chronic bronchitis patients. Sputum analysis should be reserved for patients with frequent exacerbations or in patients with purulent sputum in whom there is a suspicion of more virulent or resistant bacteria. Spirometry during an acute exacerbation has little value, but it is important to know the pre-exacerbation state FEV_1 as a predictor of an adverse outcome of ABECB.

Treatment of Bacterial Exacerbations

The treatment of a bacterial exacerbation should be directed towards three major goals:

- Relief of symptoms
- Prevention of transient loss of pulmonary function (can lead to hospitalization)
- Reassessment of the disease in an attempt to reduce the risk of any further exacerbations

Pharmacologic therapy should be aimed at decreasing the work of breathing, decreasing airway inflammation, lowering the bacterial burden of the lower airways and treating hypoxia.

The role of antimicrobial therapy in the treatment of ABECB remains controversial despite numerous therapeutic trials of antibiotics for more than 50 years. Most comparative trials have found equivalence in the use of antimicrobials. Differences in study end points, differences in patients' groups studied[6,18-21,30] and variations in antibiotics, all have made the comparison of these studies difficult. Not all antibiotics, used to treat ABECB, have the same spectrum of activity or pharmacokinetic properties; therefore, numerous factors should be considered when selecting an antimicrobial agent for treating an acute bacterial exacerbation of COPD.

The chosen antibiotic should have both *in vitro* and *in vivo* activities against the most commonly associated pathogens, including *H. influenzae, S. pneumoniae* and *M. catarrhalis*. In certain subgroups of patients with a more severe obstructive disease, coverage might need to be extended to include other pathogens such as *S. aureus, Pseudomonas aeruginosa* and *Enterobacteriaceae* species, and atypical pathogens. While treating an exacerbation, special attention should be paid to local and regional resistance profiles of the major bacterial pathogens.

Antimicrobial therapy is appropriate for patients with an ABECB if they fall into the Anthonisen type I or type II categories but is not warranted in patients with a type III exacerbation. High-risk patients, including patients who have significant pulmonary impairment (FEV_1 <50% or lower than predicted), who have four or more exacerbations per year, or who use supplemental oxygen or chronic oral corticosteroids, should be treated with antibiotics during ABECB. Due to emerging antimicrobial resistance, second-generation macrolides and some second- and third-generation cephalosporins may be used rather than the traditional first-line agents [aminopenicillins, doxycycline, trimethoprim-sulfamethoxazole (TMP-SMX)]. A failure rate of 13 to 25% can be expected with a traditional first-line antibiotic. Patients, who have structural lung disease, chronically use corticosteroids and who frequently use antimicrobials are at higher risk for *P. aeruginosa* infection, and should be treated with antipseudomonal agents such as the fluoroquinolones. Patients who have been treated in the past three months for ABECB and who present with a relapse or recurrence of ABECB, should be treated with a different class of antibiotics based on culture sensitivity.

The Role of Latent Viral Infections in COPD

Acute viral respiratory tract infections are well known to precipitate acute exacerbations, but their role in the pathogenesis and the chronicity of the disease is poorly defined. Very interesting is the role of double-stranded deoxyribonucleic acid viruses which have the ability to persist in airway epithelial cells long after the acute infection has cleared. During these latent infections, viral genes are expressed at the protein level without replication of a complete virus. The host responds to a viral insult through two immune components; an innate immunity and an adaptive immune response. This innate component is fully functional before the virus enters the host airway epithelium.[37,38] The adaptive component develops in response to the presence of the virus inside the airway epithelium.[38,39] The innate response is triggered before the adaptive immune response and generates cytokines that initiate both a local response at the site of injury and a systemic response.

The cytokines produced by the infected epithelial cells, the intraepithelial lymphocytes, natural killer cells, the Polymorphonuclear Leukocytes (PMNs) and macrophages attracted to the infected site initiate the sequence of rolling followed by firm attachment and subsequent transmigration of circulating leukocytes into the infected tissue.

Role of Beta 2-Agonists in Chronic Airway Inflammation

Bacterial infections are common in the airways of patients with chronic lung diseases.[37-39] As many as 40% of stable asthmatics test positive for atypical bacteria in airway samples.[40] Higher levels of these pathogens such as *Mycoplasma pneumoniae* (Mp) and *Chlamydia pneumoniae* are associated with more severe asthma symptoms and increased COPD exacerbations.[41,42] Treatment with antibiotics, such as clarithromycin, can improve lung function in asthmatic patients with Mp.[43] However, bacterial infections remain prevalent in patients with chronic lung diseases, such as COPD, suggesting impaired lung host defense functions in these patients. Innate immune response in airway epithelial cells provides a vital source of host defense molecules to protect against respiratory colonization and infection.

Beta 2-agonists are the mainstay of therapy to induce bronchodilation in patients suffering from COPD and asthma. The drugs work through beta 2-adrenergic receptors to exert their functions, including relaxation in smooth muscle cells.[44] The receptors are expressed in various types of cells in the lung including airway epithelial cells.[45] In addition to their bronchodilatory effect, beta 2-agonists have been shown to reduce the production of inflammatory cytokines and thereby airway inflammation.[46] Moreover, beta 2-agonist salmeterol was shown to protect airway epithelial integrity that was otherwise impaired by *Pseudomonas aeruginosa* exoproducts.[47] Interestingly, activation of beta 2-adrenergic receptors on human peripheral blood T cells could modulate production of Th2 cytokines (e.g. IL-13).[48] Thus, beta 2-agonists exert an anti-inflammatory effect in chronic airway inflammation. These agents are also shown to cause apoptosis of virus-infected cells during an exacerbation leading to clearance of the airway bacterial load and controlling the infection. Extended use of exogenous antibiotics may cause drug resistance, thereby becoming less effective at eliminating chronic infections that are prevalent in COPD and asthma patients. Therefore, it is beneficial to enhance airway production of endogenous antimicrobial substances to promote the clearance of invading bacteria.

In conclusion, respiratory infections of the airway, either viral or bacterial, play a very important role not only in the pathogenesis and progression of the already burdened COPD, but acute and latent infections in COPD have a dramatic impact on the clinical course of COPD.

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Treatment of Chronic Obstructive Pulmonary Disease

Peter J Barnes

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterized in most patients by slow progressive development of airflow limitation that is not fully reversible.[1,2] COPD encompasses chronic obstructive bronchiolitis with obstruction of small airways and emphysema with enlargement of airspaces and destruction of lung parenchyma, loss of lung elasticity and closure of small airways.[3] Chronic bronchitis, by contrast, is defined by a productive cough of more than three months duration for more than two successive years; this reflects mucous hypersecretion and is not necessarily associated with airflow limitation. Most patients with COPD have all three pathological mechanisms (chronic obstructive bronchitis, emphysema and mucus plugging), but may differ in the proportion of emphysema and obstructive bronchitis. At present, these different phenotypes of COPD do not appear to affect the choice of therapy. However, in the future as more specific therapies are developed, careful phenotyping may be important in selecting optimal therapy.

Despite the enormous advances in asthma management that have taken place over the last 10 years, there have been relatively few new developments in the management of COPD. None of the existing drug therapies are able to significantly slow the relentless progression of airway obstruction, so treatment is based largely on improving lung function with bronchodilators, together with changes in lifestyle. Since the airflow obstruction in COPD is largely irreversible and current therapies do not alter the course of the disease, existing drug treatments provide only limited benefit to the patients. There is now an urgent search for the new classes of treatment that might alter the course of the disease in the future.

The management of COPD has now been formalized in guidelines produced in several countries and all propose escalating treatment, depending on the severity of airflow obstruction.[4]

RISK FACTORS AND THEIR PREVENTION

It is likely that there are important interactions between environmental factors and a genetic predisposition to develop the disease.

Environmental Risk Factors

In industrialized countries cigarette smoking accounts for most cases of COPD, but in developing countries other environmental pollutants, such as particulates associated with cooking with biomass fuels in confined spaces, are important causes.[5] Even in developed countries nonsmoking COPD may account for over 20% of COPD patients.[6] Much less is known about nonsmoking forms of COPD. Some cases are due to a progression of asthma, which loses its reversibility but these are usually identified by early onset and a typical history of variable symptoms at least in the early history of the disease. In developing and emerging countries, such as India exposure to biomass fuels is an important cause of COPD, especially in women, and accounts for over 50% of the cases.

Air pollution (particularly sulfur dioxide and particulates), exposure to certain occupational chemicals such as cadmium and passive smoking may all be additional risk factors. The role of airway hyperresponsiveness and allergy as risk factors for COPD is still uncertain. Atopy, serum Immunoglobulin E (IgE) and blood eosinophilia are not important risk factors. However, this is not necessarily the same type of abnormal airway responsiveness that is seen in asthma. Low birth weight is also a risk factor for COPD, probably because poor nutrition in fetal life results in small lungs, so that decline in lung function with age starts from a lower peak value. Poor nutrition may contribute to COPD and a lack of antioxidants may be particularly important.

Chest infections during the first year of life are associated with COPD in later life.[7] There is some evidence that certain latent virus infections (such as adenovirus) may predispose to the development of COPD, but this is controversial.[8] Many patients with COPD have a history of previous tuberculosis, whereas patients with COPD have an increased risk of developing Tuberculosis (TB), although the relationship between COPD and TB is not clear.[9]

The most important treatment strategy is the avoidance of environmental risk factors wherever possible to prevent disease progression. Most attention has focused on smoking cessation strategies.

Stopping Smoking

Stopping smoking is the single most beneficial management strategy and the only intervention that reduces the accelerated decline in lung function and the number of exacerbations and is important even in elderly patients (Fig. 83.1). Stopping smoking also reduces the mucus hypersecretion of chronic bronchitis and markedly reduces the risks of associated cardiovascular disease.[10] Smoking cessation is more effective early in the course of the disease and becomes less effective as the disease progresses to severe and very severe disease.[11]

Nicotine is addictive and stopping smoking should be viewed as the treatment of drug addiction. Abrupt quitting is more successful that gradual reduction, but even after an intensive smoking cessation program, 75% of smokers are still smoking one year later. There are several ways to encourage smoking cessation. Psychological counseling, group therapy and smoking reduction clinics may be useful in some patients. Nicotine replacement therapy doubles long-term (6–12 month) abstinence rates and is available as chewing gum, skin patches, nasal spray and inhaler.[13,14] Bupropion is an atypical antidepressant that acts through stimulating noradrenergic activity and has double the quit rate of nicotine replacement therapies.[15] More recently varenicline, which is a partial nicotinic agonist, has been introduced and shown to be the most effective way of quitting smoking.[16] Varenicline is usually given for 12 weeks and is well tolerated but some patients develop nausea and insomnia. Sometimes severe depression may also occur.

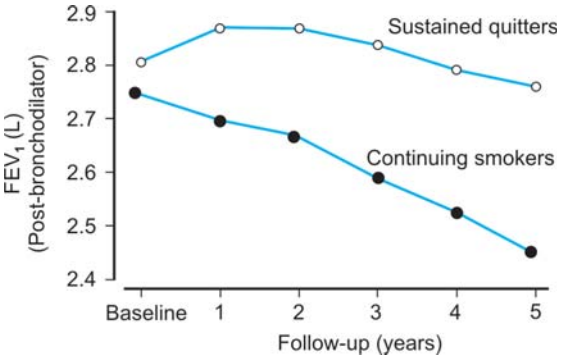

Fig. 83.1: Smoking cessation reduces the rate of decline of lung function in patients with COPD if instituted early in the course of the disease[12]

Avoiding Biomass Fuel Exposure

It is exposure to biomass fuels (wood, charcoal, animal dung) in unventilated houses which is a major risk factor for COPD in developing counties.[17,18] This may be addressed by using alternative fuels, such as Liquefied Petroleum Gas (LPG) or natural gas, ethanol or biogas, although this may not be available or affordable in poor rural communities. Improving ventilation of the cooking area, reducing cooking time or cooking outdoors may also help. Substitution of traditional open fires with locally produced improved stoves has been shown to improve respiratory health in women.

Genetic Factors

Longitudinal monitoring of lung function in cigarette smokers reveals that only a minority (15 to 40% depending on definition) develop significant airflow obstruction due to an accelerated decline in lung function (2- to 5-fold higher than the normal decline of 15 ml to 30 ml Forced Expiratory Volume in One Second (FEV_1) per year compared to the normal population and the remainder of smokers who have consumed an equivalent number of cigarettes.[19] This strongly suggests that genetic factors may determine which smokers are susceptible and develop airflow limitation. Further evidence that genetic factors are important is the familial clustering of patients with early onset COPD and the differences in COPD prevalence between different ethnic groups.[20]

Patients with alpha 1-antitrypsin deficiency [proteinase inhibitor (Pi) ZZ phenotype with alpha 1-antitrypsin levels less than 10% of normal values] develop early emphysema which is exacerbated by smoking, indicating a clear genetic predisposition to COPD. However, alpha 1-antitrypsin deficiency accounts for less than 1% of patients with COPD and many other genetic variants of alpha 1-antitrypsin that are associated with lower than normal serum levels of this proteinase inhibitor, have not been clearly associated with an increased risk of COPD. This has lead to a search for associations between COPD and polymorphisms of other genes that may be involved in its pathophysiology. So far, few significant associations have been detected and even those reported have not been replicated in other studies. A 10-fold increased risk of COPD in individuals who have a polymorphism in the promoter region of the gene for Tumor Necrosis Factor-Alpha (TNF-α) that is associated with increased TNF-α production has been reported in Chinese populations but not confirmed in Caucasian populations.

Several other genes have been implicated in COPD, but few have been replicated in different populations. Genome-wide association studies in COPD have found susceptibility related to two polymorphisms of the nicotinic receptor, which probably reflect propensity to nicotine addition.[21] It is unlikely that molecular genetics will identify new therapeutic targets. Even in patients with alpha 1-antitrypsin deficiency replacement therapy has been poorly effective as well as very expensive.[22] Techniques such as Deoxyribonucleic Acid (DNA) microarray (gene chips) to detect single nucleotide polymorphisms, proteomics to detect novel proteins and gene expression profiling to measure, which known and novel genes are expressed and are now being employed in cigarette smokers who develop COPD compared with matched smokers who do not. This may identify markers of risk, but may also reveal novel molecular targets for the development of treatments of the future.

Bronchodilators

Bronchodilators are the mainstay of current drug therapy for COPD, although the degree of bronchodilatation is less than seen in asthma (typically about 5% improvement in FEV_1, although some patients show greater responses). However, bronchodilators may improve dyspnea and exercise tolerance, despite little of no effect on spirometry, by reducing lung volumes and therefore hyperinflation (air trapping). In addition, bronchodilators may reduce respiratory muscle fatigue (controversial) and improve mucociliary clearance. The choice of bronchodilator includes short and long-acting beta-2 agonists, anticholinergics (muscarinic receptor antagonists) and high doses of theophylline and will partly be determined by patient preference and cost. The preferred bronchodilators are long-acting inhaled drugs such as Long-Acting Beta 2-Agonists (LABA, e.g. formoterol, salmeterol, indacaterol) or a Long-Acting Muscarinic Antagonist (LAMA, e.g. tiotropium bromide). Several bronchodilators are available for COPD (Table 83.1).

Anticholinergics

Atropine is a naturally occurring compound that was introduced for the treatment of asthma, but because of its side-effects (particularly drying of secretions); less

TABLE 83.1: Bronchodilators for COPD

Drug	*MDI (µg)*	*Nebulizer (mg)*	*Oral (mg)*	*Duration (hr)*
β_2-agonists				
Salbutamol	100-200	2.5-5.0	4	4-6
Terbutaline	250-500	5-10	-	4-6
Formoterol	12-24	-	-	12
Salmeterol	50-100	-	-	12
Bambuterol	-	-	10-20	
Anticholinergics				
Ipratropium	40-80	0.25-0.5	-	6-8
Oxitropium	200	-	-	7-8
Tiotropium	18	-	-	>24
Theophyllines				
Theophylline SR	-	-	200-400	12-24
Aminophylline SR			200-400	12-24

soluble quaternary compounds (e.g. ipratropium bromide) were developed. Anticholinergics are probably the most effective bronchodilators in the treatment of COPD and vagal cholinergic tone appears to be the only reversible element in the airflow obstruction of COPD. A small degree of resting bronchomotor tone is present because of tonic cholinergic nerve impulses, which release acetylcholine in the vicinity of airway smooth muscle, and cholinergic reflex bronchoconstriction may be initiated by irritants, cold air and stress (Fig. 83.2). Anticholinergics reduce air trapping by acting on small airways and thereby improve dyspnea and its symptoms.[23]

Ipratropium bromide and oxitropium bromide are administered three or four times daily via inhalation, whereas tiotropium bromide is given once daily by inhalation. Tiotropium is very effective in improving lung function and quality of life at all stages of the disease even when added to other therapies, as shown in the large UPLIFT study[24] (Fig. 83.3). Tiotropium also reduces severe exacerbations and hospital admissions, as well as mortality from COPD and cardiovascular disease.[24,25] Anticholinergic drugs may have additive bronchodilator effects with beta-2 agonists so may be given together. For short-acting drugs ipratropium-salbutamol inhalers are popular, whereas once daily combination inhalers containing tiotropium with formoterol are also available and in development.[26,27]

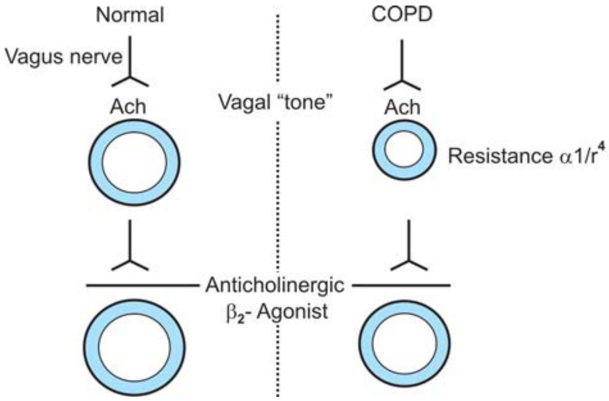

Fig. 83.2: Cholinergic control of airways in COPD. Normally there is a certain amount of cholinergic tone. This is exaggerated in COPD because of geometric factors related to the fixed narrowing of the airways (airway resistance R is proportional to $1/r^4$, where r is airway radius), so that airway resistance improves to a greater extent than in normal airways with an anticholinergic drug, which blocks the effect of acetylcholine (ACh) on muscarinic receptors in airway smooth muscle. Beta-agonists, which block all known bronchoconstrictor mechanisms, have a similar effect to anticholinergics suggesting that vagal tone is the only reversible component in COPD

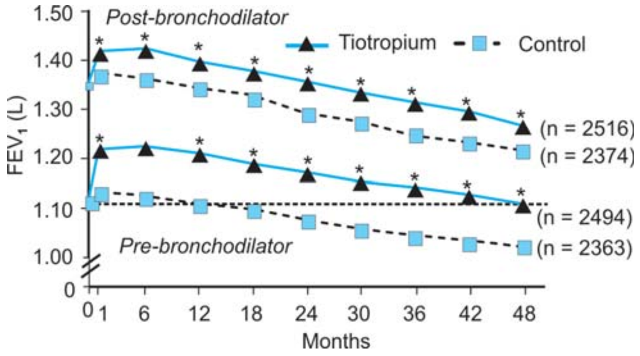

Fig. 83.3: The UPLIFT study. This large study of approximately 6,000 COPD patients compared tiotropium bromide (18 µg once daily) with placebo when added to current therapy. Tiotropium resulted in a greater increase in FEV_1 pre- and post-bronchodilator, which was sustained throughout the 4 years of the study[24]

Inhaled anticholinergic drugs are well tolerated, and systemic side-effects are uncommon because almost no systemic absorption occurs. Ipratropium bromide, even in high doses, has no detectable effect on airway secretions. Nebulized ipratropium bromide may precipitate glaucoma in elderly patients as a result of a direct effect of the nebulized drug on the eye; this is avoided by use of a mouthpiece rather than a face-mask. Dry mouth occurs in about 10% of the patients on tiotropium bromide but rarely requires discontinuation of treatment.

Beta-2 Agonists

Short-acting beta 2-agonists are used mainly for symptom relief as required but may be used four times a day on a regular basis. However LABA are preferred therapy for COPD as they give better control of symptoms and are used as a maintenance therapy.[28]

Beta-2 agonists have several beneficial effects on the airways in COPD (Fig. 83.4). These drugs act on airway smooth muscle causing a relaxation in large and small airways. They act as functional antagonists and reverse bronchoconstriction irrespective of cause. Experimentally, they reduce plasma exudation and cholinergic reflexes. They also increase mucociliary clearance (when it is reduced), but have no effect on chronic inflammation. Evidence suggests that beta-2 agonists may reduce adherence of bacteria to airway epithelial cells and this may reduce infective exacerbations.[29] There is some evidence that beta-2 agonists may increase the ventilatory drive to hypercapnia (but not to hypoxia).[30]

Side effects are not usually a problem and excessive use does not appear to be dangerous, even in patients with hypoxia and with cardiovascular disease. Muscle tremor,

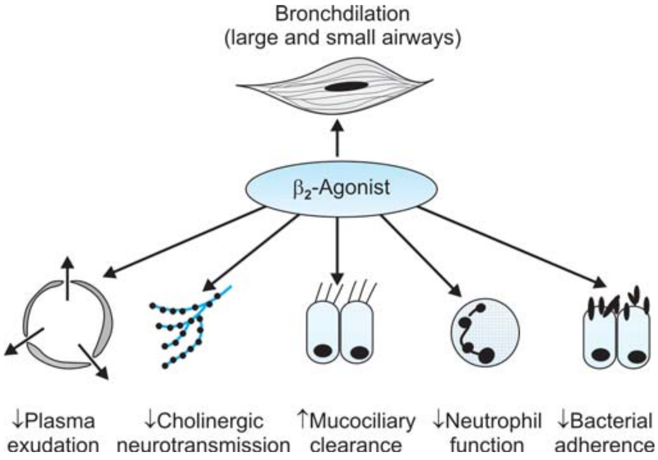

Fig. 83.4: Mechanism of action of beta-2 agonists in COPD. Although their primary action is likely to be on airway smooth muscle, there are additional effects of beta-2 agonists that may be beneficial

tachycardia, hypokalemia and restlessness are not uncommon. Occasionally hypoxemia may result from increased $\dot{V}/\dot{Q}$ mismatch due to pulmonary vasodilatation.

Short-Acting Beta 2-Agonists

Short-acting inhaled beta 2-agonists, such as salbutamol and terbutaline, are recommended for the immediate relief of symptoms. Ideally they should not be used regularly (as tolerance to their protective effects occurs), although in patients with severe COPD regular nebulized beta-2 agonists may be indicated.

Long-Acting Inhaled Beta 2-Agonists

Salmeterol and formoterol give bronchodilatation and protection against bronchoconstriction for over 12 hours[31,32] (Fig. 83.5). There is compelling evidence that these drugs are useful as bronchodilators in patients with COPD.[28] These drugs may improve symptoms, quality of life and exercise performance and reduce air through relaxant effects on small airways.[33] In long-term studies they are safe and reduce exacerbations and mortality[34,35] (Fig. 83.6). They have a similar efficacy to anticholinergics but together there may be additive effects. If the inhibitory effect of beta-2 agonists on bacterial adhesion is relevant *in vivo*, they may also reduce the frequency of infective exacerbations, although this has yet to be determined as there are no marked differences between LABA (salmeterol) and LAMA (tiotropium) in reducing severe exacerbations of COPD[25] (Fig. 83.7).

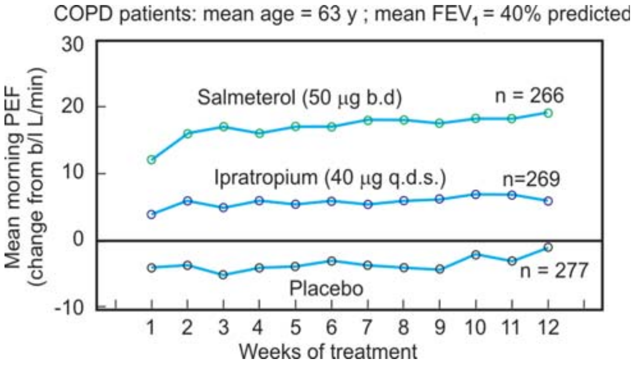

Fig. 83.5: The effect of salmeterol (50 µg BD) compared to ipratropium (40 µg GDS) in morning peak flow in patients with COPD[31]

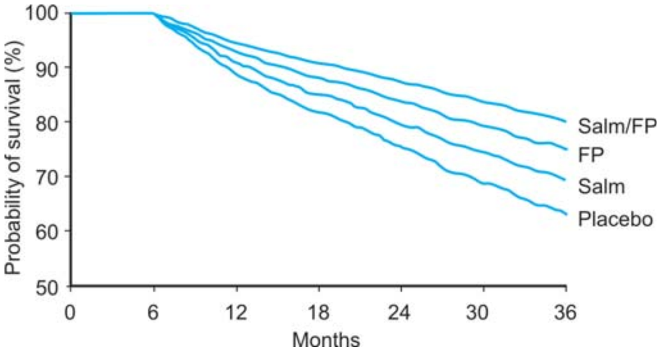

Fig. 83.6: TORCH study. This large study of approximately 6,000 COPD patients showed that fluticasone propionate/salmeterol reduced all cause mortality over 3 years, although this did not quite reach statistical significance (p = 0.052), whereas salmeterol and fluticasone alone had less effect[34]

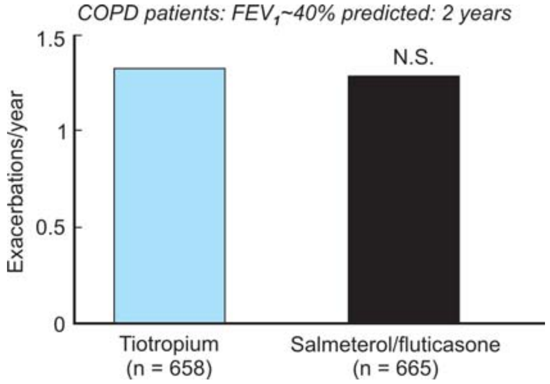

Fig. 83.7: Comparison between tiotropium and fluticasone/salmeterol in reducing acute exacerbations of COPD, showing no difference between these therapies[25]

Oral Beta-2 Agonists

Although inhaled beta-2 agonists are preferred, some elderly patients have problems with using inhalers. Slow-release oral beta-2 agonists preparations, such as bambuterol and slow-release salbutamol, are available. An advantage of these preparations is that they may treat peripheral airways more effectively, but the disadvantage is that the side effects are much more frequent than with inhaled preparations. Bambuterol is a prodrug which is slowly metabolized to terbutaline and is effective as a once-daily preparation in COPD.[36]

Theophylline

Theophylline in high doses (with plasma concentration 10 mg/l to 20 mg/l) is a useful additional bronchodilator in patients with severe COPD,[37] oral administration has the advantage of treating small airways.[38,39] It may have additional properties such as effects on mucociliary clearance and on respiratory muscles that are useful (Fig. 83.8). The major limitation to the use of theophylline is its side effects when high doses are used. More recently it has been established that lower doses of theophylline (plasma concentration 5 mg/l to 10 mg/l) have anti-inflammatory effects and specifically reduce neutrophilic inflammation in the airways of COPD patients.[40]

Theophylline acts through non-selective inhibition of phosphodiesterases, resulting in increased intracellular concentrations of Cyclic Adenosine Monophosphate (cAMP) and Cyclic Guanosine Monophosphate (cGMP). This effect is important for bronchodilator action, and might also be important in reducing neutrophilic inflammation. The drug also has some adenosine receptor antagonism, which accounts for some of the side effects, but there is little evidence that this is relevant for bronchodilator effects. Theophylline increases adrenaline secretion, but this is unlikely to account for the effects of the drug in COPD. Theophylline inhibits calcium entry and release and phosphoinositide hydrolysis. It is difficult to explain all of the beneficial effects of theophylline through these mechanisms alone, as many only occur at concentrations higher than those used therapeutically. More recently, it has been shown that low concentrations of theophylline are able to reverse corticosteroid resistance in COPD cells in vitro and preliminary studies have confirmed this in COPD patients.[41-43] This effect of theophylline is through direct inhibition of oxidative stress-activated phosphoinositide-3-kinase-δ, which results in increased histone deactylase-2 activity.[44]

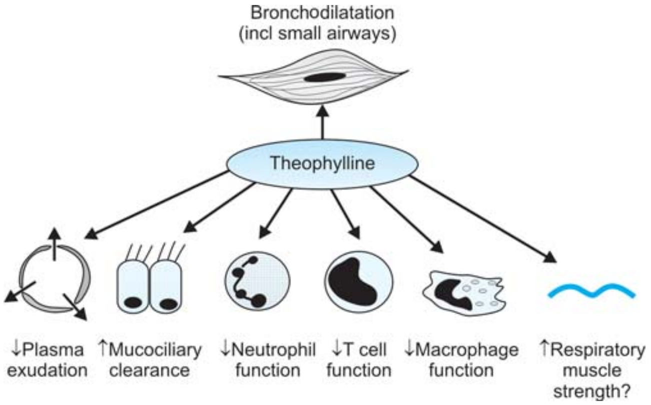

Fig. 83.8: Mechanism of action of theophylline in COPD. There may be several mechanisms of action of this drug, apart from bronchodilatation. At subbronchodilator doses theophylline reduces neutrophilic inflammation in COPD

Recommended Use in COPD: Theophylline is recommended as an additional bronchodilator in patients not controlled on regular inhaled anticholinergics and LABA. A slow-release preparation should be given twice daily to achieve plasma concentrations of 10 to 20 mg/l. The recent demonstration that theophylline has anti-inflammatory effects and reverses corticosteroid resistance in COPD may lead to the use of low doses (plasma concentration 1 to 5 mg/l) as a maintenance treatment combined with low doses of inhaled corticosteroids.[45,46] Low dose theophylline reduces exacerbations of COPD[47] and large trials studying the effects of low dose theophylline and inhaled or oral corticosteroids are needed.

Side effects are related to plasma concentration, although some patients may be particularly susceptible to side effects. They may be reduced by slowly increasing the dose when the drug is introduced. Side effects are mainly due to Phosphodiesterase (PDE) inhibition and include nausea and vomiting, headache, restlessness, gastroesophageal reflux, diuresis, cardiac arrhythmias (usually plasma concentration greater than 20 mg/l and due to adenosine receptor antagonism) and epileptic seizures (usually plasma concentration greater than 30 mg/l and due to adenosine receptor antagonism).

Clearance of Theophylline: The therapeutic effect is related to plasma concentration, which is affected by several factors that alter clearance (Table 83.2). If in doubt plasma concentrations should be measured.

Doxophylline

Doxophylline is a methylxanthine with similar bronchodilator properties to theophylline.[48] However, it

TABLE 83.2. Factors responsible for increased and decreased clearance of theophylline

Increased clearance (increase dose)
- Enzyme induction (rifampicin, phenobarbitone, ethanol)
- Smoking (tobacco, marijuana)
- Childhood
- High protein, low carbohydrate diet
- Barbecued meat

Decreased clearance (decrease dose)
- Enzyme inhibition (cimetidine, erythromycin, ciprofloxacin, allopurinol, ketoconazole)
- Congestive heart failure
- Liver disease
- Pneumonia
- Viral infection and vaccination
- High carbohydrate diet

is not an adenosine receptor antagonist so there is reduced risk of cardiac arrhythmias or seizures. In addition there are fewer drug interactions.

Corticosteroids

The role of corticosteroids in the management of COPD remains controversial. Maintenance treatment with oral corticosteroids should be avoided as there is no evidence of benefit and a high risk of side effects in COPD populations. Inhaled corticosteroids are commonly prescribed in high doses on the basis that COPD is like poorly responsive asthma, but there is little evidence that they are beneficial in patients with pure COPD. Approximately 10% of the patients with COPD have a positive response to oral corticosteroids and it is likely that these patients have coexisting asthma and should therefore be treated as if they are asthmatic with regular inhaled corticosteroids. These patients may be recognized by increased eosinophils in the sputum.[49]

Patients with COPD have a poor response to corticosteroids in comparison to asthma with little improvement in lung function. High doses of inhaled corticosteroids have consistently been shown a reduction (20 to 25%) in exacerbations in patients with severe disease and this is the main clinical indication for their use.[4] However, several large studies have shown that corticosteroids fail to reduce the progression in COPD (measured by annual fall in FEV_1)[50] and they have not been found to reduce mortality in a large study.[34] These results are likely to reflect the resistance of pulmonary inflammation to corticosteroids in COPD patients as a result of the reduction in HDAC2.[51]

Side Effects

The reduction in the frequency of exacerbations, may be offset by systemic side effects such as osteoporosis, particularly in an elderly population that is may be poorly nourished with reduced mobility. There is evidence that high-dose inhaled corticosteroids are associated with increased cataracts in COPD patients.[52] Several large trials of high dose inhaled corticosteroids have shown an increase in reported pneumonia amongst COPD patients.[53] The role of inhaled corticosteroids in non-reversible COPD is therefore currently uncertain.[54] Lower doses of inhaled corticosteroids will have less risk of side effects and budesonide may be less likely to have adverse effects than fluticasone propionate.[55]

Combination Inhalers

Several studies have demonstrated a benefit of combination inhalers containing a corticosteroids and a LABA in COPD patients. However, most of the benefit is provided by the LABA component.[35] Any superiority of combination inhalers over LABA alone in reducing exacerbations may be counteracted by the higher risk of side effects due to the corticosteroids component.[56] Combination inhalers improve symptoms and reduce exacerbations with a reduction in all cause mortality, although this does not quite reach statistical significance[34] (Fig. 83.6). The reduction in exacerbation between twice daily fluticasone/salmeterol is similar to that seen with tiotropium[25] (Fig. 83.7). Combination inhalers may be useful when patients with FEV_1 less than 50% predicted and with frequent exacerbations (less than two per year) that are already in tiotropium need further treatment.

Supplementary Oxygen

Poor oxygenation is one of the fundamental problems of severe COPD and supplementary oxygen is an important part of therapy in patients with severe disease.[57] Controlled oxygen (24%) is used acutely in the treatment of acute exacerbations in all patients who are hospitalized. Long-Term Oxygen Therapy (LTOT, domiciliary oxygen) is indicated in selected patients with COPD. Two large multicenter trials demonstrated that long-term oxygen administration (less than 15 hours daily) prolong survival (by about 30%) in patients with COPD. The goal of oxygen therapy is to increase PaO_2 to above 60 mm Hg or an oxygen saturation of greater than 90%; increasing PaO_2 above 60 mm Hg has little further benefit and increases the risk of CO_2 retention.[58] There is a danger of inducing respiratory failure if supplementary oxygen is used in patients with CO_2 retention, so careful assessment is required before oxygen is prescribed.

Selection of Patients for LTOT

In some countries, guidelines (Department of Health) have been drawn up for the provision of LTOT. LTOT should not be considered in patients who continue to smoke. All patients should be assessed by a pulmonary specialist.

Absolute indications are as follows:

- Stable COPD with hypoxemia and edema
- FEV_1 <1.5 L, FVC <2.0 L
- PaO_2 <55 mm Hg (<7.3 kPa), $PaCO_2$ >45 mm Hg (>6 kPa)
- Stability demonstrated over three weeks on optimal therapy

Relative indications are as follows:

- As above but without edema or $PaCO_2$ >45 mm Hg
- Palliative (symptom relief)

Portable oxygen is indicated in patients who desaturate during exercise and its efficacy needs to be assessed during a treadmill or six-minute walk test with patients wearing portable oxygen cylinder. Portable oxygen may also be indicated in patients with severe exercise limitation irrespective of oxygen desaturation. Portable oxygen may also be needed in such patients during commercial airline flights (provided by airline).

Oxygen Supply

There are several ways of providing supplementary oxygen:

- *Compressed Gas Cylinders* containing 100% oxygen are inconvenient as regular delivery is needed and the cylinders are large and heavy, but is still the most widely used method in the United Kingdom. Fitted with flow meters that are either medium (2 l/min) or high (4 l/min).
- *Oxygen Concentrators* are the most economic and convenient way of delivering LTOT at home.[59]
- *Liquid Oxygen* is the most portable but most expensive form of supplementary oxygen. Lightweight devices weighing 3 kg can deliver oxygen for 14 hours at 2 l/min.

Oxygen may be delivered by several devices, which includes:

- *Face Masks:* Tight fitting masks are the most efficient devices, but are uncomfortable and inconvenient for long-term use.
- *Nasal Cannulae*: They are the most commonly used means of O_2 delivery and usually have no problems. A flow of 1.5 l/min to 2.5 l/min is usually adequate to achieve a PaO_2 greater than 60 mm Hg (more than 8 kPa).
- *Transtracheal Catheter:* Transtracheal Oxygen Therapy (TTOT) may be useful in some patients who cannot tolerate face masks or nasal cannulae, but catheters have to be removed and cleaned frequently.
- *Pulsed Delivery Systems:* They use a thermistor or pressure valve to deliver O_2 only during the beginning of inspiration. These devices are expensive but reduce the amount of oxygen used by over one-third.

Antibiotics

Since infection is often the cause of progression or acute deterioration in patients with COPD, the combating of infection by the appropriate use of antibiotics is an important part of therapy.[60] In fact, the organisms causing pulmonary infections are often the same as those found normally in the upper respiratory tract and it may be difficult to know if a pathogen isolated from the sputum is responsible for the exacerbation. For most of the time the sputum in COPD is mucoid but becomes yellow or green with the exacerbations of infection and when this occurs, it is usual to begin empirical antibiotic therapy. Purulence of sputum is due to an increase in degranulating neutrophils and may not necessarily imply bacterial infection. Indeed, many exacerbations of COPD are likely to be due to upper respiratory tract virus infections, such as *Rhinovirus*, *Coronavirus* and *Parainfluenza* virus.[61] This means that the antibiotics are often used inappropriately, but it is difficult to tell clinically whether an infection is viral or bacterial in origin. In a meta-analysis of placebo controlled trials of antibiotics for COPD there was a small but significant difference in Peak Expiratory Flow (PEF) between patients treated with antibiotics and placebo.[62]

The common bacterial organisms responsible for exacerbations of COPD, include *Streptococcus pneumoniae, Haemophilus influenzae* , *Moraxella catarrhalis*, *Mycoplasma pneumoniae* (less common). The choice of antibiotic depends upon the likely organisms, the likely sensitivity of the organisms in the community, the tolerance of the patient for the drug, the response to treatment. The treatment of choice in the community will often be either amoxicillin or co-trimoxamole (Septrin). Co-trimoxamole is not recommended as its usage leads to development of resistance and side effects due to the sulfonamide component commonly. However, because many strains of *H. influenzae* are now beta-lactamase producers and hence resistant to ampicillin/amoxicillin, the treatment for initial therapy commonly lies between:

- amoxicillin/clavulanic acid (Augmentin)
- erythromycin or other macrolides (clarithromycin, azithromycin)
- a cephalosporin, e.g. cefaclor
- a tetracycline, e.g. doxycycline

There are advantages and disadvantages to each drug and the choice may finally be based on finding out which drug works for a given patient. Cost is also a factor and there is no justification for using an expensive drug when a cheaper one works just as well. In most cases, the choice usually falls between amoxicillin, amoxicillin/clavulanic acid or doxycycline for the typical ambulatory patient.

The antibiotic should be given in full therapeutic doses for a course lasting about 10 to 14 days except for clarithromycin and azithromycin which are given for shorter periods (three days). Treatment is then stopped provided the patient has responded. If there has been a poor response a change of antibiotic may be indicated, usually to one of the newer broad spectrum agents such as clarithromycin if this has not already been tried. Continuous antibiotic administration is not recommended in COPD as this has not been shown to alter the course of the disease and is likely to lead to an increase in resistant organisms. Erythromycin has been shown to reduce exacerbations of COPD but it is not certain whether this is an antibiotic or an anti-inflammatory effect of the macrolide.[63]

OTHER DRUG THERAPIES

Mucolytics

Because mucus hypersecretion is a prominent feature of chronic bronchitis various mucolytic therapies have been used to increase the ease of mucus expectoration, in the belief that this will improve lung function.

- *Stopping Smoking* is the most effective way to reduce mucus hypersecretion.
- *Anticholinergics* may decrease mucus hypersecretion.
- *Beta-2 Agonists* and *theophylline* may improve mucus clearance.
- *Steam Inhalation* (with or without aromatics) may provide symptomatic relief, but there is no evidence that it improves lung function or long-term symptom control.
- Several drugs, such as *bromhexol* and *ambroxol*, reduce mucus viscosity in vitro, but there is little evidence from controlled trials that they improve lung function in patients with COPD, and cannot be recommended as routine therapy.
- Expectorants, such as *guaifenesin* and *potassium iodide*, similarly have no proven beneficial effects.
- *Recombinant Human DNAse* (alfadornase, Pulmozyme) has beneficial effects in some patients with cystic fibrosis, but its role in COPD is not yet clear. Until there is clear evidence of benefit in COPD it should not be used in view of its high cost.

Antioxidants

Since oxidant damage may be critical in the pathophysiology of COPD, antioxidant therapy is logical. *N*-Acetyl-Cysteine (NAC) and carbocisteine were originally developed as mucolytics, but have well documented antioxidant effects.[64,65] Although a meta-analysis of several small studies demonstrated a beneficial effect of NAC in reducing exacerbations of COPD by approximately 25%,[66,67] in a large prospective controlled trial NAC failed to reduce exacerbations, improve health status or reduce disease progression.[68] However, patients not already treated with inhaled corticosteroids obtained some benefit/ a large study from China showed that carbocisteine reduced exacerbations by approximately 25% over a year of therapy in treatment naïve patients.[69] This suggests that mucolytic/ antioxidants may be used in patients who are not already treated with inhaled corticosteroids and may provide benefit in reducing exacerbations.

Vaccines

- Influenza Vaccine is recommended as patients with COPD are subject to severe exacerbations with this infection and there if evidence for a reduction in acute exacerbations and hospital admissions. There is convincing evidence that influenza vaccination is cost-effective in elderly people and should be more so in patients with COPD. Influenza vaccination reduces all cause mortality in COPD patients.[70] Influenza vaccination should be given prior to the winter season.
- Polyvalent pneumococcal vaccine is used in many countries to protect against the development of pneumococcal lung infections. Pneumococcal vaccination is cost-effective, but does not reduce mortality[70] and there are no convincing large trials to show a reduction in exacerbations.[71] Improved vaccines are now in development.
- Broncho-Vaxom (OM85-BV) is a mixture of bacterial products that activate macrophage function (the advantage of which is obscure). There is some evidence that it may reduce the severity of acute exacerbations, but it cannot be recommended as a routine treatment.[72]

Neuraminidase Inhibitors

Inhibitors of neuraminidase, such as zanamivir (inhaled) and oseltamivir (oral) speed the recovery from influenza. However, there are no specific trials in patients with COPD and it is not yet certain whether this treatment is cost-effective.[73]

Treatment of Dyspnea

Breathlessness is a problem in many patients, particularly "pink puffers." Several drugs, including nebulized opiates, slow-release morphine, dihydrocodeine and benzodiazepines, may reduce the sensation of dyspnea but the reduction in ventilatory drive is potentially dangerous and these drugs should be avoided, particularly during exacerbations.[74]

Respiratory Stimulants

There is no role for respiratory stimulants, such as doxapram or almitrine, in the long-term management of COPD, since there is no evidence that central ventilatory drive is impaired. Ventilation is limited by mechanical rather than neurophysiological factors. However, doxapram may be indicated in the management of an acute exacerbation of COPD if there is hypercapnia and hypoventilation in order to tide the patient over 24 to 36 hours until the underlying cause (e.g. infection) is controlled. However, it is likely that the use of doxapram in this situation will decline as Nasal Intermittent Positive Pressure Ventilation (NIPPV) becomes more widely available.

Antitussives

Cough is often a troublesome symptom of COPD, but may have a protective effect in clearing secretions. The regular use of antitussives is therefore not recommended in COPD.[75,76]

NON-PHARMACOLOGICAL TREATMENTS

Several non-pharmacological approaches have also been used in the management of COPD and may form part of a comprehensive rehabilitation program in elderly patients.

Exercise

Exercise training to improve cardiorespiratory function may be helpful; the type of exercise does not appear to be important and aerobic exercise or upper limb exercises are equally effective. Respiratory muscle training using resistive inspiratory loading may reduce breathlessness, but a meta-analysis of controlled studies of respiratory muscle training alone has provided no evidence of overall benefit.[77] Controlled breathing techniques, such as pursed-lip breathing and diaphragmatic breathing, result in reduced dyspnea, particularly in patients with hyperventilation.

Nutrition

Nutrition is important in patients with COPD as many of them are malnourished and underweight, although marked cachexia is now uncommon. Several patients with COPD are obese because of reduced physical activity. They should lose weight, particularly if they have sleep disturbances, metabolic syndrome or frank type II diabetes. Antioxidant vitamin supplements should also be indicated. However, there is no convincing evidence that improved nutrition and nutritional supplements with a high fat content that are marketed for use in COPD are beneficial in these patients.[78,79] The place of androgens and anabolic steroids to build muscle bulk in COPD has not been established.[80]

Pulmonary Rehabilitation

Rehabilitation concerns prevention of deconditioning and allowing the patient to cope with his/her disease. Rehabilitation programs are successful in prospective randomized trials in the terms of increased performance and quality of life, even though they may not improve lung function.[81] Patients with moderate-to-severe COPD should be considered for pulmonary rehabilitation programs, which include educational advice and physiotherapy. There is evidence that pulmonary rehabilitation also increases the efficacy of bronchodilator therapy.[82]

Artificial Ventilation

Artificial ventilation devices have improved enormously. Non-invasive ventilation using nasal intermittent positive pressure ventilation has been an important advancement in the management of acute exacerbations of COPD in hospital and more recently for the control of hypercapnic respiratory failure at home, thus reducing the need for hospitalization.[83] Nasal intermittent positive pressure ventilation corrects the hypercapnia and respiratory acidosis, while resting the respiratory muscles. Good results in the management of acute exacerbations have been reported, with significant reduction in mortality and time spent in hospital.[84]

Surgery

Several surgical techniques have been successfully applied to more severe emphysema. These include heart-lung transplantation, now largely replaced by single-lung transplantation in carefully selected patients.[85] Lung volume reduction surgery (LVRS) by excision of badly affected emphysematous lung is effective in highly selected patients with bilateral predominantly upper lobe emphysema and evidence of air trapping. There is sustained improvement in lung function and reduction in symptoms with a reduction in exacerbations.[86] Patients with a very poor diffusing capacity had an increased mortality. Therefore, patient selection is very important.[87] More recently bronchoscopic lung volume reduction surgery has been developed to avoid the surgical morbidity and mortality of LVRS. Several devices, including valves, coils and irreversible non-blocking techniques (bronchoscopic thermal vapor ablation, polymeric lung volume reduction) designed to collapse and remodel hyperinflated lung are currently in development.[88]

MANAGING CHRONIC DISEASE

It is important that an accurate diagnosis is made and that COPD is differentiated from asthma, which is usually possible from the history. Spirometry is important to diagnose airway obstruction objectively and to stage the disease in order to decide on the most appropriate therapy. In the Global initiative for chronic Obstructive Lung Disease (GOLD) Guidelines for COPD treatment of chronic disease follows a stepwise escalation based on disease severity[4] (Fig. 83.9). At all stages smoking cessation is important, particularly in the early stages of disease and patients should routinely receive immunization against seasonal influenza. In GOLD stage 1 there is usually little functional impairment and the only treatment needed is short-acting bronchodilator such as salbutamol, ipratropium or a combination of the two to be inhaled as required. In patients with GOLD 2, the preferred therapy is a long-acting bronchodilator—either tiotropium once daily or salmeterol or formoterol twice daily. Patients often prefer the once daily regime. If long-acting bronchodilators are too expensive it may be necessary to use a short-acting bronchodilator, such as salbutamol or ipratropium bromide, regularly four times daily or an oral bronchodilator, such as slow-release theophylline twice daily or bambuterol once daily. Sometimes it is necessary to use a combination of long-acting anticholinergic and LABA and a combination inhaler is preferred. For GOLD 3 patients, an inhaled corticosteroid may be added and this is often done by using a combination inhaler with a steroid and LABA. Oral theophylline may also be added at this stage as it may have an anti-inflammatory effect. Pulmonary rehabilitation is also useful is some patients if it is available. In GOLD 4 patients, it is necessary to consider the use of supplementary oxygen and for much selected patients lung surgery.

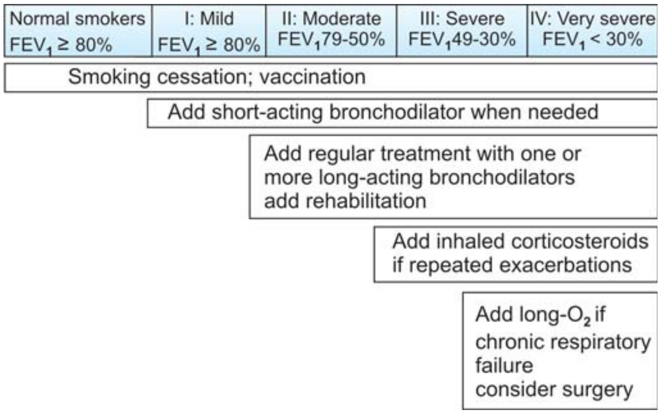
Normal smokers
$FEV_1 \geq 80\%$
I: Mild
$FEV_1 \geq 80\%$
II: Moderate
$FEV_1$79-50%
III: Severe
$FEV_1$49-30%
IV: Very severe
$FEV_1 < 30\%$
Smoking cessation; vaccination
Add short-acting bronchodilator when needed
Add regular treatment with one or more long-acting bronchodilators add rehabilitation
Add inhaled corticosteroids if repeated exacerbations
Add long-O_2 if chronic respiratory failure consider surgery

Fig. 83.9: Stepwise treatment of COPD as described in the GOLD initiative[89]

TREATMENT OF ACUTE EXACERBATIONS

An important aim of treatment is to prevent exacerbations. Several of the treatments for chronic diseases have been shown in controlled trial to reduce exacerbation rates and hospitalization, including long-acting bronchodilators (both beta-2 agonists and anticholinergic), low-dose theophylline, high-dose inhaled corticosteroids and smoking cessation.

Chronic obstructive pulmonary disease exacerbations are one of the commonest causes of hospital admission. Apart from the treatment of underlying bacterial infection with antibiotics (as discussed above), exacerbations are treated symptomatically by increasing the dose of SABA and anticholinergic bronchodilators delivered by nebulizer. The place of antibiotics is not certain as controlled trials show little clinical benefit; this may reflect the fact that over half of the exacerbations are due to viral or non-infective causes. Oxygen (24% or 28% via Venturi mask) should be given to achieve a PaO_2 of at least 60 mm Hg without a fall in pH to less than 7.26 (indicating an acute change). Blood gases should be checked within one hour of starting oxygen therapy. Oxygen saturation by pulse oximetry may be used to monitor response providing $PaCO_2$ and pH are normal. A course of oral corticosteroids is usually indicated but only reduces in-patient stay by about one day.[90] Very high does of corticosteroids, such as intravenous methylprednisolone, are not required as there is a greater risk of side effects.[91] Diuretics are indicated if there is peripheral edema. Chest physiotherapy may be useful, although there is no evidence from controlled studies that it improves recovery. Development of respiratory failure with a rising $PaCO_2$ may necessitate NIPPV or intubation.

TREATMENT OF COR PULMONALE

Cor pulmonale (right heart failure) is due to the effect of chronic hypoxia on the pulmonary vasculature resulting in pulmonary hypertension. It is usual to treat with LTOT. Diuretics are used to reduce fluid retention. Digoxin is only indicated if there is coexistent atrial fibrillation. Vasodilators may be hazardous as they lower systemic as well as pulmonary blood pressure.

FUTURE THERAPIES

There is a pressing need to develop new therapies, as existing treatments do not alter the progressive course of the disease or reduce mortality. There have been relatively few advances in the therapeutic options for the treatment of COPD, but better understanding of the molecular mechanisms involved in the pathogenesis of COPD will undoubtedly lead to improved therapies in the future.[92,93]

Several inhaled long-acting bronchodilators are currently in clinical development for COPD. Once daily inhaled beta-2 agonsits, including indacaterol, carmoterol, GW642444 and BI-1744, are in clinical development for COPD.[94] Indacaterol, if taken once daily, shows good efficacy in COPD with a similar sustained increase in FEV_1 as with tiotropium.[95] Several once daily anticholinergics, including glycopyrrolate, aclidinium and darotropium, are also in clinical development. Combination inhalers that contain a LABA and a LAMA, such as QVA149, show additivity and may be the most useful bronchodilators in the future for patients with more severe COPD.

There are currently no treatments, apart from theophylline, that reduce inflammation in COPD and there is an intense search for drugs that are effective against steroid-resistant inflammation. Drugs that block specific mediators, such as leukotriene B_4 and tumor necrosis factor, have not been shown to have any benefit. Phosphodiesterase 4 (PDE4) inhibitors have a broad spectrum of anti-inflammatory effects and are very effective in animal models of COPD. A PDE4 inhibitor, roflumilast, has been shown to significantly increase FEV_1 and reduce exacerbations, but these effects are really small and are not accompanied by any improvement in symptoms or health status.[96,97] The major problem with these drugs is the side effects due to PDE4 inhibition, which include nausea, headaches and diarrhea, and these limit the dose that can be given by mouth. There are now attempts to develop inhaled PDE4 inhibitors to avoid these side effects. Several other anti-inflammatory drugs are also in clinical development, including p38 MAP kinase inhibitors and Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB) inhibitors, but these drugs also have side effect issues and may need to be given by the inhaled route.

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Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Raja Dhar, AG Ghoshal

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) exacerbation occurs despite adequate control. Most patients experience episodes of exacerbation at least one or more times during their life-time and many suffer with these episodes at least one to three times a year. These episodes may vary immensely in the terms of frequency and severity. Chronic obstructive pulmonary disease exacerbations have a huge impact on the overall health condition of the patient, both physically as well as emotionally. Moreover, exacerbation costs a huge amount of money to the patient and the family. A moderate exacerbation, not requiring ventilation (with or without hospitalization) will cost around Rs 8,000 (approximate costs based on local data.) It must be remembered that even in patients with stable COPD, a severe exacerbation episode can cause a significant dent in pulmonary function and adversely affect the quality of his/her life. It is therefore extremely important for practicing physicians to learn the early identification of crisis, perform optimal management under appropriate settings, escalate and de-escalate the therapy based on patient's response, bring back the patient to the initial baseline status, help the patient and family to cope up with the situation with adequate support, discharge the patient in a stable clinical conditions, give necessary instruction about the proper follow-up.

Thankfully, with modern evidence-based treatment modalities, successful management of COPD exacerbation can be done in the majority of patients.

COPD EXACERBATION

An exacerbation of COPD is an event in the natural course of COPD characterized by an acute change in the patient's baseline dyspnea or breathing difficulty, cough and/or sputum production beyond day-to-day variability sufficient to warrant a change in management.

It can be infective or noninfective in nature. In the absence of a universal agreed criterion, the following operational classification can help to rank the clinical severity of the episode and its outcome.

- Level I: Treated at home
- Level II: Requires hospitalization
- Level III: Leads to respiratory failure

Causes of COPD Exacerbations

About 50% of COPD exacerbations are caused by lower respiratory tract infections, while the remaining are caused by exposure to indoor or outdoor air pollutants, changes in weather and several host factors including peer compliance to therapy (Table 84.1).[1,2]

Symptoms of COPD Exacerbation

Usually patients present with one or more symptoms of acute exacerbation (Table 84.2). During clinical assessment, further objective evaluation is necessary. Several clinical elements must be considered when evaluating patients with exacerbations. These include the assessment of the severity of the underlying COPD, the presence of comorbidities and the history of previous exacerbation. The physical examination

TABLE 84.1: Causes of COPD exacerbations

Infectious process	Viral (Rhinovirus spp., influenza); Bacterial *(Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis,* Enterobacteriaceae species, *Pseudomonas* spp.)
Environmental conditions	Sudden change in temperature, humidity, etc, air pollution exposure, exposure to tobacco smoke, noxious gases or irritating chemicals
Host factors	Patients with poor general health condition, poor nutritional status, immune-compromised status, lack of compliance with prescribed medical therapy, adoption of unhealthy lifestyle modes like lack of continuing with advised exercises, improper diet, poor level of personal hygiene, lack of compliance with long-term oxygen therapy, failure to participate in pulmonary rehabilitation

should evaluate the effects of the episode on hemodynamic and respiratory systems. The diagnostic procedures to perform such as chest radiography, sputum and blood examination and spirometry would depend on the clinical setting of the evaluation.[3,4]

Management of COPD Exacerbation

The decision to treat a patient at home or in the hospital is based both on subjective evaluation as well as objective criteria (Table 84.3). The choice of the patient/patients‘ family should also be taken into account.

However, it must be noted that there may be a sudden deterioration of condition and the decision to treat at home or at hospital can change rapidly (Table 84.4).

Development of new situations may warrant further evaluation and subsequent hospitalization.

Diagnosis of an exacerbation is primarily clinical and dependent on investigation though they are useful in assessing the severity and planning the optimum treatment (Table 84.5).

TABLE 84.2: Symptoms of COPD Exacerbation

- Increase in cough
- Chest pain
- Increase in breathlessness
- Increase in sputum volume and change in its colour (white to green, yellow or blood streaked)
- Fever
- Increased tiredness
- Increase in oxygen requirement (for those on long-term oxygen therapy)

Primary Care

In patients with an exacerbation managed in primary care:

- Sending sputum samples for culture is not recommended in routine practice.

TABLE 84.3: Clinical factors that determine whether the patient should be treated at home or hospital

Factor	*Indication to treat at home*	*Indication to treat at hospital*
Able to cope at home	Yes	No
Severity of breathlessness	Mild	Severe
General health condition	Good/Satisfactory	Poor/deteriorating
Level of activity	Good	Poor/confined to bed
Cyanosis	No	Yes
Worsening peripheral edema	No	Yes
Level of consciousness	Normal	Impaired
Already receiving LTOT	No	Yes
Social circumstances	Good/adequate support	Living alone/not coping
Acute confusion/altered mental status	No	Yes
Rapid rate of onset	No	Yes
Significant comorbidity (particularly heart disease and insulin-dependent diabetes)	No	Yes
SaO_2 <90%	No	Yes
Changes on the chest radiograph	No	Present
Arterial pH level	$\geq$ 7.35	< 7.35
Arterial PaO_2	$\geq$ 7 kPa	< 7 kPa

TABLE 84.4: The situations for immediate reassessment of the patient condition

- Marked increase in dyspnea
- Inability to eat or sleep due to respiratory symptoms
- Inadequate response to the outpatient management
- Worsening of hypoxemia
- Worsening of hypercarbia
- Change in mental status
- Poor perception of severity
- Inability of the patient to take care of himself/herself/lack of home support
- Documented noncompliance to prescribed therapy
- Development of new symptoms
- Uncertain diagnosis

- Pulse oximetry may be useful if there are clinical features of a severe exacerbation.

Patients Referred to Hospital

In all patients with an exacerbation referred to hospital:

- A chest radiograph should be obtained.
- Arterial blood gas tensions should be measured and the inspired oxygen concentration recorded.
- An ECG should be recorded to exclude cardiac comorbidities.
- A full blood count should be performed; urea and electrolyte concentrations should be measured.
- A theophylline level should be measured in patients who are on theophylline therapy at admission.
- If sputum is purulent, a sample should be sent for microscopy and culture.
- Blood cultures should be taken if the patient has fever.

Outpatient Management for COPD Exacerbation (Level I)

The treatment of exacerbation has to be based on the clinical presentation of the patient.

The essential components of treatment are shown in Table 84.6.

TABLE 84.5: Elements of the clinical evaluation and diagnostic procedures that are usually informative in patients with exacerbations according to the severity of the episode

	Level I (Treated at home)	*Level II (Requires hospitalization)*	*Level III (Leads to respiratory failure)*
Clinical history			
Comorbid conditions *	+	+++	+++
Frequent exacerbations	+	+++	+++
Severity of COPD	Mild/Moderate	Moderate/Severe	Severe
Physical Findings			
Hemodynamics	Stable	Stable	Stable/unstabe
Use of accessory muscles while breathing/tachypnea	Not present	++	+++
Persistent symptoms after initial therapy	No	++	+++
Diagnostic Procedures			
Oxygen saturation	Yes	Yes	Yes
Arterial blood gases	No	Yes	Yes
Chest radiograph	No	Yes	Yes
Blood tests†	No	Yes	Yes
Serum drug concentration§	If applicable	If applicable	If applicable
Sputum gram stain and culture	No ¶	Yes	Yes
Electrocardiogram	No	Yes	Yes

Keys:

***** the more common comorbid conditions associated with poor prognosis in exacerbations are congestive heart failure, coronary artery disease, diabetes mellitus, renal and liver failure

† Blood tests include cell blood count, serum electrolytes, renal and liver function

§ Consider if patients are using theophylline, warfarin, carbamezepine, digoxin

¶ Consider if patient has been recently on antibiotics

+ unlikely to be present

++ likely to be present

+++ very likely to be resent

TABLE 84.6: The essential components of treatment of COPD exacerbation

Bronchodilators
- Short-acting beta 2-agonist***** and/or ipratropium by metered dose inhaler with spacer or hand-held nebulizer as needed.[5-7]
- Consider adding long-acting bronchodilator, e.g. formoterol [by Metered-Dose Inhaler (MDI) plus spacer or nebulized route] if patient is not using it

Corticosteroids (the actual dose may vary)
- Oral prednisone 30–40 mg per os q.d. for 10 days[8-10]
- Consider using an inhaled corticosteroid[11]

Antibiotics[1,12-17]
- May be initiated in patients with altered sputum characteristics
- Choice should be based on local bacteria resistance patterns
- Amoxicillin/ampicillin†, cephalosporins§
- Doxycycline
- Macrolides¶[18-20]
- If the patient has failed prior antibiotic therapy consider: Amoxicillin/clavulanate[19]
  Respiratory fluoroquinolones******[13,21,22]
- Cefdinir, Cefprozil, Cefuroxime

Patient Education
- Check inhalation technique
- Consider use of spacer devices

Keys: Metered-dose inhaler*****: salbutamol/levosalbutamol, terbutaline; †: depending on local prevalence of bacterial beta-lactamases; §: cefpodoxime, cefprozil, cefuroxime, Cefdinir; ¶: azithromycin, clarithromycin, dirithromycin. roxithromycin; ******: gatifloxacin, levofloxacin and moxifloxacin.

Inpatient Management of COPD Exacerbation (Level II and III)

As mentioned earlier, the decision to admit a patient is derived from the subjective interpretation of clinical features, such as the severity of dyspnea, determination of respiratory failure, short-term response to emergency room therapy, degree of cor pulmonale and the presence of complicating features such as severe bronchitis, pneumonia or other comorbid conditions.

Very few clinical studies have investigated patient-specific objective clinical and laboratory features that identify patients with COPD who require hospitalization. General consensus supports the need for hospitalization in patients with severe acute hypoxemia or acute hypercarbia. Less extreme arterial blood gas abnormalities, however, do not assist decision analysis. Other factors that identify "high-risk" patients include a previous emergency room visit within seven days, the number of doses of nebulized bronchodilators, use of home oxygen, previous relapse rate, administration of aminophylline and the use of corticosteroids and antibiotics at the time of previous emergency room discharge.[23-26]

Pharmacologic management remains the mainstay of COPD exacerbation along with other supportive measures.

Inhaled Bronchodilators

- Short-acting beta 2-agonist (salbutamol 100–200 mcg inhaler/levosalbutamol) and/or
- Ipratropium MDI (20, 40 mcg) with spacer or hand-held nebulizer as needed.[5-7]

Delivery systems for inhaled therapy during exacerbations
- Both nebulizers and hand-held inhalers can be used to administer inhaled therapy during exacerbations of COPD.
- The choice of delivery system should reflect the dose of drug required, the ability of the patient to use the device and the resources available to supervise the administration of the therapy.
- If a patient is hypercapnic or acidotic, the nebulizer should be driven by compressed air, not oxygen (to avoid worsening hypercapnia). If oxygen therapy is needed, it should be administered simultaneously by nasal cannulae.
- The driving gas for nebulized therapy should always be specified in the prescription.

Systemic Corticosteroids

- Inhaled corticosteroids by MDI or hand-held nebulizer should be considered.[11] For example: Beclomethasone 50–400 mcg; Budesonide 100, 200, 400 mcg; Fluticasone 50–500 mcg inhaler.
- In the absence of significant contraindications, oral corticosteroids should be used in conjunction with other therapies in all patients admitted to hospital with an exacerbation of COPD.
- In the absence of significant contraindications, oral corticosteroids should be considered in patients managed in the community who have an exacerbation with a significant increase in breathlessness which interferes with daily activities.
- Patients requiring corticosteroid therapy should be encouraged to present early to get maximum benefits.
- Prednisolone 30 mg orally should be prescribed for 7–14 days.
- If patient tolerates, prednisone 30–40 mg per day should be prescribed for 10 days.[8-10]
- If patient cannot tolerate oral intake, consider equivalent dose intravenous (IV) for up to 14 days (20 mg hydrocortisone is equivalent to 5 mg prednisolone, 4 mg methylprednisolone and 0.75 mg dexamethasone).

- It is recommended that a course of corticosteroid treatment should not be longer than 14 days as there is no advantage in prolonged therapy.
- Osteoporosis prophylaxis should be considered in patients requiring frequent courses of oral corticosteroids.
- Patients should be made aware of the optimum duration of treatment and the adverse effects of prolonged therapy.
- Patients, particularly those discharged from hospital, should be given clear instructions about why, when and how to stop their corticosteroid treatment.

Antibiotics[1,2,9-19,23,27]

Antibiotics based on local bacteria resistance patterns should be started for patients with the history of producing purulent sputum. Any change in sputum characteristics like color, consistency and volume should also prompt the initiation.

- Antibiotics need not be started for patients having exacerbations without increase in sputum purulence, unless there are signs of consolidation on chest radiograph or clinical symptoms of pneumonia.
- Antibiotic choice should be based on local bacteria resistance patterns, if available. However, when this information is not available, macrolides or second generation cephalosporins can be used.

  Initial empirical treatment should consist of an aminopenicillin, a macrolide or a tetracycline. When initiating empirical antibiotic treatment, one should always take account of any guidance issued by the local microbiologists.
- When sputum has been sent for culture, the sensitivity to antibiotics should be checked to ensure appropriate therapy.
  - Amoxicillin/clavulanate[19] and respiratory fluoroquinolones (levofloxacin, moxifloxacin)[13,21,22] are commonly used.
  - If *Pseudomonas* spp. and/or other *Enterobacteriaceae* spp. are suspected, consider combination therapy [e.g. Piperacillin/tazobactam (3.375 g q 4 hours IV) or imipenem (500 mg q 6 hours IV) or meropenem (1 g q 8 hours IV) plus Amikacin (7.5 mg/kg q 12 hours or 15 mg/kg q 24 hours IV) or Levofloxacin (500 mg daily) for 10–14 days].

Theophylline and Other Methylxanthines

- Intravenous theophylline should only be used as an adjunct to the management of exacerbations of COPD if there is an inadequate response to nebulized bronchodilators.
- Care should be taken when using intravenous theophylline because of its interactions with other drugs (e.g. ciprofloxacin, clarithromycin, allopurinol, phenytoin, etc.) and potential toxicity if the patient has been on oral theophylline.
- Within 24 hours of starting the treatment, the theophylline levels should be monitored to maintain within therapeutic range (10–20 mcg/ml). Thereafter, monitoring should be done as frequently as indicated by clinical circumstances.

Respiratory Stimulants

It is recommended that doxapram is used only when noninvasive ventilation is either unavailable or considered inappropriate (e.g. hypersensitivity, pulmonary embolism, severe hypertension, cerebral edema, epilepsy, hyperthyroidism, etc.).

Oxygen Therapy

Oxygen therapy is recommended to relieve severe respiratory distress and prevent tissue hypoxia.

- The goal is to prevent tissue hypoxia by maintaining arterial oxygen saturation (SaO_2) at more than 90%
- All patients with COPD exacerbation should have their arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$) and pH measured upon admission, during the course of treatment and whenever there is any change in patient's clinical condition.
- In case of unavailability of arterial blood gas measurement facility, oxygen saturation should be measured. Pulse oxymeters should be available to all health care professionals managing patients with exacerbations of COPD and they should be trained in their use. Clinicians should be aware that pulse oximetry gives no information about the PCO_2 or pH.
- Even if oximeter is not available for any reason, oxygen should be given to all patients with an exacerbation of COPD who are breathless, even if the oxygen saturations are not known, but careful monitoring of the patient condition is essential to prevent excessive CO_2 washout and cause respiratory depression since CO_2 acts as the respiratory drive for many COPD patients.
- The principal delivery device for oxygen comprises of nasal cannula and venturi mask. Alternative delivery devices include non-rebreather mask, reservoir cannula or transtracheal catheter.
- During the transfer to hospital, the following points should be considered:

  - It is not desirable to exceed an oxygen saturation of 93%. Oxygen therapy should be commenced at approximately 40% and titrated upwards if saturation falls below 90% and downwards if the patient becomes drowsy or if the saturation exceeds 93% to 94%.
  - Patients with known type II respiratory failure need special care, especially if they require a long ambulance journey or if they are given oxygen at home for a prolonged period before the ambulance arrives. It is important to remember that the prevention of tissue hypoxia supercedes CO_2 retention issue.
- The aim of oxygen therapy during exacerbation of COPD is to maintain adequate level of oxygen (SaO_2 >90%) without worsening or precipitating respiratory acidosis or worsening hypercapnia. If pH falls below 7.35 (acidemia), consider mechanical ventilation.

Admission to Intensive Care Unit (ICU)/ Critical Care Unit

The decision to shift/admit a patient to the critical care unit largely depends on subjective assessment and clinician's judgment, although various diagnostic parameters help in decision making. Presence of the following features merit consideration for shifting to Intermediate Respiratory Care Unit (IRCU):

- Persistent respiratory distress despite standard management.
- Inability to maintain oxygen level above 90% despite oxygen therapy by high-flow mask.
- Persistent hypercapnia.
- Abnormal blood gas parameters (PaO_2 <60 mm Hg and/or $PaCO_2$ >60 mm Hg).
- Alteration of mental status, acute confusion, drowsiness.
- Increased signs of infection (pyrexia, increased sputum purulence/volume, etc.).
- Significant abnormal changes in chest radiograph.
- Clinical deterioration.

ASSISTED VENTILATION

Despite optimal pharmacologic management, severe cases of exacerbation necessitates ventilatory support, when the patient is unable to maintain the breathing function and/or unable to maintain sufficient gaseous exchange for normal physiologic function.

Ventilatory support, either "invasive" or "non-invasive," is not a therapy but a form of life support until the cause of underlying acute respiratory failure is reversed with medical therapy.[28-30]

Noninvasive Ventilation

Noninvasive ventilation is an alternative for patients who have respiratory failure and can no longer breathe on their own. It enhances the breathing process by giving the patient a mixture of air and oxygen from a flow generator through a tightly fitted facial or nasal mask. Noninvasive ventilation assists the patient in taking a full breath and helps to maintain an adequate oxygen supply to the body.[31] Noninvasive Positive Pressure Ventilation (NIPPV) is by far the most popular mode of providing noninvasive ventilation[30,32] in combination with some Continuous Positive Airway Pressure (CPAP) plus Pressure Support Ventilation (PSV).[28,33]

It improves the gas exchange by improving the alveolar ventilation, without causing significant modifications in the alveolar ventilation/perfusion mismatching and gas exchange in the lungs.[34] The application of the combination of CPAP and PSV offers a better outcome than either alone because the CPAP counterbalances the intrinsic positive end expiratory pressure.[35]

Noninvaisive Ventilation (NIV) should be used as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy. Noninvasive positive pressure ventilation should be offered to patients with exacerbations when, after optimal medical therapy and oxygenation, respiratory acidosis (pH <7.36) and or excessive breathlessness persist. All patients considered for mechanical ventilation should have arterial blood gases measured.

- If pH <7.30, NIPPV should be delivered under controlled environments such as intermediate ICUs and/or high-dependency units. If pH <7.25, NIPPV should be administered in the ICU and intubation should be readily available.
- It is important to ensure that the NIV be administered by a dedicated team by its staff, with necessary training for the same, well conversant with its application as well as the limitations.
- The combination of some CPAP (e.g. 4–8 cm H_2O) and PSV (e.g. 10–15 cm H_2O) provides the most effective mode of NIPPV.
- NIV should also be a consideration for patients who are slow from weaning from ventilator. (Factors influencing slow weaning are not provided in guideline).

- The combination of some CPAP (e.g. 4–8 cm H_2O) and PSV (e.g. 10–15 cm H_2O) provides the most effective mode of NIPPV.
- In the first few hours, the level of assistance and monitoring of NIPPV is same as mechanical ventilation.
- When put on NIV, there should be a well-defined plan for every patient on course of action on deterioration as well clear indicators of the limits of such deterioration, when the next action is to be taken.

Clinical Settings

NIPPV can be delivered in different clinical settings which are as follows:

- Medical ward: Patients with moderate acidosis (pH 7.30–7.35) and hypercapnia (6–8 kPa ($PaCO_2$ 45–60 mm Hg).[36,37]
- Intermediate or high-dependency respiratory unit[38,39] patients who present moderate-to-severe acidosis (pH <7.30); the facilities for rapid endotracheal intubation and institution of conventional mechanical ventilation should be promptly available.
- ICU:[40] Patients with severe respiratory acidosis (pH <7.25); in this particular setting, NIPPV may be as effective as conventional mechanical ventilation to reverse acute respiratory failure due to COPD.[41]

It is important to note that the one-year mortality was reported to be lower in patients receiving NIPPV for exacerbations of COPD, compared to both optimal medical therapy alone[42] and conventional mechanical ventilation.[41]

Mechanical Ventilation

Mechanical ventilation is a mode of assisted or controlled ventilation using mechanical devices that cycle automatically to generate airway pressure.[43] Intubation should be considered in patients with the following:

- *NIPPV failure:* Worsening of arterial blood gases and or pH in one to two hours; lack of improvement in arterial blood gases and or pH after four hours.
- *Severe acidosis* (pH <7.25) and hypercapnia [$PaCO_2$ >8 kPa (60 mm Hg)].
- *Tachypnea* >35 breaths/minute.
- *Other complications:* Metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion.[40]
    - During exacerbations of COPD, functional status, body mass index, requirement for oxygen when stable, comorbidities and previous admissions to ICUs should be considered, in addition to age and Forced Expiratory Volume in One Second (FEV_1), when assessing suitability for intubation and ventilation. Neither age nor FEV_1 should be used in isolation when assessing suitability.
    - Noninvasive positive pressure ventilation should be considered as the first-line intervention, in addition to optimal mechanical therapy, for the management of patients with respiratory failure due to exacerbation of COPD.[32] In the first few hours, NIPPV requires the same level of assistance as conventional mechanical ventilation.[44]
    - The fact that NIPPV is cost-effective is clearly demonstrated by a study[21,45] and it can also be used as a potential successful strategy of weaning[22,46] the patients from mechanical ventilation, in cases where the patients need an intermediate care between complete machine-dependent and totally independent for breathing.
    - The NIPPV may also be considered for those with history of previous persistent weaning failure.[47]

De-escalation of Therapy

- Patients' recovery should be monitored by regular clinical assessment of their symptoms and observation of their functional capacity.
- For patients with nonhypercapnic failure, nonacidotic failure can be monitored with pulse oximetry.
- For hypercapnic or acidotic patients, intermittent blood gas monitoring should be done to evaluate the situation. The frequency of such tests largely depends on the clinical judgment of the treating physician.
- During recovery from an exacerbation from COPD, daily performance of FEV_1 or peak expiratory flow is not advised since the magnitude of change is small as compared to the variability of measurement.

Discharge should be planned when:

- There is significant improvement in the clinical status of the patient.
- Significant improvement of symptoms like breathlessness, cough, remission or steady improvement in infection symptoms (reduction in sputum volume, non-pyrexial status, nonpurulence of sputum as confirmed by culture).
- Ability to maintain blood gas at acceptable range.
- Ability and inclination to perform day to day activities, even with some degree of assistance.

On the other hand of the spectrum, discharge or hospice care needs to be planned when the patient has already reached the end-stage and no significant improvement in clinical and cognitive status is unlikely.

- Spirometry measurement is a must for all patients before discharge. This helps in assessing the impact of the exacerbation episode on the pulmonary function and reassign the baseline values, in case of any alteration.
- Patients should be re-established on their optimal maintenance bronchodilators.
- Patients and/or home carers must be given the necessary information so that they fully understand the correct usage of medication including oxygen (if applicable).
- Follow-up visits must be scheduled and communicated to the patient/family.
- Follow-up care like refilling of medication, visiting nurse, oxygen delivery and referral for other support must be made before discharge.
- Before the patient is discharged, the patient, family members and the treating physician must be confident that the patient will be able to manage successfully. In case of doubts, formal assessments can be initiated.
- All aspects of the routine care that patients receive (including appropriateness and risk of side effects) should be assessed before discharge.
- It is useful to hand over a written plan on daily self care, medication management, emergency action plan during exacerbation to all patients/carers before discharge, with adequate explanation.

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85

Long-term Oxygen Therapy

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Long-term Oxygen Therapy (LTOT) is now a popular mode of therapy for a variety of respiratory disorders. When LTOT at home was first introduced, it was largely limited to patients with Chronic Obstructive Pulmonary Disease (COPD) and chronic respiratory insufficiency.[1-3] Subsequently, the indications continued to expand to include almost any chronic respiratory disease characterized by hypoxemia. In fact domiciliary oxygen is also useful in those patients who do not demonstrate hypoxemia such as those with breathing disorders during sleep or exercise. Hypoxemia in such patients is absent when they are alert and awake, but gets precipitated during sleep or exercise. Some of the common conditions for which LTOT has been used with variable degrees of benefit include COPD, interstitial lung disease, bronchiectasis, cystic fibrosis, kyphoscoliosis, sleep apnea syndrome, severe cardiac failure and other causes of chronic breathlessness.[4-15] More important than the underlying disease are the other selection criteria required to be fulfilled for LTOT.

SELECTION OF PATIENTS[5,16,17]

All patients with chronic hypoxemic lung disease are potential candidates for LTOT. Following guidelines are used to select patients for instituting the treatment.

i. A definitive documented diagnosis responsible for chronic hypoxemia.
ii. An optimal medical treatment should be in effect.
iii. Patient in a stable condition.
iv. Oxygen administration should have been shown to improve hypoxemia and provide clinical benefit.

It is important to ensure that the patient is compliant with the general medical regimen and follows instructions, such as to quit smoking. Continued smoking not only aggravates the disease process but also reduces the full physiological benefits of oxygen and poses inherent safety risk of accidental fires.

Following specific indices are used while prescribing long-term oxygen:

i. At rest, in non-recumbent position the PaO_2 of 55 mm Hg or less.
ii. Patients with PaO_2 of more than 55 mm Hg are considered in the following conditions:
   a. Patient on optimal medical treatment, with demonstrable hypoxic organ dysfunction, such as secondary pulmonary hypertension, cor pulmonale, polycythemia or central nervous system dysfunction.
   b. When there is a demonstrable fall in PaO_2 below 55 mm Hg during sleep, associated with disturbed sleep pattern, cardiac arrhythmias or pulmonary hypertension. These patients may be benefited by nocturnal oxygen therapy.
   c. When there is demonstrable PaO_2 fall during exercise and oxygen administration is shown to improve exercise performance, duration or capacity. These patients may benefit by oxygen during exercise. They may also be administered supplemental oxygen before and after the exercise.

It is important to mention that PaO_2 (of 55 mm Hg or less) is not the only guide to prescribe oxygen. It is the presence of a chronic hypoxemic pulmonary disease.

Healthy people living at an altitude of 10,000 feet or more do not require oxygen. They are able to acclimatize to even severe degrees of hypoxemia. In fact man has survived without oxygen even at the top of Mount Everest (altitude 29,028 ft). It is a patient with a chronic pulmonary disease who loses the ability to adapt and requires long-term oxygen therapy.

BENEFITS[5,16-20]

Long-term oxygen therapy is definitely shown to benefit patients with COPD (Table 85.1). It has been used in other chronic pulmonary hypoxemic diseases as well, however with limited experience. In COPD, it improves survival, and the quality of life. Exercise tolerance is increased and cognitive mental function improved. Some other conditions, where LTOT has been used, include idiopathic pulmonary fibrosis, severe heart failure, extensive bronchiectasis and severe kyphoscoliosis. In the authors' experience, its use in chronic interstitial pulmonary fibrosis and respiratory insufficiency was associated with signficant reduction in breathlessness and overall comfort. There was an appreciable reduction in pulmonary hypertension and right ventricular failure attributable to supplemental domiciliary oxygen therapy when added to the optimal medical regimen.

Indications

Stable Chronic Obstructive Lung Disease[16-23]

There is evidence in literature to support the role of long-term domiciliary oxygen therapy in stable COPD; however, the role of oxygen therapy in patients who have only nocturnal hypoxemia or hypoxemia during exercise only, is logical but not well supported by evidence from the literature.

TABLE 85.1: Benefits of long-term oxygen therapy

1. Improvement in duration of survival
2. Improved intellectual function
3. Pulmonary hypertension: Decrease in pulmonary vasoconstriction and vascular resistance. This improves the severity of right heart failure.
4. Decrease in red cell mass and hematocrit level. Complications of polycythemia are therefore diminished.

Potential benefits

- i. Increased exercise ability
- ii. Improved quality of life – patients resuming gainful employment and participating in their own care more actively
- iii. Decrease in dyspnea
- iv. Decrease in hospitalization and exacerbations of respiratory failure
- v. Delayed development of cor pulmonale.

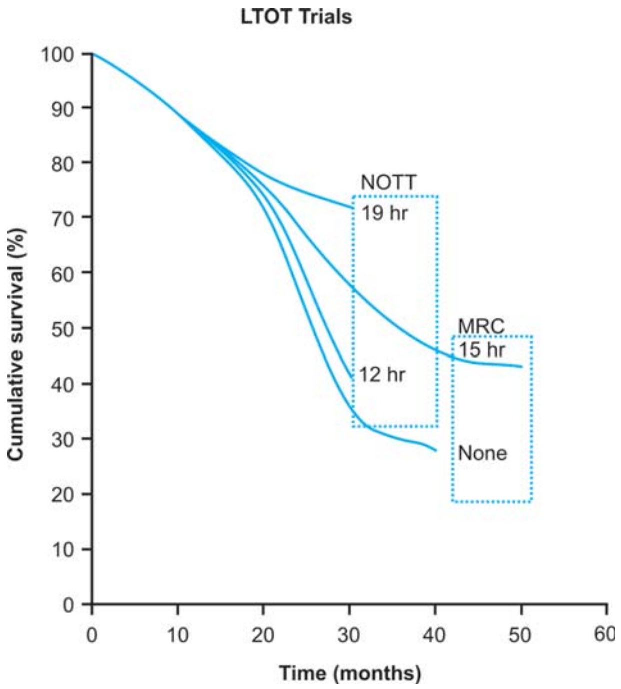

Fig. 85.1: Graph showing increased survival in patients receiving LTOT

1. *Long-term oxygen therapy in patients who have daytime resting hypoxemia:* Two landmark studies, i.e. the Medical Research Council (MRC) trial and the Nocturnal Oxygen Therapy Trial (NOTT) have shown that continuous long-term oxygen therapy can improve survival in patients with COPD and resting daytime hypoxemia (Fig. 85.1). The results of both the randomized controlled trials are summarized below:

Nocturnal Oxygen Therapy Trial (NOTT)[2]

A total of 1,043 patients from six centers in the United States were screened for inclusion in the study. Only 203 patients were finally included; others were excluded because of many reasons, including major concomitant diseases and patients who had previous oxygen therapy or PaO_2 greater than 59 mm Hg. The study was not blinded.

One hundred and two patients with hypoxemic COPD were randomly allocated to nocturnal oxygen therapy and 101 to continuous oxygen therapy. The oxygen source was an oxygen concentrator, liquid oxygen or compressed gas (flow 1-4 LPM). The mean age was 65.7 years in the nocturnal oxygen therapy group and 65.2 years in the continuous oxygen therapy group. Most patients were male, 80.4% in the nocturnal oxygen therapy group (82% used oxygen for 13 hours or less) and 77.2% in the continuous oxygen therapy group (56% used oxygen for 19 hours or more). The mean PaO_2, $PaCO_2$, Forced Expiratory Volume in One Second (FEV_1), were 51 mm Hg, 43 mm Hg and 29% respectively, and were not different between the two groups.

There was a significant difference in survival in favor of the continuous oxygen therapy group, and the overall mortality in the nocturnal oxygen therapy group was 1.94 times that of the continuous oxygen therapy group. The continuous oxygen therapy group also showed improvement in stroke volume index, pulmonary vascular resistance and pulmonary artery pressure but not in other hemodynamic parameters compared to nocturnal oxygen group.

Medical Research Council (MRC) Oxygen Therapy Trial[3]

Eighty-seven patients with a diagnosis of COPD with hypoxemia (PaO_2 40 to 60 mm Hg) and right failure were randomized to receive continuous oxygen therapy (15 hours a day) or no oxygen. The study was not blinded. The treatment group received oxygen therapy for at least 15 hours a day at a flow-rate of a minimum of 2 LPM. The mean age, FEV_1, PaO_2, $PaCO_2$, were around 58 years, 0.7 liters, 50 mm Hg and 54 mm Hg respectively. There was an improvement in survival in the group receiving oxygen therapy (Peto Odds ratio 0.42, 95% CI 0.18 to 0.98) but only beyond 500 days of treatment. Although, the mortality was improved in female patients for the oxygen-treated group from the commencement of treatment, the numbers were too small for any meaningful interpretation. Although the total pulmonary resistance and the pulmonary artery pressure increased in the control group, this was not statistically significant but suggests benefit from oxygen therapy.

Data from these two trials clearly showed that there was a survival benefit with continuous oxygen therapy but none with nocturnal oxygen therapy alone. Recent studies have also shown that LTOT can decrease hospitalization in patients with COPD. Importantly, oxygen should be taken for as long as possible as hypoxemia related pulmonary vascular changes could occur rapidly. In fact there is some data to show that these changes can occur in less than three hours. The current widely accepted indications for LTOT in COPD are summarized below:

Indications for oxygen therapy in patients with chronic obstructive pulmonary disease:

- $PaO_2 \leq 55$ mm Hg
- PaO_2 56-59 mm Hg plus either pulmonary hypertension or hematocrit ≥ 55%.

On the other hand, there is no justification for the prescription of LTOT in patients with mild hypoxemia defined as PaO_2 between 56 to 65 mm Hg. In a recent study by Gorecka et al, 135 patients with COPD who had severe airflow limitation (FEV_1 less than one liter) with PaO_2 of 56 to 65 mm Hg, were randomly allocated to a control (n = 67) or LTOT (n = 68) group. The patients were followed every three months for at least three years or until death. There were no significant differences in survival rates between patients treated with LTOT and controls, nor did longer oxygen use (over 15 hours per day) improve outcome. Younger age, better spirometric values, and higher body mass index predicted better survival. It can be therefore concluded that domiciliary oxygen treatment does not prolong survival in patients with COPD and moderate hypoxemia. It is the airway limitation which seems to determine survival in this group of patients.

Initiation and reassessment of LTOT: Patients with COPD who have FEV_1 less than 40% and/or pulmonary hypertension should be routinely screened for LTOT. Before prescribing LTOT, the indication should be confirmed on at least two occasions two to three weeks apart with a resting arterial blood gas analysis performed on room air. Patient should be stable on maximal and optimal medical therapy including a complete pulmonary rehabilitation program. Smoking cessation should be strictly enforced. The oxygen flow rate should be set to maintain a PaO_2 greater than 60 mm Hg during waking and at rest; usually 1 to 2 LPM through nasal prongs would generally suffice. The oxygen flow rate should be increased by 1 LPM during sleep, exertion and air travel.

The goal of LTOT should be confirmed by performing an arterial blood gas analysis after one to two months of initiating oxygen therapy, and documenting a PaO_2 greater than 60 mm Hg; a repeat blood gas analysis also helps in assessment of the hypercapnic response to oxygen therapy. Patients with significant hypercapnia with oxygen therapy may also require domiciliary noninvasive pressure support ventilation.

2. *Oxygen therapy in patients who have no daytime resting hypoxemia but develop hypoxemia during sleep:* The role of oxygen therapy, in patients who have no daytime hypoxemia but are hypoxemic during sleep only, is controversial. Patients with COPD can experience prolonged episodes of oxygen desaturation during rapid eye movement sleep, and studies have shown that

nocturnal hypoxemia can exacerbate pulmonary hypertension in patients with COPD, but recent studies have challenged this finding. Although it seems logical to administer oxygen in patients with nocturnal hypoxemia, the current literature does not support this fact. Data is insufficient to make general recommendations, and further studies are needed. The current practice is to rule out concomitant obstructive sleep apnea in patients with COPD and those who have got nocturnal symptoms, and to intensify medical management (smoking cessation, inhaled corticosteroids, long-acting β_2 agonists and anticholinergic agents, pulmonary rehabilitation) if the patient is found to have nocturnal hypoxemia without daytime hypoxemia. Oxygen therapy in this subgroup of patients may be indicated, if the patient has evidence of chronic hypoxia-related sequelae like polycythemia or pulmonary hypertension. Another subgroup of patients whose oxygen saturation repeatedly falls below 88% for more than one-third of the night may also benefit from nocturnal oxygen therapy.

3. *Oxygen therapy in patients who have no daytime resting hypoxemia but develop hypoxemia during exercise:* Intermittent oxygen therapy can be used in patients for indications described above, where the benefits of LTOT are well known. The benefits of pulmonary rehabilitation on exercise capacity and quality of life in COPD patients support the use of ambulatory oxygen in all patients on LTOT to allow them to achieve their full potential in the terms of reduced mortality from continuous oxygen therapy. The role of intermittent ambulatory oxygen therapy in patients, who do not fulfill the criteria for LTOT, is controversial.

There is evidence to show an improved exercise tolerance and improved quality of life in patients who use intermittent oxygen therapy prior to exercise. On the other hand, some studies do not show significant benefit. There are some studies, which have shown benefit even with room air itself, and the hypothesis is that the cold effect of the air probably helps in the resolution of dyspnea. Thus, the evidence from the available literature is inadequate on the role of intermittent oxygen therapy, and more studies are required to amicably solve this issue.

In the absence of any definite data, intermittent oxygen therapy may be prescribed in individual patients in whom the benefits (dyspnea, exercise capacity) have been definitely proven by an exercise test (complete incremental exercise testing, six-minute walk test, shuttle test) especially in those patients awaiting lung transplantation or lung volume reduction surgery, to maintain an increased level of fitness prior to surgery.

In conclusion, oxygen therapy in COPD has several definite benefits such as improvement in survival, improvement in intellectual functioning, decrease in pulmonary vascular resistance and pulmonary arterial pressure, decrease in red cell mass and diminution in the complications of polycythemia; other potential benefits include increased exercise capacity, decrease in dyspnea, improved quality of life and decrease in hospitalization. In view of these benefits, oxygen therapy now occupies a key role in the long-term management and rehabilitation of patients with COPD.

Acute Exacerbations of COPD[24-27]

Patients of COPD often have chronic hypoxemia with or without CO_2 retention. An acute exacerbation of airway obstruction, mostly occurring after a respiratory tract infection causes worsening of hypoxia. Oxygen in this situation is required until the exacerbation is settled. While a high FiO_2 of up to 50% can be initially administered in case hypoxemia is severe, it is soon tapered to around 24 to 30% FiO_2. The goal of supplemental O_2 is to maintain a PaO_2 of 55 to 60 mm Hg which corresponds to SpO_2 of about 90%.

Higher concentration of oxygen blunts the hypoxic ventilatory drive, which may precipitate hypoventilation and CO_2 retention. It is not uncommon for CO_2 narcosis to occur following excessive concentrations of FiO_2. A recent study on 65 patients admitted with acute COPD exacerbations showed that a majority of patients who achieved a PaO_2 greater than or equal to 74.5 mm Hg compared with those with a PaO_2 less than 74.5 mm Hg had a longer hospital stay, more frequent admission and the greater use of noninvasive ventilation. It is better to use a regulated flow device such as a ventimask, which guarantee oxygen delivery to a reasonable extent. Once the patient is stabilized, one can shift to nasal prongs—a device which is more comfortable and acceptable to the patient.

Oxygen Prescription

Most of the COPD patients are prescribed low flow concentrations at 1 to 2 l/min. Higher flow rates are required for some of the patients, especially those with other chronic respiratory diseases. The treatment is guided by PaO_2 which should be maintained at 60 mm Hg or so (SaO_2 of 85 to 90%). During the period of exercise, sleep or other activities, the flow rate may be increased by another 1 to 2 l/min. While continuous therapy is required for patients who show hypoxemia at rest, intermittent treatment during specific periods may be used for patients who demonstrate intermittent hypoxemia.

Supply Sources[28-32]

There are three main types of systems commercially available for the supply of oxygen at home: Compressed gas cylinders, liquid oxygen and oxygen concentrators.

Compressed Gas Cylinder

The commonly used gaseous system in the home consists of H or K cylinders containing compressed oxygen. A pressure regulator and a flowmeter are required to adjust the amount delivered to the patient. When continuously used at 2 l/min, each cylinder will last for about two and half days necessitating frequent fillings. They are also heavy giving an unsightly look to the bedroom. Moreover, regulation of pressure and flow require some effort and additional help. For the present, compressed gas cylinders are most commonly used for domiciliary use in India. It is because of its lower costs and relatively easy availability in even small towns compared to the other systems. Gas cylinders also form a good back up facility in case of a failure of other systems. Portable D and E cylinders are available for ambulatory use. Aluminum cylinders are also available. These are lighter in weight than the cast iron cylinders. They are better suited for portability, but are costlier.

Liquid Oxygen System (LOX)

The LOX system for use at home is a smaller version of the bulk liquid system used in the hospitals. The reservoir (stationary) unit contains about 70 to 90 pounds of oxygen in the liquid state at –273ºF. It lasts for 4.5 to 10 days at a continuous flow rate of 2 l/min. The vessel is about 3 to 4 feet tall and about 18 inches in diameter. The internal pressure is about 22 to 50 psi which can generate flow rates of 0.25 to 15 l/min. In addition to the stationary unit, there is a light weight portable unit which can be carried by the patient on the shoulder for ambulatory and outdoor activities. The portable units are designed to be filled from the stationary reservoir unit with safety.

There is a minor loss of gaseous oxygen from the liquid gas units at a rate of about 1 lb/day. Therefore, the units should not be stored in a small and closed space to avoid gaseous accumulation posing a fire hazard.

Liquid gas system is more practical but expensive. It is not easily available in this country as yet.

Oxygen Concentrator

It is an electrical device that provides oxygen from the atmospheric air. It employs a molecular "sieve" that filters out the nitrogen molecules, water vapor and other trace gases. It can deliver 85 to 90% oxygen at flow rates of up to 4 l/min. The polymeric membrane concentrators can deliver 30 to 40% oxygen at flow rates of up to 10 l/min.

A concentrator is ideal for use at home. It obviates the need of regular filling of the tank. Its initial cost is high but the running cost is negligible. Proper maintenance of equipment and replacement of filters is required. A back up source of oxygen supply (e.g. compressed oxygen cylinder) is necessary in case of a power failure.

There is generation of some noise and heat that some patients may find bothersome. This can be avoided by placing the concentrator in an adjacent room and using a longer oxygen tube. This may increase the back pressure necessitating the use of a pressure compensated flowmeter to assure accurate oxygen flow.

Delivery Devices[31,32]

Devices used to deliver oxygen include cannulae, prongs and masks. Those are essentially the same as used in the hospitals. Nasal cannulae and prongs are preferred because of the cosmetic reasons. It is easy to conceal oxygen tubing by applying it to ordinary thick rimmed frames of eye-glasses ("Oxyspecs"). Different kinds of "Oxyspecs" and other devices are now commercially available for this purpose. There is no difference in the type of delivery devices used with different types of oxygen sources.

Humidification is not essential at flow rates of less than 4 l/min unless the patient complains of dryness of the nose or mouth, nasal irritation or crusting. Humidifier is a potential source of infection and needs regular cleaning and disinfection. Disposable humidifiers significantly increase the costs.

Oxygen-conserving Devices[33-35]

Oxygen therapy on long-term basis is a costly proposition. Many patients tend to conserve oxygen by reducing the flow as well as the duration of administration. Moreover, the standard oxygen supply devices allow the flow of oxygen both during inspiration and expiration. In fact it is only 15 to 20% part of respiratory cycle during inspiration which delivers the oxygen to the alveoli effectively. A lot of oxygen delivered to the patient is therefore, wasted in the surroundings.

Several methods have been devised to conserve oxygen in the recent years. It is possible to save up to 50% oxygen with some of these methods. There are three types of devices commercially available for this purpose.

i. *Reservoir oxygen delivery:* With this method, oxygen which is stored during exhalation in a reservoir (approximately 20 ml) becomes available at the beginning of inhalation. There are two types of reservoir cannulae in use:

Pendant reservoir (Oxymizer pendant): The reservoir coupled to the nasal prongs consists of a collapsing chamber that hangs at the chest. It saves oxygen between 2:1 and 4:1 over continuous flow oxygen therapy.

"Moustache configured" oxymizer: The reservoir sits right on the face thus being noticeable and cosmetically unsightly. Its efficiency is similar to that of pendant reservoir.

Both the reservoirs provide equivalent oxygen saving at flow rates of 0.5 l/min. But the Pendant reservoir can be operated at 0.25 l/min to achieve the oxygen saturation similar to those of a flow of 1 l/min with a steady flow delivery system. The reservoirs maintain a saving of 3:1 to 4:1 over steady flow during exercise as well.

Recently, a pendant which allows pursed lip breathing has been described. It combines oxygen saving mechanism of the Pendant with that of pursed lip breathing. It increases the efficiency of oxygenation to about 7:1 compared with standard steady flow systems.

ii. *Electromechanical pulsing devices:* The electromechanical demand devices deliver oxygen only during inhalation. Delivery of oxygen during exhalation is saved. It consists of a box shaped unit attached to the outlet of the oxygen source and a solenoid valve which opens on sensing the decrease in pressure as the patient inhaled. A "pulsed" volume of 15 to 35 ml of oxygen is delivered each time. It reduces the amount of oxygen usage by 35 to 75% producing a saving of about 7:1 compared with continuous flow system.

Electronic demand devices are also available for use with portable cylinders as well as with piped-in-oxygen system in the hospitals. Some of the demand devices available in the Western market include Pulsair, DO2S, Oxymatic, etc. They significantly add to the costs and produce a "clicking" sound at the bed side. Both these factors make it unacceptable to many of the patients.

iii. *Transtracheal catheters:*[35] It is a narrow lumen catheter which resembles an angiocatheter. It is inserted directly into the trachea. Oxygen is delivered through a tubing attached to a small fitting at the neck. There are several reasons to believe that it is more effective:

- Oxygen is delivered ahead of the nasopharynx bypassing some of the anatomical dead space.
- The upper airways serve as a reservoir towards the end of expiration.
- The oxygen delivered is not diluted with atmospheric air prior to entering the respiratory tract.

Transtracheal catheters are useful for patients receiving very high liter flows. They save oxygen by an efficiency factor of 2:1 to 3:1. Its efficiency can be further enhanced by combining it with pulsed oxygen delivery. Intratracheal catheter is more acceptable to the patient since the look is not unsightly. There is nothing on the face and it can be easily hidden beneath the collars. Moreover, there is no nasal or auricular irritation; it does not get dislodged during sleep.

There is a small risk of infection and subcutaneous emphysema when the catheter is introduced. It can get plugged with mucus and thick secretions. It should therefore be cleaned on daily basis. Patients with transtracheal catheters should have conventional cannulae at home for use in an emergency when the transtracheal catheter gets blocked due to kinking or plugging.

Some of the transtracheal catheters available commercially are Heimlich MicroTrach, the SCOOP catheter and the Intratracheal Oxygen Catheter (ITOC). The ITOC is implanted through a subcutaneous tunnel from the chest wall to the trachea. It is of more permanent nature.

Risks of Long-term Oxygen Therapy[36-41]

There are three types of risks associated with long-term use of oxygen: Physical, functional and cytotoxic.

i. *Physical risks:* Since oxygen supports combustion, the tanks are potential risks of fire hazard and tank explosion. In fact these risks are rather small. It is highly desirable that smoking is stopped with its use. The supply source (such as a cylinder) should not be kept in a small closed room to avoid accumulation of the vented gas.

The other minor risks of oxygen therapy include the injury to the nose and face from catheters and masks. Dryness and crusting may occur from dry, non-humidified gas.

ii. *Functional risks:* Oxygen therapy may accentuate hypoventilation in patients with COPD. This may induce hypercapnia and carbon dioxide narcosis. In practice, with low-flow oxygen therapy, the risk is rather small.

Therefore, chronic carbon dioxide retention is not considered a contraindication for long-term oxygen therapy. It has been suggested that arterial pH is a better guide to monitor therapy than $PaCO_2$. Patients with carbon dioxide retention also tolerate and benefit from long-term oxygen as long as pH does not show acidemia.

iii. *Cytotoxic damage:* Long-term oxygen can cause structural damage to the lungs. Both proliferative and fibrotic changes of oxygen toxicity have been shown at autopsy on COPD patients treated with long-term oxygen. But there is no significant effect of these changes on clinical course or survival of these patients. Most of the structural damage attributable to hyperoxia results from high FiO_2 administration in acute conditions.

Oxygen Therapy for COPD during Air Travel[42]

Modern aircraft are pressurized to cabin altitudes up to 2,438 m (8,000 ft) although this limit may be breached in emergencies. At 2,438 m (8,000 ft), the PaO_2 will be equivalent to that of breathing 15% oxygen at sea level. In a healthy individual, the PaO_2 at 2,438 m (8,000 ft) will generally fall to 53 to 64 mm Hg. This may exacerbate hypoxemia in patients with COPD, especially those who are hypoxemic at sea level. There are three common methods of assessing the requirement for oxygen therapy during air travel, the so-called preflight hypoxia testing.

i. *Six-minute walk test:* Although not specifically evaluated for the purpose of preflight hypoxia testing, failure to complete the task in terms of distance or time, or moderate-to-severe respiratory distress recorded on a visual analog scale, will alert the physician and the patient to the possible need for in-flight oxygen.

ii. *Prediction equations:* Another method is the use of prediction equations that have been derived from patients with COPD who have had measurements of PaO_2 in a hypobaric chamber, while breathing FiO_2 at 15%. The accuracy can be improved by the inclusion of FEV_1 in the equation. These equations are reliable to establish upper and lower thresholds for "no in-flight oxygen required" (SpO_2 >95%) or "in-flight oxygen needed" (SpO_2 <92%). One commonly used prediction equation is given below: $PaO_2\,(\text{Alt}) = 0.519 \times PaO_2\ \text{ground (mm Hg)} + 11.855 \times FEV_1\ (\text{L}) - 1.760$

iii. *Hypoxia challenge test:* The ideal test is to expose a subject to hypoxia in a hypobaric chamber. The facility for this testing is not widely available. A surrogate is to administer FiO_2 at 15% and measure the PaO_2. Although not validated, a PaO_2 less than 50 mm Hg predicts requirement of in-flight oxygen therapy.

In practice, oxygen is generally prescribed on the basis of the prediction equations as the six-minute walk test is cumbersome and hypoxia testing is not routinely available in developing countries.

PERSPECTIVES OF DOMICILIARY OXYGEN USE IN INDIA

An organized domiciliary oxygen and rehabilitation program is yet to establish at most places in India. In spite of the several limitations, we have used home oxygen therapy in COPD and other chronic lung diseases since 1970s. On an average, 10 to 12 new patients are recruited every year. Chronic obstructive pulmonary disease remains the chief indication for LTOT. Idiopathic pulmonary fibrosis, chronic bronchiectasis, kyphoscoliosis and post pneumonectomy pulmonary hypertension and respiratory insufficiency have been a few other common conditions. Most patients had relied on commercial oxygen supply. In fact some patients from smaller towns had used oxygen tanks procured from vendors using oxygen for welding and other industrial purposes.

In this country, it is important to assess the educational and psychological status of the patient (and the family), social background, place of residence, income and employment position before prescribing the therapy. Availability of an organized supply of O_2 is lacking and the costs are high. Feasibility of supply is poor, much more so in the rural areas and small towns. Occasionally, patients even from smaller towns have succeeded in overcoming difficulties.

Some of the important problems stated by most of the patients related to the difficulties of procurement and costs. There are limited sources of supply. Moreover, the medical expertise and advice to supervise domiciliary treatment is lacking. Patients' resources to afford the treatment are also scanty. There are no clear guidelines available regarding reimbursement of costs on oxygen and the apparatus: A facility available to government and several other private/public sector employees for other treatments. One does expect that most of the difficulties shall resolve in due course of time.

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Patient Education in Chronic Obstructive Pulmonary Disease

Tushar Sahasrabudhe

INTRODUCTION

The best possible quality of life to the patient of Chronic Obstructive Pulmonary Disease (COPD) is possible only through better understanding of the patient in the perspective of his/her overall life situation. Active participation of the patient in his/her own care is the key. A free communication between the treating physician and the patient is essential and forms the basis of patient education.

The advantages of the patient education in COPD are many:

- Understanding the disease takes away the fear that arises out of uncertainty.
- The sequence of expected events and the understanding of the impact of treatment on them strongly motivate the patient to adhere to the treatment.
- Understanding of pathophysiology helps the patient to understand the symptoms and the role of interventions.
- Understanding the etiology and exacerbation triggers help in reinforcing the smoking cessation and environmental control strategies.
- Well understood action plan takes away the fear of managing exacerbations and the feeling of helplessness.

The physician should involve the family members in education and motivate the family members in the patient management. This has remarkable impact on overall quality of patient's life and his/her medical care. Once well informed, the COPD patient can become an active partner of the physician. Their contribution in following respects can be extremely valuable.

Patient education is often a neglected area in the overall COPD management, more emphasis is laid on symptom control and prescribing medicines. The education can be gradually imparted, can be easily incorporated in the follow-up schedule of the patients. There is no great need for any extraordinary infrastructure or facilities. The requirements for a good patient education program include:

- An enthusiastic and motivated physician with good communication skills.
- Well motivated patient.
- Charts, posters on lung anatomy, physiology, spirometry, etc.
- Lung models.
- Animated videos that can better explain the disease
- Slide shows on COPD.
- Interviews with other COPD patients.
- Group discussions.

EDUCATION ABOUT THE DISEASE

Disclose and Describe the Disease

It is not unusual for the patient to construe that he suffers from bronchial asthma. As a result, he "considers himself" to be allergic to many food items and inhaled substances, follows many restrictions which are unnecessary. It is essential to explain that despite the similarities, COPD is different than asthma. The disease is the topmost cause of death in Maharashtra, India; but a major section of the society has never heard this term.[1] The physician should avoid using the term "Bronchitis", which is very broad and does not convey the seriousness of the illness.

Discuss the Etiology

Most patients are interested in knowing the cause of their suffering and will actively enquire about it. The first consultation with patient is therefore the right time to begin with smoking cessation, if tobacco smoking is the cause of COPD in that patient. The patient should be made aware that it is a self-inflicted disease and that the tobacco smoking habit is responsible for it.

The best way is to make the patient understand the chronological relation between the smoking and the drop in the lung function.[2]

The lung function usually drops at a steady pace as the age advances. The drop is approximately 25-30 ml per year in a normal healthy person.[3]

There is accumulating evidence to suggest that biomass fuel is largely responsible for the cases of COPD occurring in nonsmokers especially amongst the rural women.[4] It is also important to impart and implement various educational measures to minimize their use and exposure.

Explain the Pathophysiology

Explaining the pathophysiology provides good insight to the patient on his disease. Cough and sputum are very disturbing symptoms for patients with predominant chronic bronchitis. They often wonder where this excess phlegm is generated and urge the doctor to stop it, somehow. They actually change doctors and try many cough suppressants in an attempt to stop the phlegm.

Explanation on the bronchial gland irritation and hypertrophy and assurance that the phlegm can be managed with good clearance techniques eases their discomfort and improves the acceptance of the symptom.

Presence of dyspnea is another disturbing symptom that needs explanation. Attempts at relief with bronchodilators are usually only partial and do not take care of the baseline dyspnea. Exercise is increasingly difficult due to the compromised inspiratory capacity. A thorough explanation of air trapping and bullae formation can improve their understanding. Simple techniques such as "pursed lip breathing" may provide relief from the "balloon" feeling; the significant improvement in dyspnea boosts the confidence of the patient.

The dysfunction of diaphragm due to air trapping can be explained, with the help of figure depicting how a contracted muscle may not be able to perform better mechanical function.

A stretched arm can lift 10 lb of weight easily with the powerful biceps muscle. However, if the elbow is fully flexed, the shortened biceps cannot contract further. The power is therefore greatly reduced and it cannot even hold a tennis ball properly. The diaphragm undergoes the same disadvantage in COPD. The flattened diaphragmatic muscle due to hyperinflation of the lung parenchyma cannot contract further and therefore loses its power, dramatically. It tends to fatigue earlier because of the mechanical disadvantage. Moreover, the work of breathing is exaggerated in COPD, which further tires the diaphragmatic muscle.

The understanding of effect of COPD on pulmonary circulation and consequent right heart failure often alleviates the fear of heart disease and adherence to salt restriction, diuretics and oxygen therapy improves.

Sarcopenia, weight loss and muscle weakness are considered as grievous signs by the patient and he starts losing hope. Explanation of the systemic consequences of COPD including skeletal muscle dysfunction and ischemic heart disease and assurance of the improvement by rehabilitation techniques reduces anxiety and depression to a large extent. It also improves the compliance with the exercise schedule. The knowledge that COPD is a major risk factor for heart diseases may act as a strong motivator for smoking cessation and adherence to the treatment, the heart is usually a more cause of concern then the lungs for a lay man.[5]

Explain the Medical Tests

Tests such as X-ray, spirometry and the six-minute walk test are often advised frequently to the COPD patients. Most patients do not understand the results and are dependent on their doctors for the interpretation. Spirometry values show marginal change or even no improvement over the time. This may be misinterpreted as treatment failure by the patient and this may even lead to treatment default.

The six-minute walk test is valuable as it gives a fair idea of the exercise tolerance of the COPD patient. Recently, it is also been shown to be predictive of disease progression and mortality.[6] Insight into the six-minute walk distance and oxygen desaturation usually helps in the motivation of the patient for the rehabilitation schedule.

EDUCATION TO HELP REDUCE COPD EXACERBATIONS

A patient who has experienced a severe COPD exacerbation recently is at a high risk of another severe exacerbation and death. Even a single exacerbation has a large impact on the patient's life with recovery period stretching over months.[7] The frequency of exacerbations also determines the overall quality of life of COPD patients.[8] Every exacerbation avoided thus has a positive impact, this can be attempted by the means discussed below.

Environmental Control

Most exacerbations in COPD are related to infections and most respiratory infections are transmitted from person-to-person by coughing or spitting. In one study, the responsible pathogen could be identified in 50% of patients hospitalized with non-pneumonic acute COPD exacerbation and 12% were due to viruses.[9] Another study could identify the pathogens in almost 64% of cases.[10] These infections can be avoided by good environmental control although infections related to airway colonization may still occur.

COPD patients should preferably avoid close contact with people suffering from common cold and other respiratory infections. They should use facemasks if necessary. Avoiding crowded places is rewarding. Cleanliness in the surroundings reduces the chances of infection.

Exposure to smoke is also a known trigger for exacerbations. The COPD patients should be instructed to avoid direct smoke exposure such as to domestic smoke, kitchen smoke, mosquito repellants, etc. They should always be motivated to avoid cigarette smoke as well. Long distance road travel in polluted cities can also trigger the COPD exacerbation. Simple measures like shutting the windows, or covering the nose and face are helpful. Environmental pollution due to firecrackers can be harmful for COPD patients, they should remain indoors during such periods.[11]

Vaccination

Since most of the COPD exacerbations are due to infections causes, vaccination plays an important role in reducing the exacerbation rate. It is recommended to give the influenza vaccine annually and the pneumococcal vaccine, once to all COPD patients.[12]

COPD exacerbations are usually due to gram-positive and atypical pathogens, which tend to get colonized in the airways. Attempts to reduce colonization by improving immunity using sublingual or oral freeze dried bacterial lysate of common airway pathogens has been tried. They are able to induce specific antibody response as well as local IgA response. Such preparations are available in market and they have been shown to reduce the exacerbation rate as well as the duration of antibiotic therapy.[13,14]

Regular Medication

Studies have showed that in the cases of severe COPD ($FEV_1 < 50\%$ predicted), use of long-term inhaled corticosteroids reduced the exacerbation rate significantly.[15] It has also been documented in the COPE study that the discontinuation of fluticasone propionate in COPD patients was associated with a rapid onset and higher recurrence risk of exacerbation and significant deterioration in components of health-related quality of life.[16]

This highlights the importance of regular pharmacotherapy. The information on this literature, if shared with the patient, can improve his compliance and reduce the exacerbation rate.

EDUCATION FOR IMPROVING BASELINE LUNG FUNCTION

Bronchodilator Treatment

Unlike asthma, inhalation treatment in COPD does not give dramatic relief from the symptoms. They also do not give apparent "Cure" of the disease. This usually disheartens the patient who is looking for a cure and relief of his symptoms. He then starts questioning the role of inhalers in his treatment and tends to default. The bronchodilator treatment in COPD is usually lifelong and the patient often gets the feeling of getting dependent on it. "Withdrawal" symptoms of discontinuing inhalers strongly demotivates the patient who starts demanding for short courses of treatment with some recovery days in between the courses.

Despite the poor bronchodilator reversibility of FEV_1 in COPD, bronchodilators have appreciable impacts on breathing. Even a marginal improvement in the radius of the airway leads to a much larger reduction in the airway resistance. The explanation of these facts encourages the patient to take his treatment regularly.

Large one-year trials have found the combination of LAMA and LABA to significantly improve health status as assessed by Saint George's Respiratory Questionnaire (SGRQ).[17]

The patient needs to be fully aware of the dosages, effects and side effects of all his long-term medication. Possible effects on glaucoma, urine retention need to be informed as the old man often has prostate enlargement. Regular use of tiotropium has been shown to improve inspiratory capacity and reduce dyspnea leading to 41% increase in cycle endurance in a study.[18] Presences of ischemic heart disease, hypertension or use of beta-blockers, all need consideration in formulating the treatment strategy.

Alternate Therapy

Many patients of COPD, fed up of long-term medicines, are still looking for cure. They are likely to try alternate therapies, such as ayurveda, homeopathy, yoga or naturotherapy.

Alternate medicines should be tried with caution without defaulting the current pharmacotherapy. Yoga needs a special mention. With recent popularity of yoga, many COPD patients may attempt doing "Pranayama" for improving their lung capacity. Deep-breathing exercises may actually be helpful for these patients. However, they should avoid forced expiratory exercises. This may increase the risk of pneumothorax in patients with emphysema and bullae.

Sputum and Cough Management

The sputum in COPD patients is often sticky and difficult to expectorate. Vigorous bouts of coughing may exhaust them quickly. A simple advice on steam inhalation eases their expectoration. Oral mucolytic can be prescribed intermittently. COPD patients should always be discouraged to use cough suppressants. Stagnated mucus may actually increase the chance of an infective exacerbation. Sufficient intake of water is very important.

Oxygen Therapy

Most patients with very severe COPD do develop significant hypoxia. Domiciliary oxygen therapy has been shown to improve survival, also reduces the morbidity and delays diaphragm fatigue.[19] It is important to explain that oxygen therapy is meant only to supplement the body's need for oxygen which the lungs and ventilatory system are not able to fully satisfy. The therapy has no impact on the disease as such. However, the body organs starved of oxygen, function better and for longer period with oxygen supplementation. This improves both the quantity and quality of life.

Correct Use of Inhalational Devices

The success of inhaled therapy largely depends on the correct technique of using the device. Today, a large range of inhalational devices are available. Selection of the device that suits the patient the most and demonstration of correct inhalation technique are of primary importance. In addition to the erroneous technique of inhalation, the elderly COPD patients have additional problems. Diminished eye sight, poor hand-mouth coordination, and senile tremors, all can reduce the efficacy of inhaled treatment. These issues need to be addressed carefully by the treating physician.

Treatment of Pulmonary Hypertension (PH) and Cor Pulmonale

Severe COPD patients eventually develop significant pulmonary hypertension, followed later by congestive heart failure. Reduction in pulmonary arterial pressures have shown to improve the exercise capacity of patients. Oxygen therapy is an important supplement for successful reduction of PH.

PULMONARY REHABILITATION (SEE CHAPTER 89)

It is an art of medical practice wherein an individually tailored, multidisciplinary program is formulated, which through accurate diagnosis, therapy, emotional support and education; stabilizes or reverses both the physiology and psychopathology of pulmonary diseases and attempts to return the patient to the highest possible functional capacity allowed by his pulmonary handicap and overall life situation.[20]

Simple exercises form the basis of rehabilitation programs, and patients need good training on them preferably by a trained physiotherapist. Pulmonary rehabilitation can reasonably improve the physiological and psychological status of the COPD patients.[21]

Lower Limb Muscle Training

Simple walking, climbing or more sophisticated exercise, such as the treadmill significantly, improves the muscle power, reverses the deconditioning, increases aerobic enzymes in skeletal muscles and reduces lactate levels. Exercise also has a strong antidepressant effect. It motivates the patient and reduces the fear of dyspnea.

Upper Limb Training

Arm elevation, arm cranking and weight lifting can improve vital capacity, oxygen uptake and arm function.

Ventilatory Muscle Training

Diaphragm, the main muscle of inspiration is fatigued in sever COPD patients. Techniques such as abdominal breathing, incentive spirometry and breathing through devices with resistance valves improve diaphragm strength and delay fatigue.[22]

Pursed Lip Breathing

The main mechanism behind air trapping is the closure of bronchi at the equal pressure point where the intraluminal and intrathoracic pressure matches. Voluntary increase in intraluminal pressure can keep the airway patent and help in the release of trapped air. This can be achieved by ballooning the cheeks and slowly exhaling the air. This maneuver called as “Pursed Lip Breathing” is effective, many patients learn it on their own.

EDUCATION AND DISCUSSION ON DAILY LIFE ISSUES

A patient with very severe COPD feels significantly handicapped while performing day-to-day chores. Inability to perform simple activities such as changing the clothes or taking bath can be really demoralizing for the patient. Patients with moderate-to-severe COPD however suffer from more subtle frustrations. These need to be carefully probed and resolved.

Recreation

A man who has spent years of active life gets gradually bed ridden as his COPD progresses, he starts needing help for even simple daily routine. “Take plenty of rest” is an advice easier given than followed. Lying on the bed for most of the time can be really frustrating. Careful assessment of the functional capacity of the individual followed by planning of recreational activities within his reach acts as a good motive for active living.

Sexual Dysfunction

Patients of COPD commonly have sexual dysfunction. Erectile dysfunction is observed in 75.5% of patients of COPD as per the International Index of Erectiole Dysfunction (IIEF), it was proportionately more common in advanced COPD.[23] Failure to perform a sexual act can be a hidden cause of frustration and depression, which the patient may never discuss with his doctor.

Diet

It is common for the COPD patients to follow plenty of dietary restrictions, such as the avoidance of lemon, ice creams, curds, pickles, juices, bananas, etc. Except for the patients with predictable triggering of exacerbation with a particular food item, no specific dietary restrictions are necessary. Patients with hypoventilation should however be more careful about their diet. A high calorie and low carbohydrate diet is recommended. Carbohydrates are more completely metabolized and the end product is carbon dioxide. Patients with existing hypoxia and hypercapnia may then end up consuming more oxygen and producing more carbon dioxide which their lungs and ventilatory system cannot handle.

Sleep Apnea

Daytime sleepiness, morning headaches and hypertension should alert the physician to the possibility of sleep apnea. Unfortunately, daytime sleepiness is frequently attributed to old age, boredom and general weakness, and patient may not even complain about it to the doctor. Hypertension, common in an aged smoker, is also similarly not attributed to the possibility of sleep apnea. COPD patients may desaturate significantly in sleep. Vascular changes can occur very fast leading to rapid rise in pulmonary arterial pressures. The possibility of sleep apnea therefore, needs to be looked into.

DISCUSSION ON SPECIAL ISSUES

Travel

In the modern times, air travel has become common, and it is estimated that about 5% of the patient’s traveling by air may be suffering from chronic respiratory diseases such as COPD. Most commercial aircrafts are pressurized to 8000 ft altitude where the air/oxygen pressure drops to 15%. This may be detrimental for a patient whose baseline oxygen saturation is below 92%. These patients need to make arrangements with the airlines for in-flight oxygen. The cabin air is usually dry. Prolonged air travels with dry oxygen, sitting position and high altitude, all can precipitate respiratory and/or congestive cardiac failure in a COPD patient. Careful pre-flight assessment with oxygen saturation monitoring and hypoxia test is therefore recommended[24] (See Chapter 104).

Patients on domiciliary oxygen planning to travel by train need to arrange for portable oxygen cylinders. Prior permission from railway authorities is necessary.

Fear of Exacerbation

Patients who have experienced a severe exacerbation, especially the one requiring hospitalization or mechanical ventilation, are under constant fear of another exacerbation. The physical and financial dependence on other family members aggravates the fear. Although it is important to detect and treat an exacerbation early, it may be impossible for the COPD patient to see the doctor in time.

Having a handy self action plan is very useful and the treating physician should provide this information. Forming the support groups of COPD patients staying in nearby areas and conducting their quarterly meetings are useful. A list of available medical resources and the community services with the phone numbers is handy. Sharing of experiences, knowledge, treatment options as well as emotional support, all help in alleviating the fear of an exacerbation.

Depression

It is estimated that 20 to 60% of the COPD patients are depressed. The reasons are many fold. Poor effort tolerance makes travel difficult. Disturbing cough and dyspnea lead to social withdrawal. Anxiety about illness, fear of exacerbation adds to the stress levels of the patient. Guilt, either self-imposed or by constant criticism by the family members makes the situation worse. Actually, a patient with severe COPD needs help rather than criticism for his past habit of smoking; in this case the counseling of family members is helpful. Sleep disturbances, sexual dysfunction and disability make life less enjoyable. A strong feeling of dependency on the family members hurts the ego badly, especially for a person who was the family head in a dictating position for years. Indoor treatment of exacerbation especially if needing mechanical ventilation is very costly. Daily pharmacotherapy and oxygen therapy are also not cheap. These financial issues add to the depression.

Psychological interventions, cognitive behavioral interventions and counseling helps alot.[25] Rapport with treating doctor and his moral support are vital. Family members can help in daily activities, supervision of medical treatment, and purposeful involvement in family/social gatherings.

Surgery

An old patient of COPD requiring surgical intervention for some unrelated problem such as acute abdomen or for fixation of a fracture is a challenge. Optimization of medical treatment, good bronchial hygiene techniques and good preoperative preparation are necessary and helpful to reduce the complications.[26] These patients are at particular risk of some postoperative complications, such as mucus plugging, pneumonia, COPD exacerbation and pulmonary embolism.

Frequent discussions with family members on need for surgery are essential. Generally, early ambulation helps. A COPD patient getting bed ridden for a longer time is likely to develop complications.

PREVENTION OF COPD

COPD has been redefined as "a treatable and preventable disease". Early detection and early intervention have been shown to increase the lifespan as also the quality of life. The prevention or halting progression of COPD would then revolve around: Smoking cessation, reducing biomass fuel exposure and early detection of COPD. Smoking cessation and prevention is the most important issue. Information on the subject is widely available on the Internet as well as in published literature, including from India.[27] Other measures of protection from air pollution are also important.

Alternate means of cooking, such as using natural gas, biogas or improvised stoves for cooking, can reduce this risk to a large extent.

Vehicular air pollution is also shown to increase the risk of developing COPD and efforts to tackle the same are necessary. People with occupations such as auto-rickshaw drivers or traffic policemen should use necessary personal protective equipments such as face-mask.

EARLY DETECTION OF COPD

The National Lung Health Education Program (NLHEP) recommended spirometry testing for all smokers above the age of 45 years and for anyone with chronic cough, mucus hypersecretion or wheeze.[28]

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End-of-life Communication and Palliative Care in Advanced COPD

Sujeet Rajan

INTRODUCTION

This is by far the most challenging part of managing advanced Chronic Obstructive Pulmonary Disease (COPD) for respiratory physicians. Physicians managing COPD must be both confident and competent in caring for their patients in the final phase of their illness. Both the patient and his family must be assisted to face inevitable death. It is not surprising that in a study of 100 patients with COPD, 58% preferred a plan of comfort care over a plan to extend life and 78% did not want ventilation in intensive care.[1] Decisions to limit support in terminal illness have become routine in Europe and the United States. In India, however, these decisions are far more difficult due to the lack of palliative care orientation, unawareness of ethical issues, culture of "fighting till the end" and legal and administrative prejudices.[2] (See also Chapter 168 on End-of-life Care)

ADVANCED TERMINAL COPD

Advanced terminal COPD comes under the spectrum of "end-stage lung disease" which basically implies that the patient now has very severe airflow obstruction, often with a Forced Expiratory Volume in One Second (FEV_1) of 0.5 liter. There is chronic hypoxemia with or without hypercapnia. The terminal phase of COPD is difficult to define, it can vary from one patient to another based on the actual lung function, presence of pulmonary hypertension, personality and attitude towards illness, and of course, the social status of the patient. At one spectrum, one could get a patient with an FEV_1 of 45% of predicted, from a lower socioeconomic strata who has almost permanently confined himself to his home, to another from a higher socioeconomic strata with an FEV_1 of 34% who is raring to play golf.

A good way to define terminal disease is when survival is expected to be less than two years. This allows the primary care physician with help from the specialist to guide the patient and the family on how the future is likely to evolve. Though two years sound a realistic end-point before which to start communicating, it isn't so easy in COPD, which reflects certain death at an uncertain time. Many, in fact most patients with COPD, do not die of progressive respiratory failure, but of cardiac disease or cancers. This was clearly evident from the review of the mortality data from the Towards a Revolution in COPD Health (TORCH) Study.[3] Therefore, a reasonably healthy COPD patient may actually and very often die suddenly of myocardial infarction. This may not be easily predictable. However, that needs to be a factored point when discussing end-of-life issues with the patient.

PROGNOSIS OF ADVANCED COPD

Equally important is to realize the prognosis of patients with COPD. Table 87.1 lists a good guide in deciding when to bring up the topic for discussion with patients discharged after an Acute Exacerbation of Chronic Bronchitis (AECB).

TABLE 87.1: Post-discharge mortality in two studies

Ai Ping et al[4]	*Breen et al*[5]
• 6 Months: 39%	6 Months: 41%
• 1 Year: 43%	1 Year: 49%
• 3 Years: 61%	2 Years: 58%
• 5 Years: 76%	3 Years: 64%

A Canadian study suggested that after six months of discharge from a hospital following AECB, only 25% of patients were well and with a good quality of life; 44% of them had been re-admitted by then.[6] This illustrates how important it is to bring up this issue at the stage of hospital discharge from an AECB. The author will discuss other situations to define advanced terminal COPD, but equally important is the presence of pulmonary hypertension and right ventricle (RV) dysfunction, the presence of which itself, is indicative of a four-year mortality of 73%.[7] The timing of death, however, remains almost impossible to predict. As mentioned in the example earlier of myocardial infarction as a cause of death, the timing of death is poorly estimated even within a week of death.[6]

Issues Involved in Treating Advanced Terminal COPD

When the disease gets worse, and as the pharmacological options become limited, the care gets harder and more challenging. Some of the questions to handle at this stage are as follows:

- Handling the fear of a dying patient. The fear of suffocation or choking to death is real; watching someone going through this stage can be equally devastating for the family.
- When the next exacerbation occurs, should the patient be *actively* treated to prolong life, or treated so as to allow smooth transition from life to death?
- How *much* active treatment is appropriate? Should the next exacerbation be treated at home (esp. in a financially drained patient) or at a Hospital?
- If treated at home, should noninvasive ventilation be used (machines can now be rented or bought by patients)?
- If treated in the hospital, should the patient be treated in the room/ward or intensive care unit (distanced from relatives and loved ones)?
- If a decision has been taken that patient is not to be transferred to intensive care unit (ICU), what is the maximum time for the patient to remain in the ward/room setting?
- If a decision to transfer to ICU is taken, is the patient agreeable to be *invasively* ventilated?
- If *no* to the above question, what will be the maximum care offered to the patient in the ICU, which cannot be given in a room/ward?
- If the patient has said no to any of the above "active treatment" options, has an "advance directive" been obtained from the patient?
- Are the relatives taking most of the decisions for the patient (common in Indian scenario, where shielding the patient from an adverse diagnosis or prognosis is common)? Is the patient educated enough to take a better decision himself? If so, is the "relatives" opinion/decision final?
- If the patient is unconscious (with no advance directives), how does the discussion with family ensue?

GOOD DEATH IN COPD: IMPLICATIONS

An excellent study identified five issues that a patient may wish to see addressed before he dies.[8] As a physician it is important to be very sensitive to these issues:

- Adequate relief of symptoms, especially pain and dyspnea
- No inappropriate prolongation of life
- Sense of control of their own person
- Relief of the burden to their family
- Strengthening of family relationships

Patients with COPD are not always able to die quietly, peacefully, or in their own homes. The patient and the families' descriptions of breathlessness challenge the definitions of a 'good death'. Patients often die in the ICU or hospital, and it could be argued that dying in an environment away from the home setting has meant that we have lost our ability to communicate with the dying patient.[9]

For the COPD patient this is a constant dilemma. By suffering at home all the time, he has already experienced a "social" death for years. He is often "dying and living" at the same time. At the end, when brought to a hospital, he is additionally subjected to the regular procedures of a "hospital management," which could range from simple intravenous lines to endotracheal intubation and invasive ventilation. Having undergone a prolonged period of reduced physical and social functioning, they are actually hardly "living" in the true sense much before they die. The COPD patient, therefore, challenges the concept of a "good death." This remains one of the most difficult situations in dealing with patients with any kind of advanced lung disease.[10]

Appropriate Time to Begin Discussions on End-of-life Issues with COPD Patients

As mentioned earlier, when survival is expected to be below two years, the time has come to start a discussion with the patient. Studies have shown that patients appreciate physicians who discuss these issues with them, in contrast to many physicians believing that patients may not be ready for the same.[11] Patients appreciated physicians who are honest and straightforward, are willing to talk about dying, are good at listening, give bad news in a sensitive way and most importantly, are sensitive to the timing of such discussions. By avoiding the topic, patients are less satisfied. Introduction of the topic actually allows patients to engage in a good discussion and maintain a sense of hope with less depression, even when the prognosis is poor.

Patients perceive their physicians based on ***what*** (the content) they communicate and ***how*** (the process) they do it largely. Unfortunately, most of these discussions take place outside the ICU, and often when the patient himself is unable to take a decision on his own. This delay in communication must be avoided and every attempt should be made at the out-patient level to start such discussions where appropriate, and of course after a full review of diagnostic tests and ongoing treatments. Sometimes, even a second opinion helps before deciding that the patient and the family needs such a discussion. End-of-life discussions in COPD can be started in the presence of different disease criteria (Table 87.2).

TABLE 87.2: Different criteria in COPD when end-of-life discussion can happen

- $FEV_1 < 30$ % (during the stable period)
- Oxygen dependence
- One or more hospitalizations in the past one year with AECB
- Left heart failure
- Weight loss/cachexia and increasing dependence on others
- Age more than 70 years

PRINCIPLES OF END-OF-LIFE COMMUNICATION IN COPD

1. **Ethical Principles:** The basic ethical principles consist of Beneficence; Nonmaleficence; Autonomy and Justice, i.e. fairness in the physician's approach. Physician should not provide investigation or treatment that will harm or serve no purpose. Avoid imposing futile treatments on the patient. Treatment aimed at a specific symptom may have adverse effects that may shorten life, e.g. morphine. When the benefits of alleviating the patient's suffering outweigh the risks, then such therapy is acceptable, and is not considered euthanasia.
2. **Cultural Principles:** Surprisingly, there is very little information on how the influence of culture affects the patient and family. Culture encompasses the patient's beliefs, life's experiences, values, attitudes and assumptions. This is not necessarily related to the ethnicity of the patient. Culture can affect the entire way in which a patient approaches his life, disease and death. This culture needs to be respected by the physician. Eye contact with the patient, physical touch and privacy often varies between cultures. The entire communication process of "breaking bad news" can vary between cultures, and understandably, this can have profound effects on management planning. Respect given to the patient's cultural preferences has a tremendous positive impact on the patient and the family. Trust is immensely improved and strengthened when this aspect of the patient's whole is also respected.
3. **Incompetent Patient:** Depression can often affect the decision-making process of COPD patients. This must be carefully looked for before labeling the patient as poorly responsive to suggestions *or* incompetent in making a decision. For the actual incompetent patient, one has to often ask the family for end-of-life directives. Ideally, this should be the spouse or children. It is important here to understand if the patient had ever expressed any desires about the way he should be managed towards the end of his life. Often, the patient has expressed such views to the family, such as not being ventilated or brought to ICU at all. Our culture often shields the patient from bad news, despite the patient realizing, long before the family, that he is headed in a downward trajectory.

Sadly, even in competent patients, the family often incorrectly states a patient's wishes.[12] When life and death decisions are at play, the family must be told that the decision is not their responsibility, but that they are simply guiding the physicians in their decisions.

Place Where End-of-life Communication Should be Done

Communication is most often done outside an ICU cubicle! This should be avoided as far as possible. A large quiet room with privacy and confidentiality is the best. Emotional outbursts are not uncommon by family members. In some cultures, the patient is asked as to whom he would like to have present in the room. In others, the patient is often left out of the discussion, leaving this to responsible family members whom he entrusts with all decisions pertaining to his life and death. It is important to counsel these members extensively.

When such discussions occur, ensure that everyone's opinion in the room is heard out and try to end it on a final collective decision that everyone is agreeable to.

How and What Needs to be Done[13]

- After listening well to the patient and the family, you will be able to understand their expectations and come to a consensus on what needs to be done. The levels at which things for advanced COPD can be planned are outlined below:
  - Level 4: All conditions investigated and treated, including Cardiopulmonary Resuscitation (CPR)
  - Level 3: Above, except CPR (the patient can still be intubated and ventilated)
  - Level 2: Potentially reversible conditions are investigated and treated (can be done at home or hospital)
  - Level 1: Main focus is on palliative care—symptom relief is the focus of all treatment. (intravenous feeds and RT feeds are avoided)
- As mentioned earlier, when planning the foreseeable level of care, always use words like "if" rather than "when." "When" seems to be a prediction of doom, but "if" is more often seen as uncertainty and allows patients to balance hope and acceptance.
- Discuss the implications and consequences of treatments, in the light of the disease prognosis. It is imperative that patients' and their families' understand the "misery of doing everything." Often patients with unlimited financial resources believe that "everything" must be done for a dying patient. "Everything" includes more drugs with adverse effects; mechanical ventilation; more procedures on an ill patient; and not to forget the ongoing mental stress to the patient and the family members, many of whom have not been actively involved in this decision to do "everything."
- Don't Forget About Depression and COPD: Depression often affects decision-making by the COPD patient and this should not preclude the introduction of an intervention when it can actually help to improve the patient's quality of life.
- Manage symptoms as possible in the following ways:
  - *Dyspnea:* Over 50 % patients suffer from dyspnea, 90% by the end of their life. Dyspnea is often aggravated by anxiety, low-dose anxiolytics like alprazolam can often help, especially if back-up noninvasive ventilation is available. Pharmacologic therapy is often limited after nebulized bronchodilators and systemic steroid have been used. Though oxygen and noninvasive ventilation help, morphine may need to be used when dyspnea worsens. The benefits are largely related to reduced ventilation and the sensation of dyspnea. Unlike pain management, the long-term effects are not so beneficial and side effects are common. Relaxation breathing, upright posture and sometimes music therapy can also help in palliative care. Slow-paced music is usually preferred over fast pace. Music therapy is shown to be superior to progressive muscle relaxation in acute exacerbations.[14]
  - *Cough:* Often, suppressive therapy works for cough. Sometimes systemic steroids are needed. Inhaled local anesthetics can help at times. Physiotherapy may help to control secretions, but adequate hydration goes a long way in ensuring that thick secretions do not impair the ability of the patient to protect his airway.
  - *Insomnia:* Not uncommon in advanced COPD, usually due to orthopnea. Anxiety, depression and theophylline can also contribute. Oxygen to relieve nocturnal desaturation often helps. Non-benzodiazepine sedatives like zolpidem and amitriptyline may help. Benzodiazepines should be avoided as far as possible.
  - *Fatigue:* Lack of exercise, low body mass index and insomnia all contribute to fatigue. Never miss out treatable causes like anemia (iron or B_{12} deficiency) or thyroid disease. Sleep disturbance is often a cause of fatigue and must be addressed.
  - *Delirium:* Confusion occurs in a large number of patients as they approach death. Medications, especially opioids and metabolic disturbances can contribute. After correction of hypoxia and hyponatremia, haloperidol can be tried as a good first-line choice for this symptom. As the need for haloperidol increases, more aggressive sedation may be required and the family should be informed about this requirement.
  - *Cachexia and weight loss:* A poor prognostic sign, this catabolic state often is a result of increased minute ventilation. Mouth breathing and aerophagy aggravate anorexia. High calorie supplements can help. Sometimes, prokinetics help by improving gastric emptying. Foods liked by patient should be provided, including alcohol. Though weight loss can be explained to families as a body's way of shutting down, it is often followed by desperate attempts to feed (and often overfeed) the patient. This must be avoided as metabolism will increase further, putting further load on the respiratory system.

- Judicious use of Noninvasive Ventilation: Noninvasive ventilation has significantly helped many COPD patients die a more comfortable death. Just the ability to speak and eat a bit too makes noninvasive ventilation so much less intrusive than an endotracheal tube or a tracheostomy. Noninvasive ventilation at home has also reduced the number of terminally ill COPD patients reaching the hospital for the inevitable. Though the machines are expensive to purchase, rentals on a daily or monthly basis are now available in several cities.

CONCLUSION

To conclude, end-of-life communication and palliative care is cardinal in the overall management of severe, advanced COPD. As the disease gets more and more severe, less and less specific therapies are likely to benefit the patient and more supportive and palliative care becomes the order of the day. It is imperative that not just respiratory physicians, but primary care physicians too, better understand the process of dying in these patients. It will help them deal with death much better.

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Smoking / Tobacco Control

Virendra Singh, Bharat Bhushan Sharma

INTRODUCTION

Tobacco smoking is one of the most important factors in the occurrence and progression of chronic respiratory illnesses. It is also considered the most preventable factor leading to morbidity and mortality.[1] Tobacco cessation confers health benefits, which are evident in former smokers who have lower relative risk of death in all disease categories.[2] Quitting smoking slows down the accelerated rate of lung function decline that occurs in susceptible smokers.[3] Despite the knowledge of beneficial effects of cessation of tobacco, a large number of users fail to stop smoking. Although, 70% of the smokers think of quitting and approximately 40% try to quit each year, hardly 5% remain abstinent.[4] In addition, tobacco contributes to the generation of revenue and employment for people of many developing countries. Tobacco product manufacturing companies have exploited all these factors nicely to their advantage.

Recent scientific advancements have led to the development of effective treatment modalities for tobacco addiction. However, overall emphasis on smoking cessation activities is poor, at the same time there is a growing number of new smokers, especially in developing countries. Thus, tobacco smoking continues to remain a big public health problem. The present chapter is divided into two parts. First part gives a brief description of magnitude of problem related to tobacco use and smoking. The second part deals with evidence based recommendations for smoking control methods.

TOBACCO SMOKING

Historical Aspects

Tobacco cultivation was started around 8,000 years back in the American continent. Nevertheless, it was introduced to the rest of the world only about 500 years back. In later part of 15th century, Christopher Columbus while discovering America, found that native people cultivated and used tobacco.[5] Columbus brought tobacco to his country, Spain.[6] Within a few decades, tobacco use spread to the rest of the world from Europe. Portuguese merchants brought tobacco to India. Harmful effects of tobacco use were identified quite early and many European countries started imposing bans on smoking in the 17th century.[7]

However, smoking bans were lifted subsequently because medicinal properties of tobacco were highlighted and tobacco trade became an important source of income for governments. Around middle of the 20th century, tobacco use was linked to development of lung cancer.[8] Subsequently, it was linked to many other diseases. Environmental tobacco smoke exposure (passive or secondhand smoking) was also linked to a variety of health problems. Despite of all these, tobacco use continued to increase, especially in the developing countries.

Epidemiology

Prevalence of Use

India is the second largest producer and consumer of tobacco products worldwide.[5] According to a national survey on adults in India, 47% of males and 14% of females are current tobacco users. Among male tobacco users, 30% are smokers while the rest use chewing tobacco.[9] Though in adults, tobacco use among males is 10 to 15 times higher in comparison to females, in adolescents this gap is reducing fast. Global Youth Tobacco Survey (GYTS) has shown that in 8th to 10th grade school-going adolescents, in 13–15 years age group, male users were only about one and a half times the female counterparts.[10]

In developed countries tobacco use is showing a decreasing trend. Among adults in USA, 27% males and 19% of females are current tobacco users. More than 75% of them are smokers and the rest use smokeless tobacco.[4]

Type of Smoking

Cigarettes are the most common mode of tobacco use globally. Smoking pattern in India shows that around 70% to 80% of people use *bidis*, 15% to 25% cigarettes and about 4% smoke *hookah*.[11]

Mortality Attributed to Tobacco Use

Almost half of people who use tobacco are killed by tobacco-related diseases. World Health Organization (WHO) estimated that 100 million deaths were caused by tobacco in the 20th century. If current trends remain unaltered, there will be up to one billion deaths due to tobacco use in the 21st century. There are around one billion smokers in the world today and 500 million are expected to die due to tobacco-induced diseases. Approximately, one million people are killed by tobacco-related diseases each year in India, where 10% of the world's smokers live.[12] Tobacco-related diseases are important cause of death among middle-aged men in India; almost 25% deaths in this group are due to tobacco-related diseases.[13]

Factors Responsible for Smoking

It is still quite intriguing why some people are able to quit smoking quickly and easily while others smoke right up to their untimely death. Apart from strong addiction power of tobacco, the answer to this question lies in variable nature of tobacco smoking behavior. Tobacco habit may be considered as a complex chronic disease just like diabetes or Chronic Obstructive Pulmonary Disease (COPD). Early life exposures, environmental factors like living in an area that restricts smoking and genetic factors play important role in the continuation of smoking (Fig. 88.1).[14] A study among school children in Rajasthan showed that children were more likely to smoke when they were exposed to smoking advertisement or to other smokers in the family.[15] Therefore, strategies to persuade a person to stop smoking must address all of these issues.

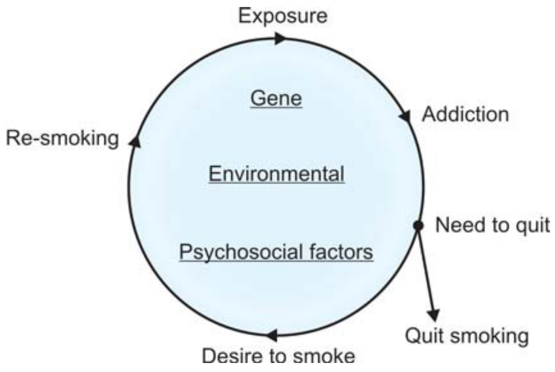


Fig. 88.1: Origin and perpetuation of addiction[5,14]

Neuronal Pathophysiology

Various neural pathways and transmitter systems have emerged to explain the psychoactive and addictive properties of nicotine. Nicotinic acetylcholine neurons located in the ventral tegmental area show increased activity with nicotine administration. They concomitantly trigger the increased release of dopamine into the nucleus accumbens (Fig. 88.2). Addiction to nicotine is believed to result from increased release of dopamine in the region of nucleus accumbens.[16,17] Recent evidence suggests that excitatory amino acid systems, in particular, *N*-methyl-*D*-aspartate (NMDA) receptors are implicated in the behavioral changes that occur following long-term nicotine use, including tolerance, sensitization and physical dependence.[18]

Withdrawal Symptoms

Similar to addiction with other drugs, nicotine withdrawal leads to a number of clinical manifestations (Fig. 88.2). Nicotine withdrawal symptoms are time-dependent, at times lasting for many weeks. These include symptoms like irritability, anxiety, depression, difficulty in concentrating, weight gain, restlessness and many more.[19,20] The level of nicotine dependence is the most important factor that determines the intensity of withdrawal symptoms. We can assess the level of nicotine dependence by objective measures such as Fagerström's test for nicotine dependence, which measures addiction on a 0–10 scale. The two most important parameters of the test are the length of time after waking before the first cigarette is taken by

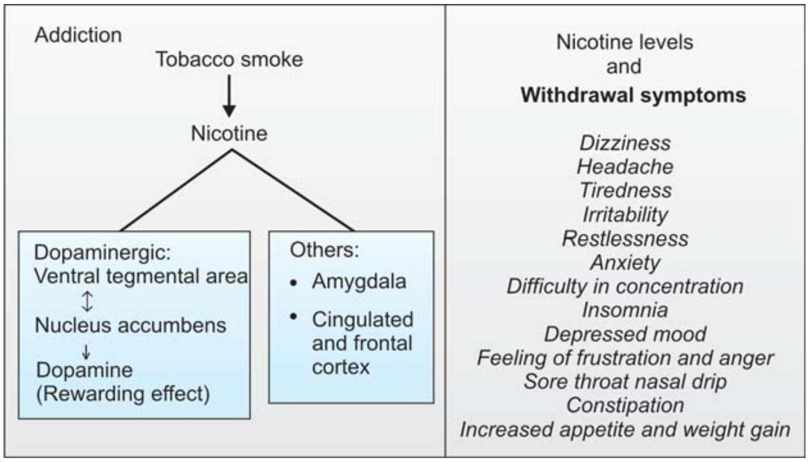

Addiction
Tobacco smoke
Nicotine
Dopaminergic:
Ventral tegmental area
Nucleus accumbens
Dopamine
(Rewarding effect)
Others:
Amygdala
Cingulated and frontal cortex
Nicotine levels and Withdrawal symptoms
Dizziness
Headache
Tiredness
Irritability
Restlessness
Anxiety
Difficulty in concentration
Insomnia
Depressed mood
Feeling of frustration and anger
Sore throat nasal drip
Constipation
Increased appetite and weight gain

Fig. 88.2: Nicotine addiction and withdrawal symptoms[16,17]

individual and the number of cigarettes smoked per day.[21]

Harmful Effects of Smoking

Toxins of Smoke

Cigarette smokes contain a significant concentration of oxidants, which are responsible for damage and causation of respiratory and other illnesses. Approximately, 4,000 chemicals have been identified in tobacco smoke of which at least 250 are known to be harmful (Fig. 88.3). These substances generated by smoking stimulate inflammation in the lung and its airways.[22] Cigarette smoking leads to inflammatory changes in the central and peripheral airways as well as the lung parenchyma. These changes finally lead to structural remodeling because of repeated injury and repair.[23] Respiratory morbidity due to tobacco smoking is varied and vast in nature, includes obstructive as well as restrictive lung diseases and lung cancer.[24]

Type of Smoking and Harm

Bidis produce three times more carbon monoxide and nicotine and five times more tar than regular cigarettes.[25] *Bidi* smokers have a three-fold higher risk of oral cancer compared with nonsmokers and are also at increased risk of lung cancer. *Hookahs*, a popular form of smoking in rural areas of India, are also linked to lung disease and cancer.[26]

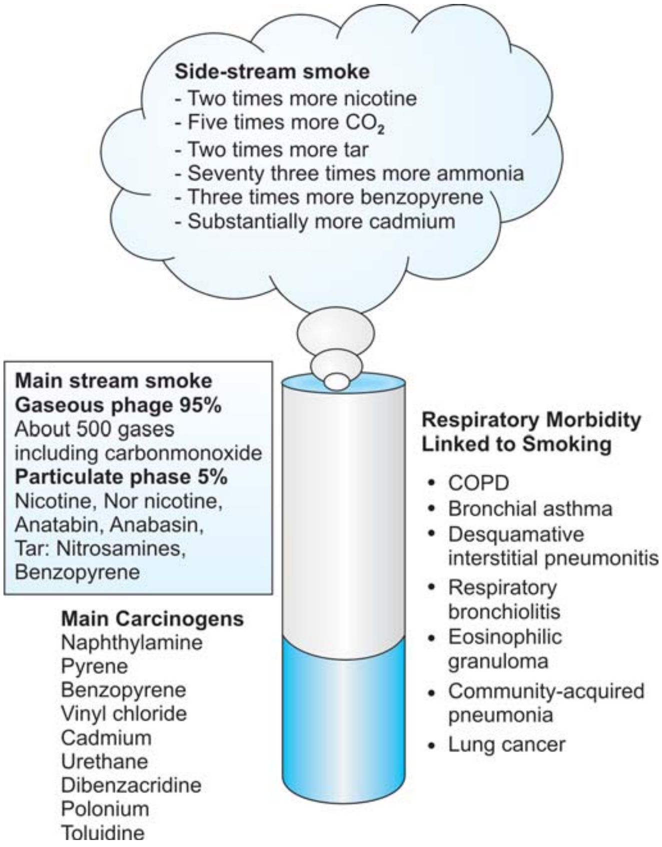

Side-stream smoke
- Two times more nicotine
- Five times more CO_2
- Two times more tar
- Seventy three times more ammonia
- Three times more benzopyrene
- Substantially more cadmium
Main stream smoke
Gaseous phage 95%
About 500 gases including carbonmonoxide
Particulate phase 5%
Nicotine, Nor nicotine, Anatabin, Anabasin,
Tar: Nitrosamines, Benzopyrene
Main Carcinogens
Naphthylamine
Pyrene
Benzopyrene
Vinyl chloride
Cadmium
Urethane
Dibenzacridine
Polonium
Toluidine
Respiratory Morbidity Linked to Smoking
COPD
Bronchial asthma
Desquamative interstitial pneumonitis
Respiratory bronchiolitis
Eosinophilic granuloma
Community-acquired pneumonia
Lung cancer

Fig. 88.3: Tobacco toxins and respiratory ailments[24,26]

Sidestream or Secondhand Smoke

Smoke emitted from the burning end of a cigarette or *bidi* while not being smoked, is called sidestream tobacco smoke. Both the mainstream and the sidestream smoke contain similar components, but the sidestream smoke is three to four times more toxic per gram of particulate matter than the mainstream tobacco smoke (Fig. 88.3).[27] Toxic chemicals from secondhand tobacco smoke stick to rugs, curtains, clothes, food or furniture and can remain in a room even for weeks and months after someone has smoked there.[28] Tobacco toxins that build up over time, coat the surfaces of room and materials are sometimes referred to as thirdhand smoke, approximately 50 of which are known to cause cancer.[29]

Passive smoking during childhood is considered as a risk factor for the development of asthma. Uncontrolled asthma is associated with parental smoking. Furthermore, asthmatic symptoms decline sharply after the Environmental Tobacco Smoke (ETS) exposure is controlled.[30]

Tobacco-Related Diseases

Smoking causes cancers of many organs. Cancer of lungs, tracheobronchial tree, mouth, esophagus, stomach and urinary bladder are mainly linked to tobacco use. Tobacco use is associated with higher rates of coronary artery disease, stroke and atherosclerosis.[31] Respiratory diseases caused by smoking include COPD, tuberculosis and lower respiratory tract infection[31] (Fig. 88.4). Globally, COPD is the most common cause of death among smokers. Likewise, smoking is responsible for half of all male deaths from tuberculosis in India.[13]

Loss of Revenue due to Tobacco

In India, the cost of treating tobacco-related disease is more than double than the revenue the government gets from the tobacco industry.[32] Besides this, there is an uncountable fiscal and personal loss to the families and society due to early deaths of the smokers.[33]

Benefits of Smoking Cessation

Smoking cessation has definite personal and health benefits that may be divided into short- and long-term benefits (Table 88.1)[20,34]

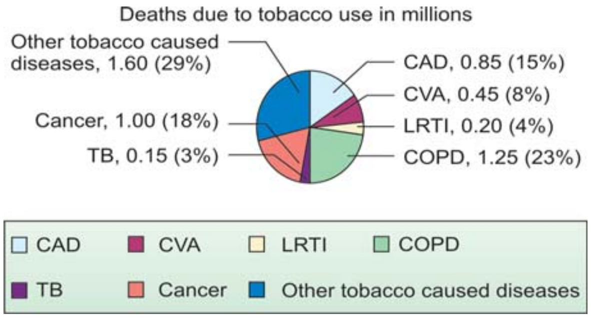


Fig. 88.4: Leading causes of mortality due to tobacco: Globally[31]

TABLE 88.1: Beneficial effects of smoking cessation [20,34]

Immediate rewards of quitting	*Respiratory benefits over time*
These rewards can improve day-to-day life to a great extent: • The breath smells better • Stained teeth get whiter • Bad smelling clothes and hair disappear • Yellow fingers and fingernails disappear • The food tastes better • The sense of smell returns to normal • Breathlessness on everyday activities is reduced	**8 hours after quitting:** Oxygen levels in the blood return to normal. **12 hours after quitting:** The carbon monoxide level in blood drops to normal. **48 hours after quitting:** Nicotine is no longer detectable in body. The ability to taste and smell improves. **72 hours after quitting:** Breathing becomes easier as the bronchi. relax. Energy levels increase **2 weeks to 3 months after quitting:** Circulation improves and lung function increases. **1 to 9 months after quitting:** Coughing and shortness of breath decrease; cilia regain normal function in the lungs, reduce the risk of infection. **10 years after quitting:** The lung cancer death rate is about half that of a person who continues smoking. Risk of cancer of the mouth/ throat also decreases.

Short-Term Benefits

Immediate benefits of smoking cessation include a decline in carbon monoxide levels in the blood, return of pulse rate and blood pressure to normal levels. Personal benefits include improvements in breath smells, stained teeth, bad smelling clothes or hair, colored fingers and fingernails, taste of food, sense of smell and breathlessness on everyday activities.

Long-Term Effects

In persons who quit smoking before 50 years of age, the risk of dying in the next 15 years is half that of a smoker. Even in persons who quit at 60 to 64 years of age, the risk of dying is reduced by 10% compared to persons who continue to smoke. There are enormous respiratory benefits. Smoking cessation is the most effective way to reduce the risk and improve prognosis of COPD.[1] Smoking cessation reduces the risk of developing cancer. Ten years after cessation of smoking, the risk of dying from lung cancer is about one-third to that of smoking persons. Smoking cessation also reduces the risk of acquiring a second primary cancer.[35]

The rate of decline in lung function in COPD among former smokers returns to that of never smokers. Smoking cessation also decreases the risk of influenza and pneumonia. If a mother stops smoking before becoming pregnant or within three to four months of pregnancy, the birth weight of the infant will be the same as that of infants of nonsmokers. Even cessation at later stage of pregnancy will lead to higher birth weight than those of babies of regular smokers. Smoking cessation also eliminates the risk of passive smoking induced diseases, including pneumonias and exacerbations of bronchial asthma in relatives.[36]

SMOKING CONTROL INTERVENTIONS

Controlling smoking addiction is quite demanding and also unpredictable. A multitude of interventions have been tried with variable rates of success. Smoking cessation is defined as validated sustained abstinence from cigarettes and/or other tobacco products for at least six months, preferably for a year.[37]

The available smoking cessation interventions can be classified into behavioral, pharmacologic, combined and alternative methods. Behavioral interventions are physician guidance, individual counseling and group counseling, or counseling by telephone. Pharmacologic interventions include Nicotine Replacement Therapy (NRT), sustained-release bupropion, varenicline as first-line agents and clonidine and nortriptyline as second-line agents. The alternative, less evidence based, interventions are hypnosis, acupuncture, aversive therapy, exercise, lobeline, anxiolytics, mecamylamine and silver acetate. Nicotine vaccine is among some of more promising agents for future therapy of tobacco dependence. Above all, it is most important to prevent the initiation of smoking in unexposed individuals.

How to Restrict Tobacco Use in the Society: First Level Prevention

Smokers may be divided in two categories children and adolescents in the first group and grown-up adults in the second group. They may be further classified as sick and healthy smokers.

Children and Adolescents

They belong to the age group when a smoker learns smoking. Efforts should be made to make these children aware of harmful effects of smoking. It is easy not to start than to quit smoking. Pamphlets, stickers, articles in newspapers, television serials and a chapter in curriculum books may play an important role in dissuading adolescents from initiating smoking. In a recent study, use of posters; curriculum changes; parental involvement and peer-led activism reduced self-reported tobacco use, as well as future intentions to start tobacco chewing or smoking.[38]

Grown-up Adults

Usually grown-up nonsmoker adults are unlikely to initiate smoking in later years of life. They are probably most receptive in accepting dangers of passive smoking and therefore must be motivated to resist anyone else smoking in their presence. Efforts should be made to make these people aware that breathing clean air is very important for health. It will ensure the compliance of ban on smoking at public places.[39]

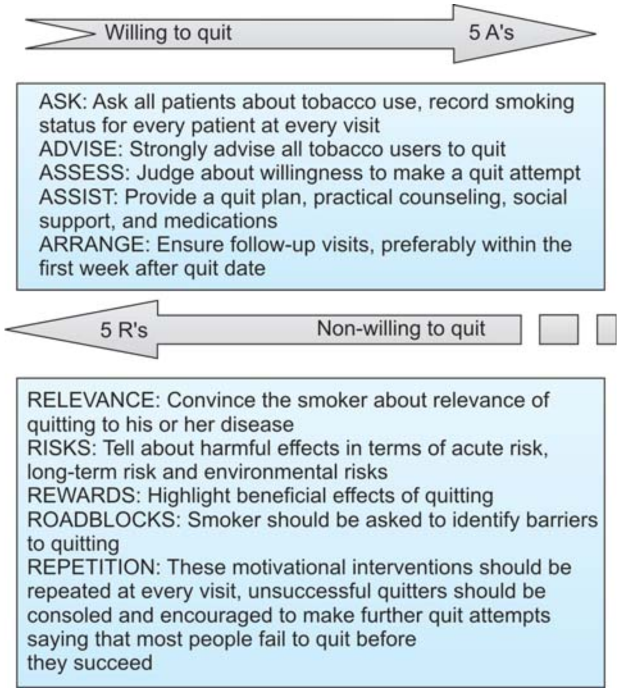
Sick Smokers

Sick smokers can be motivated more readily. Appropriate advice by health care workers can motivate a sick smoker for cessation of smoking. Timely advice by doctors, nurses, pharmacists and other health care personnel is crucial for a smoker who is interacting with them during his illness. Current evidence-based opinion regarding smoking cessation is that it should be done for every smoker during every health care visit.[40,41] Even a short period of counseling at the clinician's office, to ask a smoker to quit, results in cessation rates of up to 10%.[42,43]All smokers including those at risk for COPD already having disease should be offered the most possible and rigorous cessation intervention. The rate of successful smoking cessation at one year is 7% to 16% if the smoker undergoes behavioral intervention alone and up to 24% when receiving pharmacological treatment plus behavioral support.[44]

Healthy Smokers

Healthy smokers are least receptive to no-smoking advice. However, their tobacco use can be restricted by means such as making cigarettes more expensive, ban on public smoking and ban on sale to minors. Sometimes, peer pressure, family persuasion and religious appeal may motivate smokers in this category.

Efforts must be made to register the smokers for subsequent detailed interventional plans. This form of counseling takes less than 10 minutes of clinicians. For such brief intervention used to initiate smoking cessation, a mnemonic five "A's" is commonly used. All patients



ASK: Ask all patients about tobacco use, record smoking status for every patient at every visit
ADVISE: Strongly advise all tobacco users to quit
ASSESS: Judge about willingness to make a quit attempt
ASSIST: Provide a quit plan, practical counseling, social support, and medications
ARRANGE: Ensure follow-up visits, preferably within the first week after quit date

RELEVANCE: Convince the smoker about relevance of quitting to his or her disease
RISKS: Tell about harmful effects in terms of acute risk, long-term risk and environmental risks
REWARDS: Highlight beneficial effects of quitting
ROADBLOCKS: Smoker should be asked to identify barriers to quitting
REPETITION: These motivational interventions should be repeated at every visit, unsuccessful quitters should be consoled and encouraged to make further quit attempts saying that most people fail to quit before they succeed

Fig. 88.5: Initiation of smoking cessation effort [43,45]

should be **asked** about tobacco use and their smoking status is recorded. A strong **advice** is given to all tobacco users to quit. Their willingness to make a quit attempt is **assessed**. The smokers are **assisted** with a quit plan, practical counseling, social support and medications. Finally, follow-up visits are **arranged** for the smokers willing to quit. For those smoker not willing to undergo cessation, five "R's" are used to enhance motivation and decrease mental inertia to quit: Relevance, Risks, Rewards, Roadblocks and Repetition (Fig. 88.5).[45]

Behavioral Interventions

Initial approaches to smoking cessation during mid 20th century were based on the behavioral therapy alone. For next few decades, cognitive therapy gained momentum but finally pharmacotherapy started emerging around 1990s. Behavioral interventions are effective in smoking cessation, although there is insufficient information to know which elements of behavioral support or type of approach (like motivational interviewing or cognitive behavioral therapy) is more effective.[40]

Basically, three behavioral interventions approaches are utilized: 1) Practical counseling- problem solving or skill training, 2) Giving intra treatment support, 3) Provision of extra treatment support. The physician, nurse or telephone counselor may assist in the process or it is performed as self-help by the patient himself. Among the simplest of behavioral interventions, even brief, but direct physician advice to quit smoking is effective. Furthermore, the rate of smoking abstinence increases when the intensity of advice is increased and when follow-up visits are included.

Types of Behavioral Interventions

1. *Individual counseling:* A review of studies about individual behavioral counseling by trained therapists with a follow-up of at least six months indicated benefits of counseling as compared to no intervention. Individual counseling usually consists of one or more direct interview sessions, often followed by telephone contact for the support.[19]
2. *Group counseling:* Available studies also suggest that group counseling is effective in promoting smoking cessation.[19,46] Overall, the evidence supporting the efficacy of group counseling satisfies level A.[46]
3. *Telephone counseling:* It is simple, can reach a large number of people at a time. Proactive telephone counseling, which the counselor initiates, is more effective than reactive counseling, which is client initiated.[19]
4. *Self-help information:* It is marginally beneficial for increasing smoking cessation.[19,46] Examples of self-help materials include booklets, leaflets, brochures, videotapes, compact discs, help lines, and various other computer and Internet interventions. Enhanced or tailored self-help material was associated with better cessation rate than standard self-help material.[47] Though the effectiveness is nominal, self-help also achieves evidence level A.[46] Other reasons that self-help, despite its small impact, should be included in smoking programs are increased population awareness, low expense and the opportunity to customize the message. Cessation programs available on the Internet are also found to be effective in smoking cessation.[48,49]

Increasing Effectiveness of Interventions

Another lesson from available meta-analyses of behavioral interventions is that adding cessation formats confers incremental effectiveness. Combining up to three to four formats, e.g. self-help with individual counseling or individual counseling and telephone counseling, may increase the absolute cessation rate by 12%.[46] Also, increasing the intensity of interventions enhances smoking cessation rates. Factors increasing effectiveness include the duration of each individual session, the total time spent in all sessions and the number of sessions.

With minimal counseling of up to three minutes, the cessation rate was 13.4%; with low-intensity counseling (3 to 10 minutes), the rate was 16.0%; with high-intensity counseling (more than 10 minutes), the rate was 22.1%.[46]

A review of the impact of the number of counseling sessions suggests that the greater the number of sessions, the greater the chance for cessation. Programs with 0 to 1 sessions had a quit rate of 12.4%, whereas those with more than eight sessions had a quit rate of 24.7%. [40] In another study Simon, et al. randomized 228 patients to either low- or high-intensity intervention, with all receiving NRT via patch; the one-year abstinence rate was significantly higher in the higher-intensity counseling group.[50]

Pharmacotherapy

Pharmacotherapy aimed to quit smoking is very different from that used for the treatment of a disease. Success of pharmacotherapy of quit smoking depends substantially on the desire or motivation of a patient. Pharmacotherapy fails to produce effect if the patient does not have a desire or motivation to quit. Unfortunately, we do not have any medicine to induce a desire to quit smoking. Personalized counseling to induce motivation for quitting smoking should be a prerequisite for the use of pharmacotherapy.

A number of meta-analyses have revealed that all current medications for smoking cessation are twice more efficacious than placebo.[51] However, there is limited data to guide clinicians to advocate one type of medication over another or the use of combinations. Lately, a Delphi method was used by a group of international experts for clinicians to guide the tailoring of medication for individual smoking cessation.[19] Levels of scientific evidence, patient preference, previous experience and failed attempts with monotherapy are some of the factors which should determine the prescription. Other important factors include the presence of comorbidities and contraindications to the medications.[1]

Current Medications for Smoking Cessation

All smokers who have previously relapsed when attempting to quit are questioned about their prior use of pharmacotherapy and their perceptions of the treatment options. Even light smokers or those who have failed in earlier attempts to give up, can benefit from pharmacotherapy.[52]

Besides decreasing the withdrawal symptoms and craving, pharmacotherapy decreases the short-term reinforcing effects of tobacco. This form of relief can help to ease the process of a patient learning new coping skills. The addition of a pharmacologic agent to a quit plan can have a positive psychological impact on those making quit attempts, especially if previous quit attempts had fared poorly (Table 88.2).[53,54] All first-line medications appear to similar effectiveness, but there have been few direct comparisons.

TABLE 88.2: Various medications for smoking cessation[50,51]

Type		*Requirements*	*Dose*	*Duration*	*Drawbacks*
NRT	Gum	Start on quit date	2 mg- up to 24 cigarettes/d 4 mg- >25 cigarettes/d	Up to 12 weeks	Mouth soreness, dyspepsia
	Patch	Start on quit date Worn 24 hours	21 mg, 14 mg, 7 mg depending on level of addiction	8 weeks	Insomnia, Local skin reaction
	Inhaler	Start on quit date, inhaled into mouth, not lungs	6 to 16 cartridges/d	Up to 6 months	Local irritation of mouth and throat
	lozenge	Start on quit date	2 mg- 1st cigarette > 30 min, post-awakening 4 mg- 1st cigarette < 30 min, post-awakening	8 weeks	Mouth soreness, dyspepsia
Bupropion SR			150 mg OD for 3 days then 150 mg BID for rest of treatment	Up to 6 months	Insomnia, dry mouth, contraindicated in seizures
Varenicline		Quit date two weeks after initiation Taken after meals with a full glass of water	0.5 mg OD for 3 days, 0.5 mg BID for next 4 days then 1 mg BID for rest of treatment	12 weeks treatment and 1 week maintenance	
Clonidine		Quit date one weeks after initiationTaken after meals with a full glass of water	0.15 to 0.75 mg /d	3 to 10 weeks	Dry mouth, dizziness, drowsiness, sedation, rebound hypertension
Nortriptyline		Quit date two to three weeks after initiation. Taken after meals with a full glass of water	75 to 100 mg/d	12 weeks	Dry mouth, sedation, risk of arrhythmia

The medication is selected on the basis of: Medical conditions, potential adverse effects, individual preference, previous smoking cessation, level of dependence and any apprehension of weight gain. Current medications may be grossly divided into nicotine replacement therapy and non-nicotine pharmacotherapy.

A. Nicotine Replacement Therapy

Nicotine replacement therapy is the most common medication to assist smoking cessation, probably because there are more data available on its effectiveness and safety.[53] It is important to explain to the patient that NRT will help diminish nicotine craving, will make it controllable but will not completely eradicate.

Rationale: Nicotine is the substance to which a smoker is addicted. In smokers, when the blood level of nicotine decreases, withdrawal symptoms begin within a few hours after having the last puff of smoke. Smoking relieves these symptoms immediately. If smoking is not done, withdrawal symptoms will continue to manifest with increasing severity. Nicotine replacement therapy will maintain a stable nicotine level in the bloodstream of the smoker, who is trying to quit, avoiding withdrawal symptoms.[55] When NRT via transdermal patch is used, more constant delivery of nicotine helps to desensitize nicotine receptors and therefore further inhibit withdrawal symptoms. Nicotine replacement therapy is available in form of nicotine gum, patches, lozenges and inhalers. In tobacco chewers, nicotine gum may be more effective since it provides the physical sensation of manipulating tobacco in the mouth.

A recent systematic review of randomized clinical trials including smokers not ready to stop, reveals that with NRT, twice as many quitters achieve six months of sustained abstinence.[56] It is also shown that the nicotine patch used along with another NRT is more effective than any of the single NRT.[57] It is customary to equate 1 mg of NRT to each cigarette smoked and start two weeks prior to the quit date while the patient goes on smoking on NRT. However, both these practices are not based on sound scientific evidence. Ideally, smoking should be stopped before starting NRT.

1. *Transdermal nicotine patch:* It is the most common form of NRT, which has been available for more than two decades. It is available in different strengths but 21-mg patch over a 24-hour period is commonly used. Current trend involves increasing the NRT patch dosage and duration for heavy tobacco users. The final goal is to supply the dosage necessary to equate the nicotine level to body's accustomed state. Side effect may consist of local irritation, headache, dizziness, nausea and sleep disturbances.
2. *Nicotine gum or lozenge:* They contain polacrilex compounds that are resin carriers. Both forms (gums and lozenge) of polacrilex are sugarless and available in different flavors. One should not eat or drink just before and during the use of these compounds. Acidic food and drinks like coffee or carbonated beverages interfere with drug delivery by these compounds, hence best avoided. Side effects of nicotine gum include dyspepsia, hiccups and mandible pain.
3. *The nicotine inhaler:* Unlike the usual pressurized metered-dose inhaler, nicotine inhaler is a cartridge, from which, on suction a nicotine vapor is released in mouth and throat. For heavy tobacco users, it is not a good option as a monotherapy because of its poorer dose delivery. To deliver high doses, nicotine nasal spray can be used, but it is not popular as it is costly and can cause substantial nasal and eye irritation. Nicotine replacement therapy is usually considered safe for most patients[53,58]

Contraindications to NRT's

Nicotine replacement therapy should not be started if within the past six weeks there is a history of myocardial infarction, unstable angina, uncontrolled hypertension, hypertension during treatment and severe rhythm disturbance. Relative contraindications include severe COPD, uncontrolled diabetes mellitus, and some cardiovascular disorders like coronary artery disease. Vivid dreams or insomnia may indicate a high NRT dose. Nicotine replacement therapy may interact with other drugs; it can lead to an increase in blood pressure when used along with bupropion. Drugs taken concomitantly, like insulin, benzodiazepines, caffeine and ergot may need dose adjustment. Irritation at application-site may suggest a need for a change in type of NRT. Insomnia with NRT is dealt by removing patch one hour prior to bedtime or by reducing the dose. Sublingual tablet is a new form of NRT, but the superiority of this formulation over NRT lozenge has not been proved.[59]

B. Non-nicotine Pharmacotherapy

1. *Bupropion:* Bupropion can reduce the severity of nicotine cravings and withdrawal symptoms. It was originally introduced in 1997 as a smoking cessation aid. Now it has been approved in more than 50 countries across the globe.[60] The proposed mechanism of the effectiveness of bupropion in smoking cessation is blockade of the reuptake of dopamine and norepinephrine.

For tobacco dependence treatment, sustained release variety of bupropion is preferred over the instant release. Bupropion SR needs to be taken twice daily and bupropion XL only once daily.

Side effects: Most common adverse effects of bupropion are dry mouth and insomnia. Agitation is an adverse effect that can be mostly avoided by the gradual escalation of dose from 150 mg to 300 mg daily by one week rather than just three days. Duration of treatment is typically 7 to 12 weeks with no tapering. The risk of seizures (one-in-a-thousand) is more common in epilepsy and some eating disorders. In a dose of 450 mg in treating depression, bupropion increases the risk of seizures, but the 300 mg dose used for tobacco cessation has very little risk of seizure. Bupropion should not be used by people with active use of alcohol who take more than three drinks per day or by people with sudden alcohol withdrawal. It should also not be used by pregnant women. One significant advantage of bupropion is that it typically does not cause weight gain, may rather suppress it.

2. *Varenicline:* Varenicline is an effective oral smoking cessation product to be approved by the US Food and Drug Administration. It was launched in mid-2006 in some parts of the world and was launched in India in 2008. Several trials have shown the benefits of varenicline in cessation rates. Bupropion was compared with varenicline in recent randomized controlled trials. In a meta-analysis it was found that rates of smoking cessation associated with varenicline were superior to those of bupropion and NRT.[61-63]

   Varenicline acts as a partial agonist of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor through which nicotine dependence is mediated. It also stimulates the dopaminergic system, which results in reduced withdrawal symptoms. The drug also blocks nicotinic receptors, which prevents the dopamine release in response to nicotine. Additionally, reinforcing effects of nicotine exposure is blocked because varenicline is expected to occupy this receptor.[64]

   The current recommendation states that the drug should be started one week prior to quit date, the full therapeutic effect may not occur until following a few weeks.

   Side effects: The most common side effect of varenicline is nausea occurring in about 30 percent of patients. The nausea is generally short-lived, taking varenicline with a full glass of water and after eating helps to reduce this unfavorable effect. Less common side effects are insomnia, abnormal vivid dreams, constipation and flatulence.[53]

   Varenicline has been associated with some psychiatric adverse effects. These include erratic behavior, new appearance of depressed mood, agitation, suicidal ideation, suicidal attempts and completed suicides within days to weeks after initiating varenicline.

   Patients should be asked about any prior history of mental illness before starting varenicline and monitoring for changes in mood and behavior. It is important to note that in clinical trials, prevalence of behavioral changes with varenicline were similar to those with placebo. Varenicline poses a low burden on the kidney and liver, therefore may be used in end-stage renal disease with a reduced dosage.

C. Second Line Drugs

1. *Nortriptyline:* Nortriptyline is a second-generation tricyclic antidepressant used in the treatment of major depression. It is recommended as a second-line medication in recent guidelines for the treatment of tobacco dependence.[53,59,65] Nortriptyline can have a sedating effect, it is more practical to take it in the evening. There are a number of other potential adverse effects including dizziness, blurring of vision, tinnitus, tremor, weakness, insomnia, nausea, constipation and rash. In patients with cardiovascular disease, it can increase the risk of serious dysrhythmia.[59] Nortriptyline can interact with a variety of medications. It is usually started earlier than other tobacco cessation medications, i.e. up to three weeks prior to quit date, to allow for a gradual build of dosage.
2. *Clonidine:* Clonidine, also a second-line tobacco-cessation drug, is effective in reducing symptoms of opioid and alcohol withdrawal.[59] It can be taken orally in tablet form or via transdermal patch, and is started a week prior to quit date. Possible adverse effects include drowsiness, dizziness, fatigue, agitation, depression, constipation, nausea, weight gain and rebound hypertension.[53] A specific dosing regimen for tobacco cessation has not been established and there are several important drug interactions.

D. Combination Treatments

Nicotine patch can be combined with other formulations of NRTs in the cases of heavy addiction. Bupropion or varenicline should not be combined together or theoretically, with any of NRTs, no sound evidence is available for such an approach. They also should not be given to children, pregnant or lactating mothers. However, both of these can be used safely for people with stable cardiovascular disease.

Any of above pharmacological therapy may be advantageously combined with all types of behavioral interventions.[66]

E. Novel Therapies: Hope for the Future

We have seen that drug therapy for smoking is effective, but a significant number of patients fail to gain significant advantage on a long-term basis. Therefore, there is a continuous need for search of an agent, which would be ideal to tackle this problem more effectively. Agents which are of some hope include new non-nicotine replacement medications such as selegiline, fluoxetine and naltrexone.[19,67]

Newest strategies are related to search for a vaccine against nicotine addiction and application of pharmacogenetic principles to smoking cessation. A safe and effective vaccine would lead to better compliance than the existing pharmacotherapy. Such a proposed vaccine is based on stimulation of immune system to form specific antibodies (Nic-IgG) to nicotine to make the molecule too large to cross the blood-brain barrier and act on its central receptors.[68-70]

Nicotine is principally metabolized by cytochrome-450 enzyme coded by CYP2A6 gene. Fast metabolizers need high amount of nicotine to maintain the addiction, and hence chance of high level addiction. Original Text Various other genes related to signaling molecules and CYP2B7P1/CYP2B6 gene responsible for bupropion metabolism are under evaluation. With better knowledge of pharmacogenomics, we will be able to design the medication for individual patients better.

CONCLUSION

Tobacco smoking is responsible for enormous adverse respiratory health consequences. Smoking cessation interventions are rewarding and should be attempted for all patients and at every health care visit. Effective and relatively safe pharmacotherapy in the form of first-line drugs like NRT, bupropion and varenicline are now available all over the world. India and other developing countries have started developing an antismoking momentum that needs to be build up with greater force by health care providers, supported by better responsiveness of smoking individuals. Tobacco cessation clinics and self-help material, including the information books on the subject are now widely available.[71] World Health Organization with its resolve to create smoke free and tobacco free world has taken several steps towards accomplishing the ultimate goal of a smoking-free society.

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89

Pulmonary Rehabilitation

Rachael A Evans, Roger S Goldstein

SYMPTOMS AND DISABILITY ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with chronic obstructive pulmonary disease (COPD) commonly present with exertional breathlessness and fatigue[1] and typically they become less active to avoid these symptoms. This reduction in activity can lead to loss of confidence, depression, loss of work or inability to perform hobbies and social isolation, resulting in substantial disability. Although the primary pathological process of COPD results in a progressive reduction in airflow, the correlation between the degree of lung function impairment and the severity of symptoms is weak. Abnormalities in gas exchange, as well as the restrictive ventilatory limitation associated with hyperinflation contribute to the symptoms of exertional breathlessness and diminished exercise capacity.

Systemic Consequences of COPD

In addition to the primary pulmonary pathology, there are secondary alterations in skeletal muscle function, nutrition, bone density, gonadal hormones, hemoglobin and mood,[2-4] many of which influence exercise tolerance and health-related quality of life. The skeletal muscles of locomotion are altered on multiple levels. Morphologically, there is a reduction in muscle mass and strength of the quadriceps compared to age-matched healthy controls.[5] The muscle fiber types are altered with an increase in the proportion of the type IIX, fast twitch, glycolytic fibers (more fatigable) compared to the type I, slow twitch, oxidative fibers.[6] Muscle metabolism is altered, with a reduction in oxidative enzymes and a reduction in mitochondrial density. Energy metabolism during exercise is altered with a more rapid loss of phosphocreatine at lower workloads than age matched healthy controls and a failure of ATP replenishment to meet the demand.[7]

Skeletal muscle dysfunction contributes to reduced exercise tolerance by promoting an earlier rise in the level of lactic acid, which when buffered, increases CO_2 production, which in turn, increases the ventilatory load applied to a system, which already has an impaired ventilatory capacity. Whether the skeletal muscle dysfunction relates to deconditioning or whether it relates to an underlying inflammatory myopathy, remains an area of interest. Although people with COPD do enter a vicious circle of inactivity (Fig. 89.1), which influences the function of the leg muscles, muscles not involved in ambulation, such as the adductor pollicis retain normal function. Moreover, much of the reduced ambulatory muscle function can be reversed with exercise training. In favor of an underlying systemic inflammatory process are the increased levels of systemic markers of inflammation, as well as oxidative stress and nutritional depletion. Hypoxia and medications, such as corticosteroids also contribute towards the skeletal muscle alteration.

The spiral of inactivity is also affected by the symptoms of anxiety and depression experienced by many patients with COPD. The sensation of dyspnea generates feelings of anxiety, but anxiety itself can manifest as dyspnea. Low mood is frequently reported by patients with COPD related to their disability and loss of function, but may also be a preexisting phenomenon

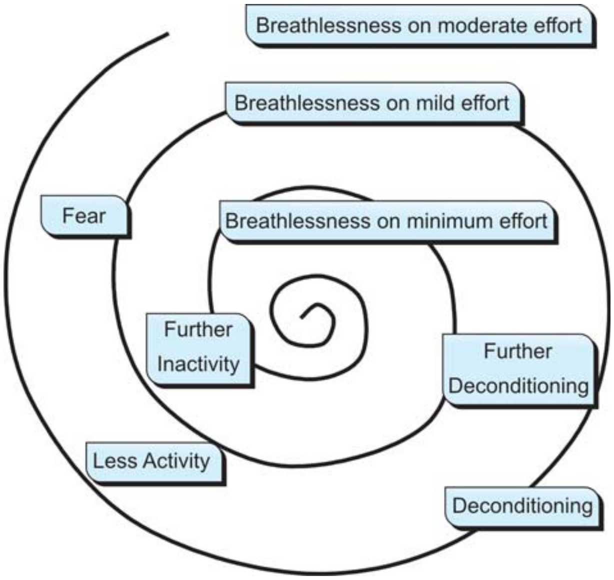

Breathlessness on moderate effort
Breathlessness on mild effort
Fear
Breathlessness on minimum effort
Further Inactivity
Further Deconditioning
Less Activity
Deconditioning

Fig. 89.1: Spiral of inactivity

Note: The diminishing cycle of dyspnea and reduced exercise tolerance.

predisposing to smoking. Unfortunately, the effect of low mood on motivation and self-esteem further impact on inactivity.

THE ROLE AND DEFINITION OF PULMONARY REHABILITATION

The term "rehabilitation" refers to the process of restoration of function despite physical or psychological disability. Pulmonary rehabilitation (PR) programs have developed over the last few decades as a therapy targeted at the secondary alterations of COPD, aiming at improving both the functional and psychosocial aspects of an individual. It is now recommended as an integral part of the clinical management of patients with COPD and has a strong, supportive evidence base demonstrating a reduction in dyspnea, and improvements in both exercise tolerance and health-related quality of life.[8] There is also evidence to support a reduction in health care costs following a rehabilitation program.[9] It has yet to be established whether PR impacts directly on mortality, although it clearly impacts on many of the factors that affect mortality, such as dyspnea, exercise tolerance and health-related quality of life.[10,11]

The international guidelines of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) adopted the following definition for Pulmonary Rehabilitation; "It is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation and reduce health care costs through stabilizing or reversing the systemic manifestations of the disease."

TABLE 89.1: Key features of a pulmonary rehabilitation program

- Assessment for suitability and safety
- Provision by a multidisciplinary team
- Individually prescribed exercise training combined with education and self-management advice
- Minimum of two supervised and one unsupervised sessions per week
- Exercise sessions each of 20–30 minutes duration
- Minimum of six weeks duration
- Individual progress assessed by appropriate outcome measures usually exercise performance and health status
- Audit for quality control
- Ideally to have a subsequent maintenance program or potentially further programs after an exacerbation

Pulmonary rehabilitation programs include several evidence-based components and should not be mistaken for more general programs of activity promotion, convalescence or pure self-management programs. It is an organized, multidisciplinary approach with defined, essential features (Table 89.1).

The Changing Pulmonary Rehabilitation Population—Who to Refer?

Patients with COPD are the traditional target population for pulmonary rehabilitation and work in this population has informed the original studies. However, the spiral of inactivity also applies to other chronic respiratory diseases; providing a rationale for rehabilitation which has been reported to be beneficial in other conditions including pulmonary fibrosis, post-tuberculosis lung disease, thoracic restriction, bronchiectasis, cystic fibrosis, asthma, pulmonary hypertension, pre and post-operatively for lung resection, volume reduction or transplantation (Fig. 89.2). Certain program adaptations for non COPD patients are required, such as the exclusion of exercise-induced arrhythmias in pulmonary hypertension and education about chest clearance for patients with chronic suppurative lung diseases.

The predominant clinical inclusion criterion, for referral to pulmonary rehabilitation, is exertional dyspnea that interferes with function as assessed by the Medical Research Council (MRC) Dyspnea Scale (Fig. 89.3). This is a simple, self-assessed scale and can

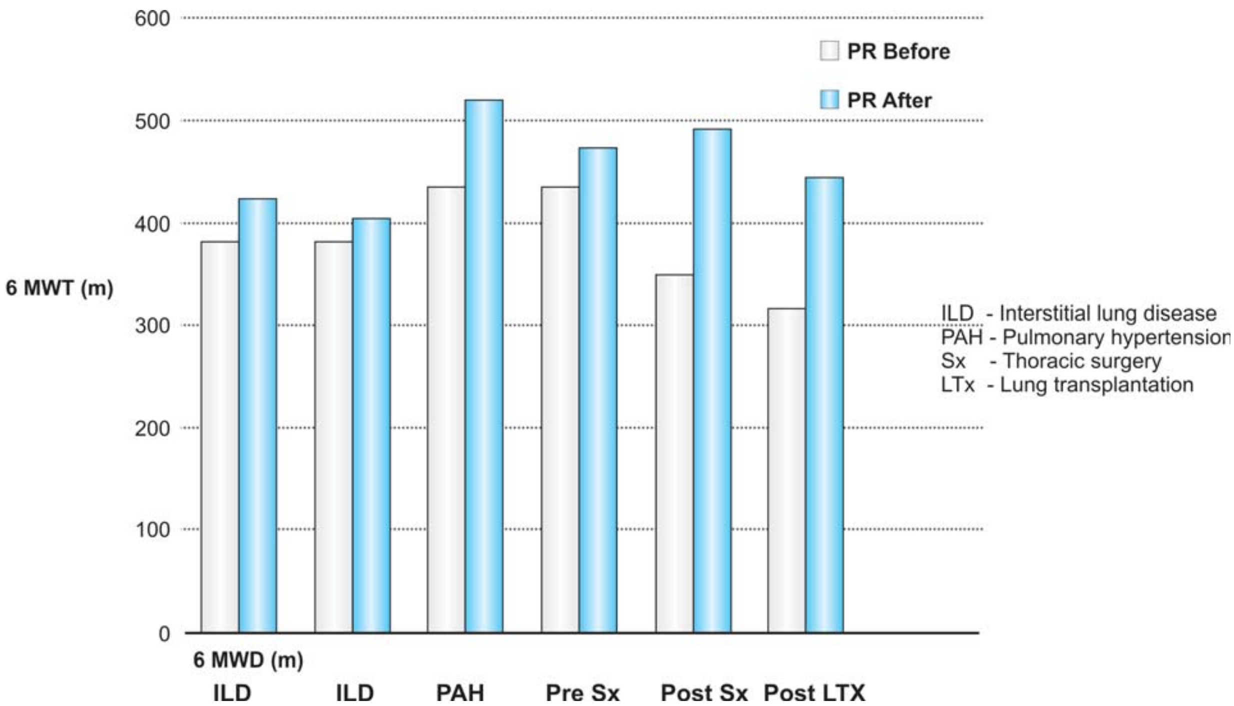


Fig. 89.2: Six-minute walk test distance before and after pulmonary rehabilitation in different population
Note: Similar increments in 6 MW test can be achieved among a variety of respiratory populations[9]

easily be used to screen those who may benefit from rehabi-litation. International guidelines suggest referral for pulmonary rehabilitation for Grades III–V. There is evidence to suggest that patients with the milder levels of breathlessness may also benefit.[12] The World Health Organization (Global initiative for Obstructive Lung Disease) recommends rehabilitation for any symptomatic patients with GOLD stage II and above (FEV_1 <80% predicted).

Both the primary respiratory disease and existing comorbid conditions should be optimally managed prior to enrolment. Patients with obstructive disease should receive optimal airway care. Any preexisting depression should be addressed as it is known to be associated with poor compliance and response to rehabilitation. Diagnostic assessment and optimizing management should occur prior to commencing PR.

Grade	Description of Limitation
I	I get breathless only with strenuous exercise
II	I get breathless when hurrying or walking uphill
III	I walk slower than people of the same age on the level or I have to stop because of breathlessness on the level
IV	I can only walk 100 yards before stopping because of breathlessness or after a few minutes on the level
V	I am breathless when dressing or undressing or I am too breathless to leave the house

Fig. 89.3: The Medical Research Council (MRC) Dyspnea Scale[7]

Patients need to be able to participate in endurance exercises and those with a predominantly orthopedic, neurological or peripheral vascular limitation to exercise are commonly excluded. Safety criteria should be adhered to, for example, a myocardial infarction sustained within three months, unstable angina, moderate-to-severe aortic stenosis or uncontrolled blood pressure would all exclude patients from being enrolled. Patients with unstable cardiovascular disease must be assessed and treated appropriately prior to inclusion to a program. Nonclinical factors may be pivotal. These include a reasonable level of comprehension, realistic expectations of the program, motivation to improve, an ability to follow instructions, acceptable health literacy and a supportive home and family.

Components of a Pulmonary Rehabilitation Program

Assessment

The assessment should systematically address the inclusion and exclusion criteria and further inform the patients about the process of pulmonary rehabilitation.

An assessment of dyspnea, exercise performance and health status is standard and can inform both individual progress and program quality.[13] An exercise assessment for the program exercise prescription, requirements for safety and as a baseline for the exercise outcome, is increasingly performed using simple, inexpensive field tests rather than expensive laboratory-based exercise equipment. Patients with resting hypoxia should exercise with supplemental oxygen. The criterion for ambulatory oxygen varies among jurisdictions. Those who desaturate markedly on exercise <85% are often offered supplementary oxygen during training. In many countries, the expense of oxygen makes it prohibitive except in patients with profound hypoxemia.

Outcome Measures

Full cardiopulmonary exercise tests: The gold standard measurement of exercise capacity is peak oxygen consumption. A maximal, incremental, symptom limited cardiopulmonary test with expiratory gas analysis can provide this, as well as comprehensive information about the precise limitation to exercise (Fig. 89.4). However, it involves expensive equipment and expertise. Typically tests are performed on a cycle ergometer providing a stable platform, but a treadmill can also be used particularly if cycling is not familiar. Endurance tests can be performed using the same equipment set at an intensity relative to the peak performance. Although the variability of endurance testing is greater than for maximal testing, endurance tests are often a more sensitive outcome measure for pulmonary rehabilitation.

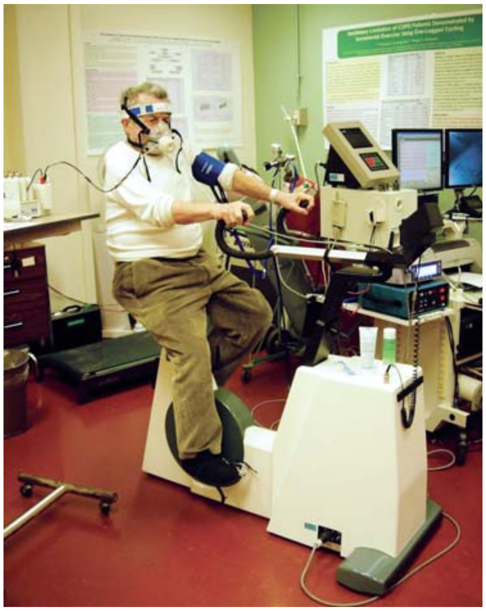


Fig. 89.4: Cardiopulmonary exercise test on a cycle ergometer

Six-minute walk test: The most commonly used field test is the six-minute walk test (6MWT).[14] The test is completed over a 30 meter flat course. It is self paced and standardized instructions are given. Patients are asked to walk as far as they can for six minutes and the result is usually presented as the distance walked, although the speed can be calculated. The test is reproducible after two practice tests and is responsive. Unlike other field tests normal reference values are available. The six minute walk test can be influenced by encouragement, which is therefore standardized. It is likely closer to peak exercise capacity although the distance walked is referred to as a measure of functional capacity. The six minute walk test distance is highly correlated with the other outcomes of COPD, such as mortality and is featured in the multidimensional severity index; the BODE index.[15] It has been used to set exercise prescription (usually as a percentage of the overall speed), but the intensity will vary between individuals. It is reliable, valid and interpretable, all important qualities for its use in clinical research[14] (Fig. 89.5).

Incremental shuttle walk test: The incremental shuttle walk test (ISWT) is a symptom limited, externally paced test, conducted along a 10 meter course (Fig. 89.6) and reflects maximal exercise capacity.[16] The walking speed increases every minute until the patient is too breathless or fatigued to continue or can no longer maintain the required speed. The result is presented as the total distance achieved. It

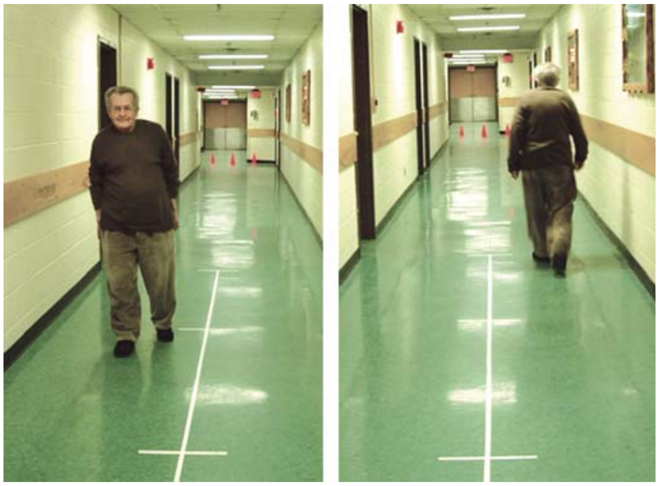


Fig. 89.5: Six-minute walk test

Note: This is carried out on a flat surface in a temperature and humidity controlled environment

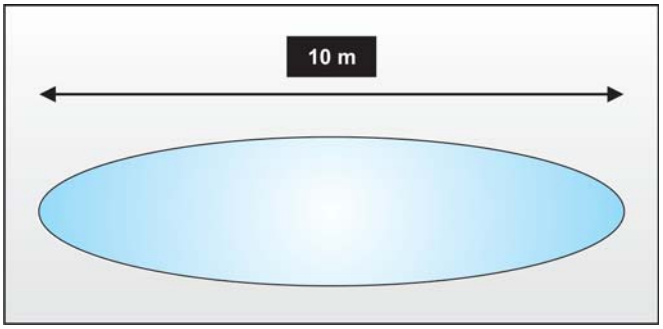


Fig. 89.6: Diagram of the shuttle walking course

is reproducible after a single practice test. In contrast to the six minute walk test the ISWT has a graded physiological response. However, normal reference values are not currently available. The test is also reliable, valid and interpretable,[16,17] making it an excellent evaluative test just like the 6MWT.

Endurance shuttle walk test: The endurance shuttle walk test (ESWT) was developed as a test of submaximal exercise capacity. It is similarly symptom limited, externally paced and uses the same 10 meter course as the ISWT.[18] After a two minute warm up, the patients walks at the set speed until they can no longer maintain the required speed or are too breathless or fatigued to continue. The result is presented as the time walked after the warm up and is reproducible after a familiarization test. The ISWT and ESWT can be used to develop individualized exercise prescriptions for pulmonary rehabilitation. The speed of the walk can be set at a high intensity (85% of the predicted peak oxygen consumption) derived from the ISWT distance. The duration of the walk can then be progressed throughout the program. Both the ISWT and ESWT are responsive outcome measures.

Health status: Health-related quality of life (HRQL) has become an important outcome for assessing chronic disease interventions. Most disease-specific questionnaires have components that assess dyspnea and activity limitation. The two most commonly used and therefore the best understood are the Chronic Respiratory Questionnaire (CRQ)[19] and St George's Respiratory Questionnaire (SGRQ).[20] They are both reproducible and evaluative, but the SGRQ has the advantage of also being discriminative. Generic questionnaires, such as the Medical Outcomes Short Form-36 Questionnaire (SF-36) can also be used. This has the advantage of being able to compare across different disease population and has normative values, but it is more discriminative than evaluative and may not identify small disease specific changes.

Dyspnea

The MRC scale is often used as an outcome measure for dyspnea. It is a valid, reproducible instrument, but not designed to be an evaluative tool. It is, however, a valuable guide to staging the severity of COPD. The Baseline Dyspnea Index and the Transition Dyspnea Index (BDI/TDI) are disease specific valid, reproducible and interpretable. Together with the SGRQ and the CRQ, the BDI-TDI is among the most frequently employed measures of outcome in PR.[21]

Clinical Important Difference

For many of the outcome measures described a "clinically meaningful" change has been evaluated. This adds to clinical interpretation of results from an intervention. A minimum clinically important difference exists for the 6MWT, ISWT, ESWT, CRQ, SGRQ and the BDI/TDI. If achieved, it provides a rationale for introducing or withdrawing a management intervention.

Core Components of a Pulmonary Rehabilitation Program

Core components of a pulmonary rehabilitation program are shown in Table 89.2.

Exercise Training

Exercise training is an essential component to pulmonary rehabilitation and has the largest supporting evidence base of all the other components.

Lower limb endurance training: Lower limb endurance training is mandatory for individuals who wish to improve exercise tolerance and reduce dyspnea on exertion. It is individually prescribed, based on an assessment exercise test and progressed throughout the program. High-intensity training is recommended in the healthy population for achieving cardio-respiratory fitness. Similar principles apply to patients with COPD and high-intensity training produces greater physiologic benefits than lower intensity training.[22] However, many are so constrained by dyspnea that they are often unable to achieve the ideal training intensity, but the highest

TABLE 89.2: Core components of a pulmonary rehabilitation program

- Exercise training
  – Lower limb endurance training
  – Lower and upper limb resistance training
- Multidisciplinary education
- Psychological support
- Self-management

intensity feasible should be the aim. The training schedule should detail the intensity, duration and frequency of training. Intensity can be prescribed from the cardiopulmonary exercise (CPX) test performed on a treadmill or a cycle ergometer, or from the various field tests. The training speed or load can be calculated from the measured (CPX) or predicted (field tests) percentage of peak oxygen consumption (typically 60 to 80% for high intensity) or from peak heart rate (similarly 60 to 80% predicted for high intensity).

An exercise session should last between 20–30 minutes. Walking and cycling are both effective training modalities. Although interval training has a good rational for allowing the symptoms to recover during the lower intensity periods, studies have not identified interval training as being more effective than constant load training for those with COPD.

Resistance training: Resistance (strength) training has received much attention over the last two decades and is recommended by international guidelines. Although muscle strength is improved compared to endurance training alone, this has not translated to additional improvements in exercise tolerance or health status. The effect of strength training on daily physical activity has yet to be thoroughly investigated. Ideally, resistance training should be individually prescribed, for example at 40 to 60% of the one repetition maximum, and progressed through the program. The studies advocating resistance training were performed on gym equipment (Fig. 89.7). Lower limb exercise often consists of sit to stand, step ups, leg raises, which can be progressed throughout the program, but these exercises have not been thoroughly evaluated. Ankle weights can also be employed to add resistance.

Upper limb resistance training is commonly performed using free weights and currently unsupported endurance exercises are recommended in the guidelines. There are theoretical reasons why improving upper limb strength may help dyspnea and activities of daily living, but the results of small studies so far are varied.[23] Nevertheless, most pulmonary rehabilitation programs include upper limb exercises.

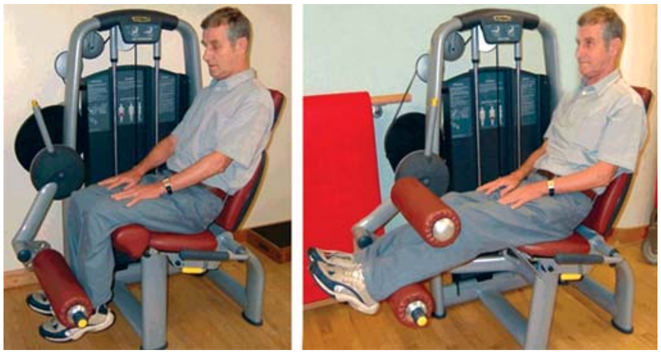


Fig. 89.7: Lower limb resistance training

TABLE 89.3: Example of topics for the education component

Multidisciplinary Education

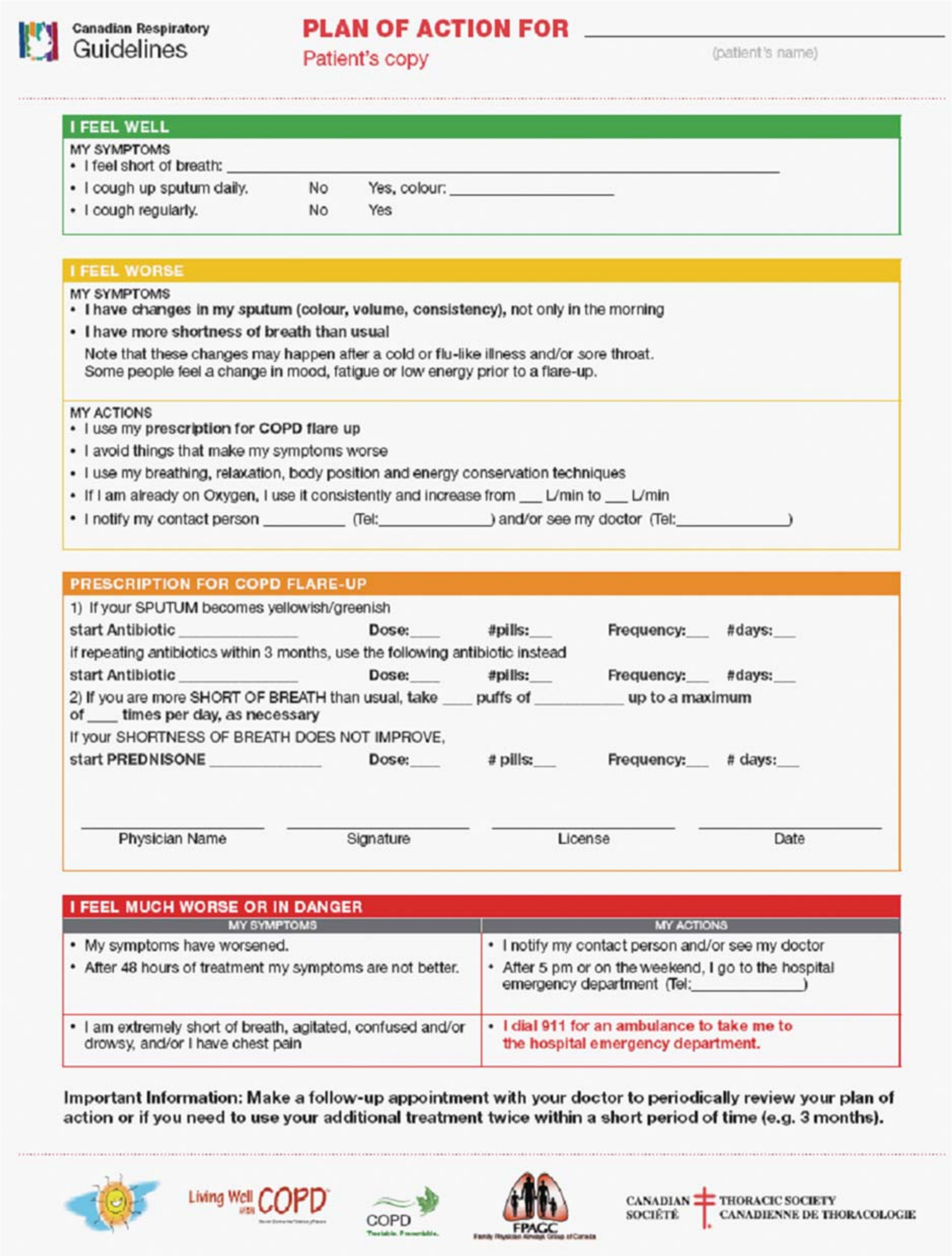
- Exercise
- Nutritional advice
- Relaxation
- Devices and oxygen therapy
- Benefits advice
- Energy conservation
- Travel
- Sexual intercourse advice
- Disease education
- Pharmacology

Multidisciplinary Education (Table 89.3)

It is widely accepted that education is a logical and necessary component of pulmonary rehabilitation, but less is known about which topics are essential. Examples of typical education topics are shown in Table 89.2. Education is commonly delivered in a group setting, but should be supplemented with individual support and other ongoing educational materials, such as computer-based and online learning modules. Psychological support is a core component of pulmonary rehabilitation as many patients experience symptoms of anxiety or depression. Psychological status should be first assessed using a standardized measuring tool, such as the Hospital Anxiety and Depression Scale (HADS).[24] Support is usually delivered by the rehabilitation team, but for some patients with more severe symptoms a psychologist is consulted. The process of pulmonary rehabilitation has been shown to improve low mood and reduce anxiety.[25]

Education—Self-management

Self-management can be taught within or outside of pulmonary rehabilitation.[26] It increases patients' involvement and control of their disease and improves their sense of well-being. It has been shown to reduce resource utilization, especially that attributable to unscheduled visits to the hospital. Patients learn to cope and react to their disease. With new skills of decision making, early symptom recognition and action plans (Fig. 89.8), patients are able to recognize and respond to respiratory exacerbations and avoid hospital admissions. Exercise, nutritional management and the correct administration of medications are all assisted by self-management education.



Canadian Respiratory
Guidelines

PLAN OF ACTION FOR ______________________

(patient's name)

Patient's copy

I FEEL WELL

MY SYMPTOMS

- I feel short of breath: ______________________
- I cough up sputum daily. No Yes, colour: ____________
- I cough regularly. No Yes

I FEEL WORSE

MY SYMPTOMS

- **I have changes in my sputum (colour, volume, consistency),** not only in the morning
- **I have more shortness of breath than usual**

Note that these changes may happen after a cold or flu-like illness and/or sore throat.
Some people feel a change in mood, fatigue or low energy prior to a flare-up.

MY ACTIONS

- I use my **prescription for COPD flare up**
- I avoid things that make my symptoms worse
- I use my breathing, relaxation, body position and energy conservation techniques
- If I am already on Oxygen, I use it consistently and increase from ___ L/min to ___ L/min
- I notify my contact person __________ (Tel:____________) and/or see my doctor (Tel:____________)

PRESCRIPTION FOR COPD FLARE-UP

1) If your SPUTUM becomes yellowish/greenish

start Antibiotic ____________ **Dose:**___ **#pills:**___ **Frequency:**___ **#days:**___

if repeating antibiotics within 3 months, use the following antibiotic instead

start Antibiotic ____________ **Dose:**___ **#pills:**___ **Frequency:**___ **#days:**___

2) If you are more SHORT OF BREATH than usual, take ___ puffs of _________ up to a maximum of ___ times per day, as necessary

If your SHORTNESS OF BREATH DOES NOT IMPROVE,

start **PREDNISONE** ____________ **Dose:**___ **# pills:**___ **Frequency:**___ **# days:**___

Physician Name	Signature	License	Date

I FEEL MUCH WORSE OR IN DANGER

MY SYMPTOMS	MY ACTIONS
• My symptoms have worsened. • After 48 hours of treatment my symptoms are not better.	• I notify my contact person and/or see my doctor • After 5 pm or on the weekend, I go to the hospital emergency department (Tel:____________)
• I am extremely short of breath, agitated, confused and/or drowsy, and/or I have chest pain	• **I dial 911 for an ambulance to take me to the hospital emergency department.**

Important Information: Make a follow-up appointment with your doctor to periodically review your plan of action or if you need to use your additional treatment twice within a short period of time (e.g. 3 months).

Living Well with COPD

COPD Treatable. Preventable.

FPAGC

CANADIAN THORACIC SOCIETY
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Fig. 89.8: Example of an action plan (*Source:* www.copdguidelines.ca)

Intensity and Duration of a Program

Intensity can refer to the intensity of the exercise prescription or the number of sessions per week. A minimum of three supervised sessions per week for six weeks are recommended, but due to recognized financial and time constraints, two supervised sessions with at least one other home session is acceptable. Additional home training alongside the supervised sessions should be commenced from the outset. There is ongoing debate about the optimum length of a program. Even very short programs (four weeks) can significantly improve exercise performance and the health-related quality of life, but longer programs (>12 weeks) may help sustain benefits. A minimum length of six weeks is recommended for the supervised program. As with many approaches to chronic conditions, the initial improvements will diminish in time in the absence of good adherence to the program guidelines.[9]

Maintenance

Follow-up and maintenance are required to sustain the benefits of pulmonary rehabilitation in keeping with the principles of long-term chronic disease management. A close relationship between primary and specialist care is also important as the majority of patients with COPD will be managed by their primary care physician or nurse practitioner.

As adherence to the exercise protocol decreases, the level of exercise achieved is often reduced. This is especially the case following a respiratory exacerbation.[27] There are many approaches to the frequency and location of the maintenance process, including whether it is necessary for this to be institutionally based or whether effective programs can be accessed through community centers. Repeat modified (short-term) programs result in similar short-term gains in exercise tolerance, but without an overall long-term benefit.[28]

Maintenance programs are modest in their effects[29] in part because they rely on behavioral changes to impact on lifestyle. In many health care systems cost is an obstacle, which makes any out of hospital solutions more attractive. Nevertheless, patients do discontinue pulmonary rehabilitation for a variety of social, motivational or medical reasons, including an acute exacerbation of COPD and intercurrent illnesses. Prediction of adherence is difficult, but it is likely that those who benefited little from the program will not subsequently maintain their exercise habits. Rolling programs have the advantage over fixed entry programs in that patients may enter or reenter at any time.

Oxygen

Supplemental oxygen during exercise may be required for safety reasons in those who exhibit profound desaturation. Under laboratory and field exercise conditions, oxygen can improve exercise performance by reducing the ventilatory requirements. However, the effects of training with supplemental oxygen have been variable[30,31] (Fig. 89.9). Carrying the weight of the

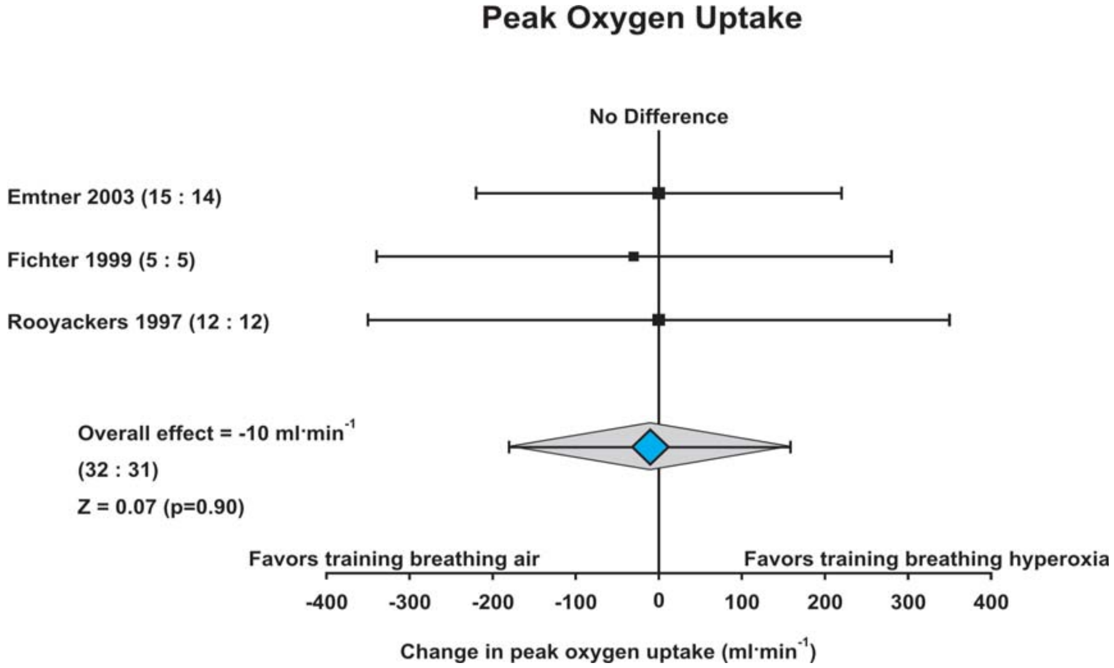

Fig. 89.9: Effect of training with supplemental oxygen

Note: The three studies included do not show evidence of change in peak oxygen uptake.[25,26]

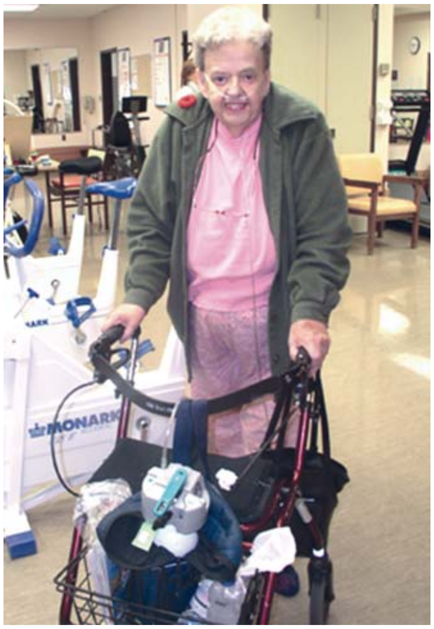

Fig. 89.10: Patient with rollator and oxygen

cylinder may negate any additional benefits. Although liquid oxygen is lighter to carry, it is expensive and not widely available.

Mobility Aids

Although walking sticks can improve balance and posture, rollators (Fig. 89.10) provide more stable support, improve balance and enable the user to sit comfortably on the seat provided. Rollators have been shown to improve walking distance especially among the more limited patients—unassisted 6MWD < 375 m.[32] These benefits are sustained if the patients continue to use the rollator at home.[33] Rollators also have the advantage of being able to carry oxygen or other small items, such as groceries.

The Rehabilitation Team

The multidisciplinary team should encompass the skills of respiratory physiotherapists, occupational therapists, nurses, assistants and physicians. It is often not possible to have the complete range of disciplines in person, but the skill set should be available. Team members should all have basic and intermediate life support skills and at least one member in the exercise sessions should have advanced life support skills. A minimum of one professional to eight patients is recommended. Experienced patients are a useful addition to the team, usually on a voluntary basis, and can provide further support to the patient group.

Quality Assurance and Audit

Programs should set up a regular audit to ensure that the results are in keeping with acceptable standards. Group aggregate data on walking distance and health status are frequently used. Feedback from patients can be collected by anonymous satisfaction questionnaire and data on compliance and dropout rates should also be recorded.

Setting

Pulmonary rehabilitation programs have been hospital based for stable disease both as in-patient and out-patient settings. There are limitations with this approach namely transport and accessibility. As in most countries, the provision of PR does not reach the demand, and community and home-based programs are sometimes available.[34,35] These alternate settings may be advantageous for patients still at work or wishing to avoid the difficulties of travel to a central site.

Exacerbations

Exacerbations are the real enemy of PR as all the components that improve with PR—dyspnea, exercise tolerance, muscle strength and health-related quality of life are all reduced following an acute exacerbation.[27,36,37] Many patients do not reach their preexacerbation level of functioning and clinical practice is of repeat referral for a shorter (booster) program. Currently most programs include patients with stable disease. There is some evidence that undergoing PR immediately post exacerbation is beneficial and not associated with adverse effects.[38] Targeting exercise therapy immediately post-exacerbation has a strong rationale, but whether morbidity can be improved in the long term needs to be investigated.

Performance Enhancement

Several approaches to enhancement have been evaluated. Calorie supplementation appears to help normal weight patients, but not those with cachexia.[39] Creatine supplementation has not been demonstrated to impact on exercise performance.[40] Anabolic agents are not currently recommended. Patients should be optimally pharmacologically managed prior to entry into PR and the addition of a long-acting anticholinergic has been shown to improve PR compared to placebo.[41]

Training Adjuncts or Strategies

These experimental strategies are included out of interest and to reflect the exciting ways in which exercise

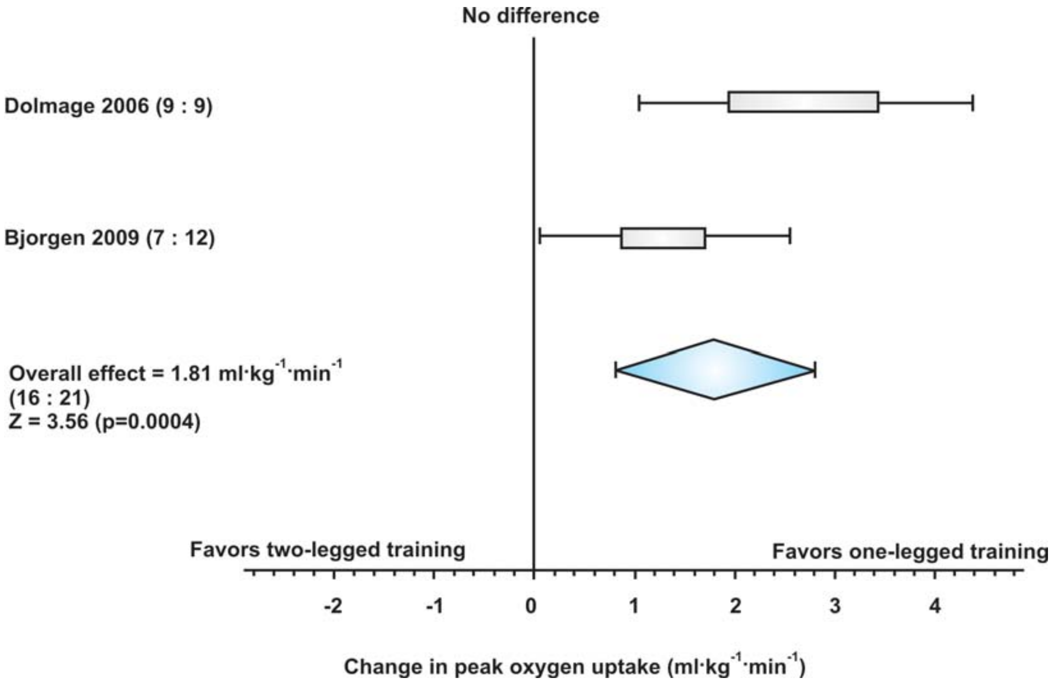

Fig. 89.11: Effect of one-legged training on peak oxygen uptake
Note: Improvement in peak oxygen uptake favors one-legged training.[41]

rehabilitation is challenging health care professionals to be creative. As ventilatory limitation is a major barrier to exercise training, the use of proportional assist ventilation (noninvasive ventilation), by means of a tight fitting mask, will improve endurance under laboratory conditions.[42] The use of a helium-hyperoxic mixture improves endurance time and enables a faster progression of training intensity, resulting in greater improvements in the health-related quality of life.[43] As helium is less dense, turbulence is reduced and laminar flow improved thereby reducing the work of breathing.

An approach that reduces the ventilatory load by limiting the muscle mass being exercised has generated considerable interest.[44] The reduced muscle mass reduces the amount of lactic acid. As the latter is buffered to release carbon dioxide, this reduction enables a lower ventilatory drive and therefore increases endurance. A training study has demonstrated that this is one of the few approaches to exercise training in COPD that will improve the peak oxygen consumption[45] (Fig. 89.11).

FUTURE WORK

Although much is known about the efficacy of short-term pulmonary rehabilitation, health care strategies are needed to ensure adequate access for the large population who stand to benefit from it. Pulmonary rehabilitation skills workshops especially when augmented by distance learning can assist with the dissemination of information required to develop small local programs. A clearer understanding of adherence requires an understanding of self-efficacy, behavioral adaptations and other determinant factors. Maintenance programs are necessary for comprehensive long-term management of chronic respiratory diseases, just as they are for nonrespiratory conditions. The frequency, content and duration of maintenance programs need to be better defined. Frequent exacerbations are likely to remain a large health care burden for patients with COPD and particular attention should be given to integrating exercise therapy early in the recovery period.

Pulmonary rehabilitation is an exciting field that has accomplished much over the last 25 years. Its growth and acceptance as mainstream management opens the way for further innovations.

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90

Upper and Central Airway Obstruction

VR Pattabhi Raman

INTRODUCTION

Upper Airway Obstruction (UAO) can be classified as acute and chronic, the causes for both are quite different. Chronic UAO poses a diagnostic dilemma, and is frequently misdiagnosed and managed as bronchial asthma. On the other hand, acute UAO poses a therapeutic challenge and is best managed in a well equipped setting that has physicians trained in difficult airway management.

Anatomical Considerations

Upper airways obstruction is defined as the obstruction of the airways at or proximal to carina, including the nose, mouth, pharynx and larynx.[1] The problems relevant to these areas are usually dealt by the otorhinolaryngologists, therefore, readers interested in details are advised to refer to otorhinolaryngology textbooks. Also, obstructive sleep apnea, an important disorder causing upper airway obstruction is dealt separately in this textbook. This chapter essentially focuses on disorders that cause obstruction between the vocal cords and the carina. Tracheal obstruction at the level of thoracic inlet, including in the vocal cords and the cervical portion of trachea is called extrathoracic UAO whereas the obstruction in the thoracic portion of trachea till the carina is called intrathoracic UAO. This distinction is helpful as the changes in the airway dynamics that happen during respiratory cycle are different in the two segments. The intrathoracic segment of trachea increases in dimension during inspiration and decreases during expiration whereas it is the opposite in the cervical trachea and the airways above. The pressure that affects the caliber of upper airways in the extrathoracic region is atmospheric pressure (Fig. 90.1) and the intrathoracic pressure is the pleural pressure.[2] It is therefore, easy to imagine how narrowed (extrathoracic) upper airways cause snoring, which is typically associated with inspiratory collapse of the airways.

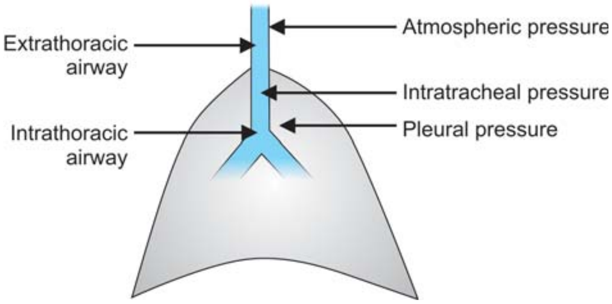


Fig. 90.1: Pressure affecting upper airways (Modified from JC Acres, MH Kryger. Clinical significance of pulmonary function tests: upper airway obstruction. Chest. 1981; 80:207-11)

Physiological Considerations

The classification of UAO on the basis of the anatomical landmark, i.e. the thoracic inlet has also got physiological significance and helps in the understanding of the differences that one sees when one assesses the flow-volume loops of extrathoracic and intrathoracic obstruction. Also, the nature of obstruction, whether it is stiff or pliable, determines whether there will be changes in severity in relation to changes in the transmural pressure. A stiff lesion as in some cases of postintubation tracheal stenosis, does not allow dynamic differences in the diameter of the stenosis and in the airflow between inspiration and expiration.[2] This is called fixed airway obstruction. In cases of bilateral abductor palsy of vocal cords, there are differences in the caliber and the airflow during the respiratory cycle. Because of the extrathoracic nature of the obstruction, inspiration worsens and expiration lessens the obstruction. This is an example of variable airway obstruction. Based on these parameters, UAO can be divided into fixed obstruction, variable extrathoracic obstruction and variable intrathoracic obstruction.

Clinical Features

Acute airway obstruction usually has a dramatic presentation and seldom poses a diagnostic challenge. It usually presents as severe breathlessness and agitation. Stridor is the usual diagnostic sign. Stridor is frequently audible unaided and stethoscope is seldom required.

Chronic obstruction is frequently misdiagnosed and managed as asthma and/or Chronic Obstructive Pulmonary Disease (COPD) for a variable period of time before the recognition of upper airway problem. The patient may also present very late in the course of the disease. The presence of stridor in UAO means a fairly severe narrowing. It has been known for almost four decades that tracheal lumen of less than 8 mm produces symptoms after exercise[3] and of less than 5 mm produces stridor.[4] High index of suspicion is usually required in chronic UAO. Diligent history-taking including the history of intubation and of thyroid surgery could serve as a clue. Many cases of chronic UAO have periods of worsening, which get better with antibiotics and steroids, further delaying the diagnosis. Certain features, such as hemoptysis, and relative refractoriness to asthma treatment should alert the physicians about the possibility of UAO and the need for further investigations.

Diagnosis

Radiology

Plain X-ray is seldom useful. It may show obvious mediastinal lymphadenopathy or sometimes a tracheal tumor with extramural extension. At times, the penetrated film may show the site of obstruction.

Computed Tomography (CT) is very valuable to diagnose airway obstruction. In particular, the reconstructed images (Fig. 90.2) provide relevant details about the site, the extent and the nature of obstruction. The diameter at the most narrow portion and the length of the stenosis are critical details that are required to plan treatment. The present generation multiplanar CT provides this information in a very short time. Some patients with very severe stenosis may not be able to lie down flat and hold their breath for the study. Magnetic Resonance Imaging (MRI) is not very commonly sought. It may give valuable information by its superior contrast resolution.

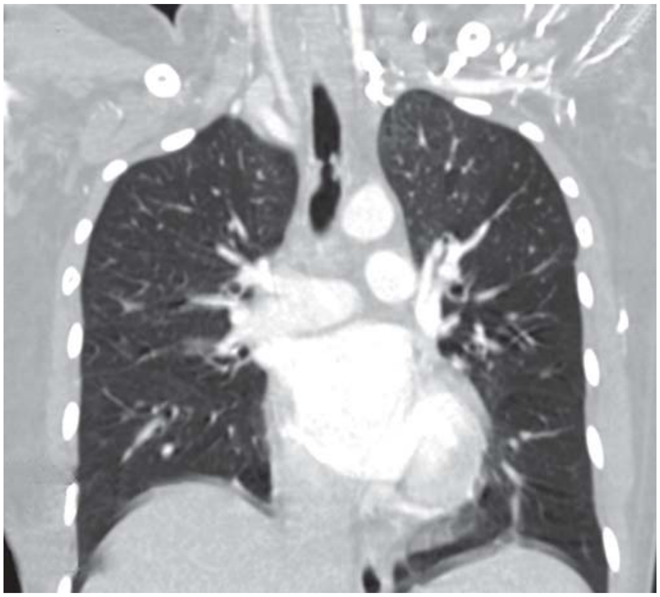


Fig. 90.2: Reconstructed CT image of a patient with tracheal stenosis

Spirometry

In normal subjects, during a forced expiration from Total Lung Capacity (TLC), the maximum airflow is achieved during the first 25% of the Vital Capacity (VC), which is directly dependant on effort and inversely to the resistance. In the remaining 75%, the flow is limited in such a way that an increase in effort (and the associated increase of pleural pressure) does not result in increased flows.[3] With UAO, flow at higher lung volume may be limited by obstruction. UAO causes more pronounced decrease in Peak Expiratory Flow (PEF) than in the FEV_1.[5] Therefore, an increased ratio of FEV_1 (ml) divided by PEF (L/ml) can alert the clinician to the need for an inspiratory and expiratory flow-volume loop.[6] This ratio is called as Empey's Index, the value of more than eight suggest the presence of central or upper airway obstruction.[7] Poor initial effort by the patient can also increase the index. Hence, it is very important that the patient's inspiratory and expiratory efforts are maximal

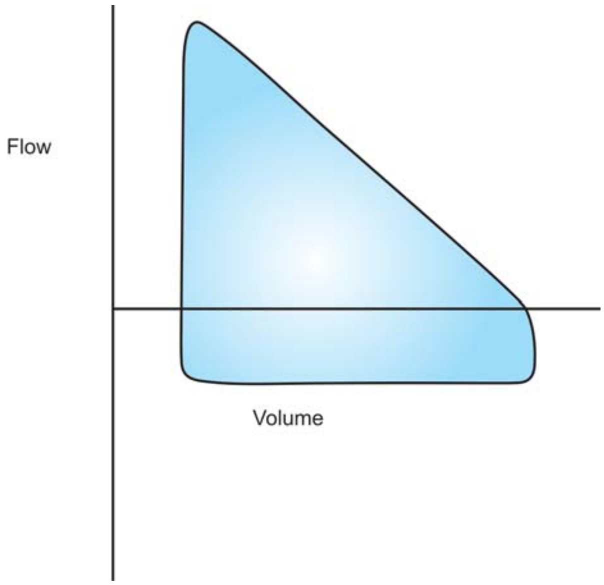


Fig. 90.3A: Variable extrathoracic obstruction

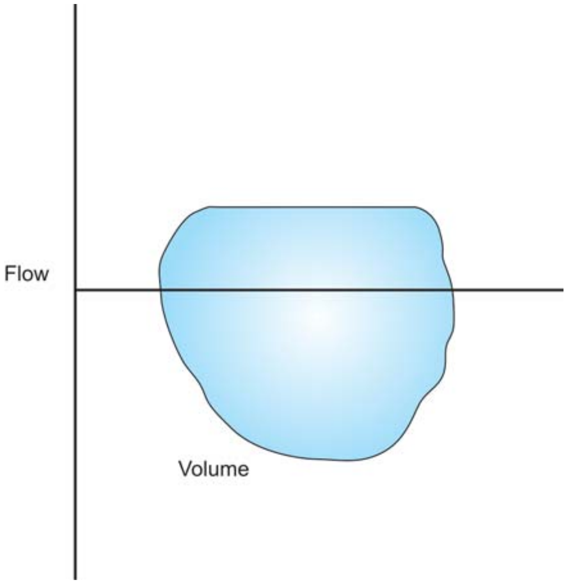


Fig. 90.3B: Variable intrathoracic obstruction

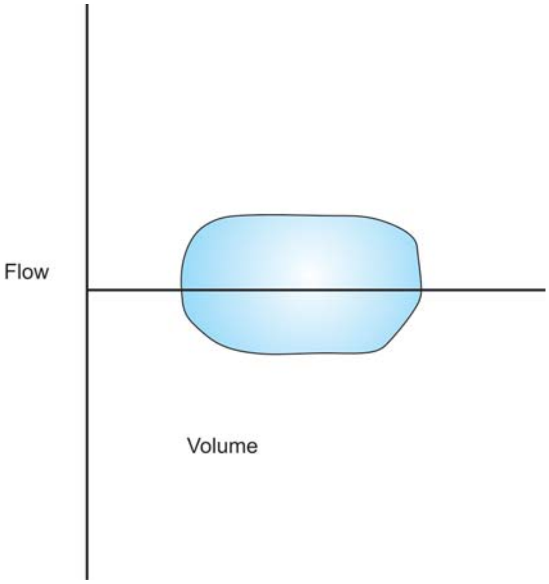


Fig. 90.3C: Fixed airway obstruction

Figs 90.3A to C: Flow-volume loop in UAO (Adapted from Miller and Hyatt. Obstructing lesions of the larynx and trachea: clinical and physiologic characteristics. Mayo Clin Proc. 1969; 44:145-61)

and the technician should confirm this in the quality notes.[5]

Flow-Volume Loop

Miller and Hyatt[8] did elegant experiments by simulating UAO in normal subjects and found that flow-volume loop would be particularly useful in diagnosing and categorizing UAO.[5] When patient's effort is good, the pattern of repeatable plateau of forced inspiratory flow, with a preserved expiratory flow loop indicates variable extrathoracic UAO (Fig. 90.3A), while the pattern of repeatable plateau of forced expiratory flow along with a preserved inspiratory loop indicates variable intrathoracic UAO (Fig. 90.3B).[5] The pattern of repeatable plateau at a similar flow in both forced inspiratory and expiratory flows suggests a fixed UAO (Fig. 90.3C).[5] The absence of classic patterns does not rule out UAO. The presence of specific UAO patterns would also warrant confirmation of the presence of UAO, hence bronchoscopy is required as the next important step.

Bronchoscopy

Bronchoscopy, which provides the most useful information in UAO, is the procedure of choice. It is useful to have an idea about the lesion with a CT done before bronchoscopy so that planning could be better. The cause of the anatomical obstruction can be diagnosed in the case of an intramural pathology like a tumor. Care however has to be taken while passing a flexible bronchoscope through a very narrow lumen, since even a minor hemorrhage can become catastrophic by causing critical airway narrowing. It is wise to employ rigid bronchoscopy in such a case of severe obstruction. During rigid bronchoscopy, ventilation can be done during the procedure and therefore, oxygenation is easy. Moreover, the larger bore of the rigid barrel allows the passage of instruments simultaneously, and procedures like biopsy can be safely done. Also, the barrel of the bronchoscope could be used to tamponade bleeding points and to mechanically dilate the tracheal stenosis. Another significant advantage of rigid bronchoscopy is the deployment of silicone stents, making it the investigation of choice in severe upper airway obstruction.

In cases of extrinsic obstruction, bronchoscopy could be valuable in assessing the mucosa, if there is a transmural invasion. It also helps in assessing the extent of involvement to guide a definitive therapy. In the cases of functional obstruction, such as in tracheomalacia, bronchoscopy is mandatory. Here, flexible bronchoscopy scores over the rigid bronchoscopy to identify abnormal airway dynamics during respiration would mandate an awake and cooperative patient on the table, which is not possible in an anesthetized patient undergoing rigid bronchoscopy.

ACUTE UAO

Foreign Body

Typically seen in children aged between 2 and 4 years, aspiration of foreign bodies can be also seen in older children and the elderly individuals. In the elderly patients, it commonly occurs in the presence of comorbidities with depressed consciousness and poor swallowing reflex.[9] In pediatric population, choking is the most common symptom followed by a protracted cough.[10] There is a male preponderance and more often when there is an elderly sibling. No predilection between right and left bronchial tree is seen, at that age the bronchial division makes a similar angle on both the sides. History may not be forthcoming in all cases and high index of suspicion is required.[11] Radiography is useful only in the case of radiopaque foreign bodies or when there is expiratory hyperinflation.[10] Normal chest X-ray does not exclude foreign body aspiration. Early intervention is important especially when vegetable matter like groundnut or bean is aspirated since granulation happens rather rapidly and at times so profusely that it may not be visible in bronchoscopy.[12] Also, delayed removal may not result in complete healing of the granulation tissue. Groundnut is probably the most common foreign body among children in India.[11] Though rigid bronchoscopy is considered the gold standard for the retrieval of an aspirated foreign body, there is a definite role for flexible pediatric bronchoscopes for both diagnosis and retrieval of pediatric foreign bodies.[13-15]

Acute Laryngeal Edema

Acute laryngeal edema may happen following anaphylactic reactions causing life-threatening angioedema, prototype being the penicillin allergy or Nonsteroidal Anti-inflammatory Drugs (NSAID) allergy in aspirin-sensitive asthma. The deterioration is rapid and early intervention is crucial. Parenteral administration of adrenaline can be life saving.

This has to be distinguished from a rare autosomal dominant condition called hereditary angioedema. This condition happens secondary to deficiency of C1 inhibitor enzyme due to mutations of its gene.[16] Localized swelling that is self limiting, can happen at any site of the body including the skin, genitalia, and the gastrointestinal tract. The angioedema is life threatening when it happens in the larynx, especially if untreated.[17] The attacks are not precipitated by allergy, but by trauma and stress.[17] The age of presentation is variable. Prophylaxis is useful if started early (with tranexamic acid) or attenuated with androgens like danazol.[18] In patients refractory to prophylaxis of danazol, pasteurized plasma-derived C1 inhibitor (pC1-INH) concentrate has been found to be useful in reducing the recurrence.[19] In acute attacks, pC1-INH concentrate (intravenous dose of 20 U/kg) and newer drugs like Icatibant, bradykinin receptor-2 antagonist (30 mg subcutaneous injection) have been shown to provide rapid relief.[20,21]

Another important cause for nonallergic laryngeal edema is the administration of Angiotensin-converting Enzyme Inhibitors (ACEI) which, like hereditary angioedema is not associated with itching or urticaria.

Prompt recognition and stopping the drug will stop the recurrence. Recent studies have described the increased incidence of angioedema in renal transplant recipients receiving a combination of ACEIs and mTOR inhibitors.[22]

Infection

Infection as a cause of acute UAO typically occurs in children. This may include infections, such as acute epiglottitis caused by either *Haemophilus influenzae* or beta-hemolytic streptococci and Ludwig's angina characterized by a rapidly progressing cellulitis involving submandibular space. The treatment involves rapid airway stabilization, antibiotics and surgical drainage of the pus.

Viral croup often caused by parainfluenza virus, is managed by nebulized adrenaline and parenteral corticosteroids. Bacterial tracheitis is usually caused by *Staphylococcus aureus* infection. Bronchoscopic appearance shows the presence of erythema, edema, thick secretions and at times, plaques in the trachea.

CHRONIC UAO

Vocal Cord Dysfunction

This is a syndrome in which the vocal cords adduct during inspiration producing upper airway obstruction like features. Patients are usually females in the age group of 20 to 40 years.[23-25] It masquerades the diagnosis of refractory asthma with multiple attacks, is usually managed as asthma. In an Indian study that evaluated difficult to control asthma, vocal cord dysfunction was seen in about 23.5%, and also frequently found to coexist with asthma.[26] A recent review described exercise, psychological stress, irritants, rhinosinusitis, gastroesophageal reflux disease as the usual triggers.[27]

The "wheeze" typically appears at lower lung volumes since the obstruction happens during the inspiration and for the same reason, the chest X-ray does not show hyperinflation. Spirometry done during the episode may show the classical loop of extrathoracic UAO. Flexible laryngoscopy is considered the gold standard for diagnosis, especially when done during the episode. The classical description during the inspiration consists of adduction of the vocal cords, with a small diamond-shaped chink in the posterior region of the vocal cords. Reassurance and breathing exercises may reduce the intensity during the acute episode and interestingly, rapid shallow breathing (like panting) has been found to be useful.[28] Speech therapy, psychological counseling and avoidance of triggers would help in long-term management.

Tracheobronchomalacia

Tracheomalacia (TM) refers to the weakness of tracheal walls, frequently due to reduction and/or atrophy of the longitudinal elastic fibers of the pars membrane; or cartilage integrity, such that the airway is softer and more susceptible to collapse.[29] Tracheomalacia may be localized or diffuse and usually affects intrathoracic portion of trachea. If main bronchi are also involved, it is called tracheobronchomalacia (TBM).

Pediatric TM

TM is the most common congenital abnormality of trachea.[30] There is a strong association with prematurity,[31] mucopolysaccharidosis and tracheoesophageal fistula,[29] and some congenital heart diseases.[29] There is a male preponderance. Acquired causes include long-standing tracheostomy, and pressure from vascular slings. Congenital TM is usually self limiting and the children outgrow the disease by the age of 2–3 years. Severe cases are managed by the use of Continuous Positive Airway Pressure (CPAP), or by surgical procedures like aortopexy.[32]

Adult TM and TBM

There is an increased awareness in recognizing and implicating TM as an important cause for pulmonary symptoms. This can be attributed to the advances in CT technology and virtual bronchoscopy, increasing availability of bronchoscopes and of better therapeutic options.

TM in adults is predominantly seen in the middle-aged male individuals who are also smokers. Adult cases most commonly happen following the trauma, including after intubation, tracheostomy, external chest trauma, and after lung transplantation. Emphysema, chronic bronchitis, chronic inflammation like relapsing polychondritis, and chronic extrinsic compression of the trachea are the other important reasons.

Acquired tracheomalacia is commonly seen in association with long-term intubation and tracheostomy. It is usually a short segment stenosis. A comprehensive in depth review on tracheomalacia describes that the length of malacic segment secondary to postintubation in usually less than 3 cm.[29] More than 50% decrease in airway caliber occurring during expiration is diagnostic of TM. Three types are described:[29]

1. Saber-sheath type (Ω)—lateral wall narrowing
2. Scabbard type (◠)—AP narrowing-crecentic type
3. Circumferential type (O)—all round narrowing.

The TM secondary to COPD is usually diffuse, and also, difficult to treat. The patient presents with symptoms such as cough, dyspnea and wheeze. Dynamic CT, which is noninvasive, is useful for diagnosis. The multidetector CT technology shows very good promise.[33]

Symptomatic cases need to be treated depending on the etiology. Focal TM in postintubation or post-traumatic cases should be respected, if possible. Alternatively, it can be managed with tracheostomy, if the segment can be bye-passed. The advantages of tracheostomy in such a situation is that the tube acts like a stent. Long flange tracheostomy tubes are available for the purpose. The tracheostomy can also be an interface for CPAP application. However, tracheostomy can also predispose to tracheomalacia of a different segment of trachea.

In TM secondary to COPD, the optimization of medications for COPD can help reduce symptoms. Severe cases can be managed with silicone stents. However, it is not effective in all patients and there is a high chance of migration of these stents. Metallic stents should be avoided because of the difficulty of removal and replacement. Different surgical means have been tried. Strengthening the posterior membranous portion using various prostheses like crystalline polypropylene mesh, has been tried with variable success.[34]

Polychondritis

Relapsing Polychondritis (RP) is a rare and interesting disease. It is a multisystem disorder with unknown etiology, characterized by recurrent progressive inflammation and degeneration of the cartilage and the connective tissue.[34] RP affects people between 2 and 80 years of age and has equal gender distribution. The airway complications in about 50% of the cases, are seen more often in females than in males, and carry a poorer prognosis.[35-37]

Diagnostic Criteria

Criteria for the diagnosis of RP were described initially by McAdam and associates.[36]

Presence of three or more of the following criteria are employed for diagnosis:

1. Chondritis of larynx, trachea or bronchitis
2. Chondritis of nasal cartilages
3. Chondritis of both auricles
4. Audiovestibular damage (Sensory-neural hearing loss, tinnitus and vertigo)
5. Ocular inflammation
6. Nonerosive seronegative inflammatory polyarthritis.

The criteria were modified by Dammantt and Levine[38] to include histological features and therapeutic responses. The modified criteria include the presence of any one of the following combinations:

1. Three or more of McAdam's criteria (No tissue confirmation needed).
2. One or more of McAdam's criteria with positive histological confirmation by biopsy of the cartilage.
3. Involvement of two or more separate anatomic locations with response to steroids and/or dapsone.

Clinical Features

Clinical features depend on the cartilage that is involved. It is important to understand that apart from cartilaginous structure of the external ear, nose, peripheral joints, larynx and tracheo bronchial tree, other proteoglycan-rich structures can become involved, including the heart, blood vessels and inner ear.[39]

Airway Complications

The prevalence of symptomatic airway involvement was reported in 21% with female preponderance in about 70% patients.[37] The usual symptoms were progressive dyspnea, cough, stridor, hoarseness, chest discomfort and features of respiratory failure. The presence of airway symptoms were the first manifestation of RP is about 50% of patients with airway manifestation. Airway obstruction in RP can occur due to any of the following:[40]

1. Acute airway inflammatory swelling and airway narrowing.
2. Tracheobronchomalacia—due to progressive destructions of the cartilage.
3. Formation of fibrous tissue and cicatricial contraction at a later stage.

Investigations

Pulmonary function tests show mixed pattern.[37] Dynamic CT scan and bronchoscopy (Fig. 90.4) provide the vital details in RP regarding the extent and severity of the airway problem. Typical CT findings include the presence of diffuse tracheobronchial stenosis (better seen with reconstructed CT images), dynamic expiratory collapse or anterior bronchial wall thickening with posterior sparing. Typical bronchoscopic findings include supraglottic and false vocal cord edema, subglottic stenosis or tracheomalacia.[37]

Treatment

Many medications, such as the steroids, mycophenolate mofetil, methotrexate and dapsone have been tried, but the response to treatment is variable. Newer biological agents like rituximab, etanercept and abatacept show

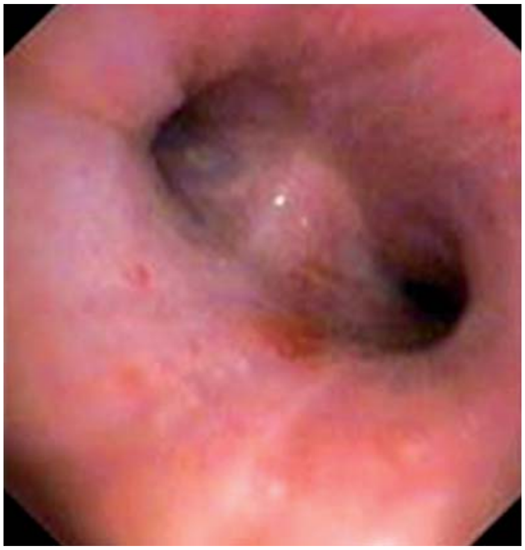


Fig. 90.4: Relapsing polychondritis. Fifty-year-old lady: Biopsy proven relapsing polychondritis. Note the absence of cartilage prominence at the level of distal trachea

some promise. Bronchoscopic techniques, such as balloon dilatation, and tracheobronchial stenting used alone or in combination might give some respite from symptoms for patients with airway complications.[41] Interventional procedures provide a good short term relief. However long-term outcome is quite variable.

Tracheopathia Osteochondroplastica (TPO)

It is a rare, slowly progressive disorder of unknown etiology. Endoluminal projections of bony and cartilaginous nodules arise from the submucosa of the trachea. There appears to be a male predominance and usually presents in the sixth or seventh decades of life.[42] The nodules characteristically spare the posterior membrane (Fig. 90.5), but may be present in the proximal, main bronchi also. The presentation is usually with chronic cough, dyspnea in advanced cases and minimal hemoptysis due to the ulceration of the overlying mucosa.[43] Diagnosis is based on typical bronchoscopic appearances, biopsy is not generally needed .There is no definitive treatment. Severe obstruction may warrant therapeutic interventions.

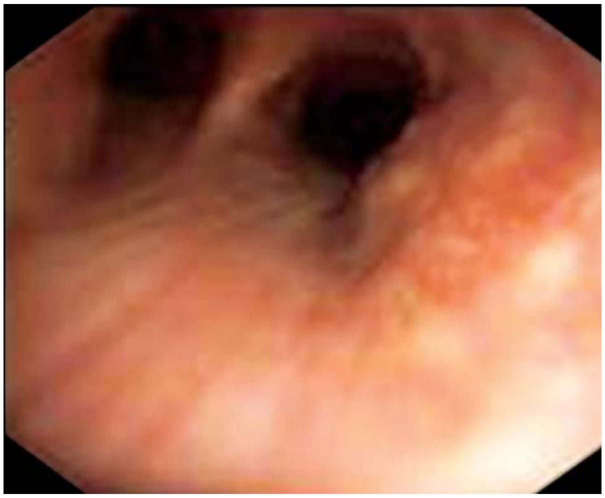


Fig. 90.5: Case of tracheopathia osteochondroplastica. Note the nodules seen only on the cartilaginous portion of trachea and sparing of membranous portion

Tracheobronchial Amyloidosis (TBA)

TBA is very rare, characterized by endoluminal accumulation of abnormal proteins in the form of fibrils, which cause obstructive symptoms. In a retrospective review of 17 biopsy proven TBA over a 26-year period, Capizzi and colleagues from Mayo Clinic described dyspnea, cough, hemoptysis and hoarseness as presenting symptoms.[44] Diagnosis is made by bronchoscopy and biopsy with specific congo red staining. Response to medications like steroids and melphalan are suboptimal, severe obstruction warrant debulking.

Tuberculosis (TB)

Endobronchial TB is not an uncommon problem in the developing world. The true incidence in patients with sputum-positive pulmonary tuberculosis is difficult to estimate because bronchoscopy is usually avoided. Endobronchial tuberculosis is seen more commonly in females, perhaps because they tend to retain the infected secretions in the bronchial tree and avoid expectoration. It is also more common in the left than the right side bronchi probably because the left main bronchus is narrow and lengthy and hence the infected sputum may remain in contact with the bronchi for a longer time. Since the infected sputum cannot remain in the trachea, endotracheal tuberculosis (Fig. 90.6) is very rare, but presents a formidable challenge to the treating clinician. The disease is quite refractory to chemotherapy alone. Chung and Lee classified endobronchial TB into seven types based on the bronchoscopic appearance: [45,46]

- Active caseating
- Edematous-hyperemic
- Fibrostenotic
- Tumorous
- Granular
- Ulcerative and
- Nonspecific bronchitic

Once the lesion becomes fibrostenotic, which is a final path for all the types, it becomes resistant to therapy.

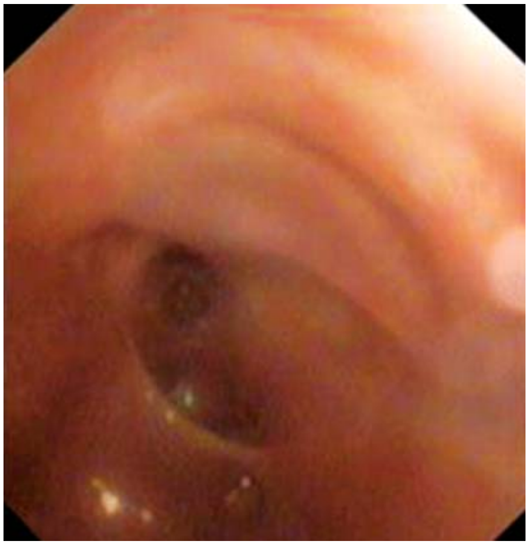


Fig. 90.6: 21-year-old lady known case of sputum-positive pulmonary kochs developed severe respiratory distress despite therapy. She had endotracheal fibrostenosis in distal trachea, which was dilated

Hence, early identification by bronchoscopy is encouraged in a suspected patient. Suspicion arises if a patient with TB develops wheeze or breathlessness. Surgery is ideal if the involved segment is small. If the disease is extensive, balloon dilatation or thermal desobstruction followed by silicone stenting can be tried.[47]

Sarcoidosis

As in tuberculosis, an airway abnormality in sarcoidosis is often overlooked. Endobronchial involvement is usually seen in the elderly age groups, smokers during advanced stages of parenchymal involvement and with thickening of bronchovascular bundles on high resolution computed tomography. It carries a relatively poorer prognosis.[48] Flow limitation is seen in about 9% of patients with sarcoidosis.[48] Sarcoidosis can affect every part of upper airway. Sarcoid involvement of the supraglottic airways, larynx, and central and peripheral airways is also described.[49] Obstructive sleep apnea syndrome is seen more often in patients with sarcoidosis, especially lupus pernio.[50]

Tracheal obstruction secondary to sarcoidosis is very rare. After an early case in 1981, not many reports of tracheal obstruction have appeared.[51] The classic endobronchial sarcoidosis is characterized by mucosal islands of waxy yellow mucosal nodules, measuring 2 to 4 mm in diameter.[49] The nodules are sparse in the trachea, but abundant in the main, lobar and segmental bronchi. Other changes are mucosal erythema, granular mucosa, cobblestone mucosa, mucosal plaques, bronchial stenosis, airway distortion due to cicatricial changes in parenchyma, bronchiectasis, extrinsic compression due to mediastinal lymphadenopathy or airway hyper responsiveness.[49]

Tracheal Stenosis

Tracheal stenosis is an important cause of upper airway obstruction. It may happen secondary to trauma to trachea, following prolonged intubation, i.e. post-intubation tracheal stenosis (PITS) and after tracheostomy, i.e. post-tracheostomy tracheal stenosis (PTTS). Idiopathic stenosis is rare.

Mechanical ventilation has made a great difference in the outcome of many sick patients with respiratory failure, but the use of endotracheal tube have resulted in a group of diseases that have become more common than before. Despite the use of low pressure cuffs, which have reduced the incidence of tracheal stenosis significantly, the incidence of PITS and PTTS is high, i.e. 0.6 to 21%.[52-57] It is seen predominantly in females, presumably because of smaller tracheal lumen and hence, prone to injury.[52,53,58,59]

Classification

Brichet and colleagues[60] classified the postintubation tracheal stenosis based on bronchoscopic appearance into three types:

1. *Web-like membranous stenosis:* A short segment (<1 cm) concentric stenosis with no cartilage damage (Fig. 90.7A).
2. *Pseudoglottic stenosis:* "A" shaped stenosis secondary to lateral impacted fracture of cartilage in patients following tracheostomy. Since the stenosis resembles a vocal cord, it is called pseudoglottic stenosis (Fig. 90.7B).
3. *Complex stenosis:* It includes all other varieties, including extensive (>1 cm), circumferential hourglass-like contraction scarring or malacia. Basically, there is a cartilage damage along with the narrow lumen (Figs 90.7C and D).

The membranous and complex types are most common.

Pathogenesis

Usage of high cuff pressure in an intubated patient predisposes to mucosal ischemia, which also worsens in the presence of hypotension when the capillary pressure is lower. Pressure necrosis and chondritis result, which lead to either the development of cicatricial tissue and

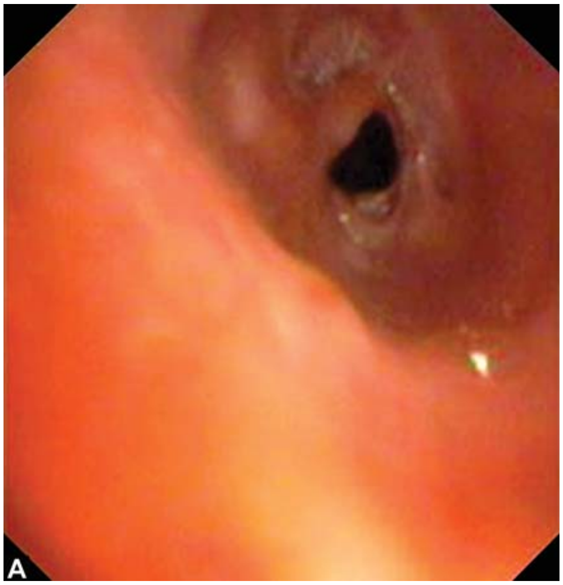


Fig. 90.7A: A 24-year-old lady, postintubation with membranous stenosis

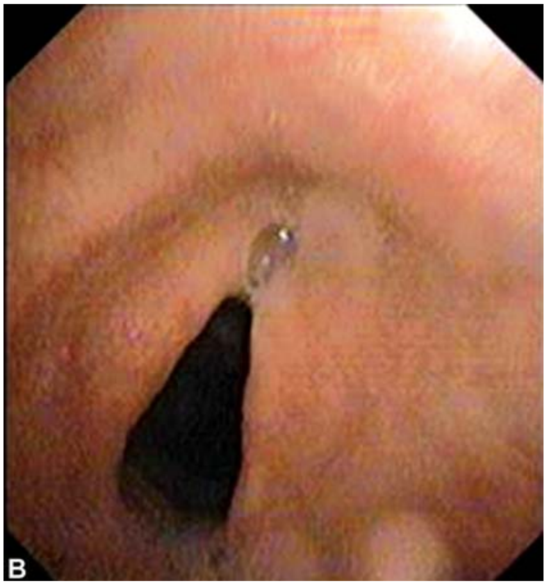
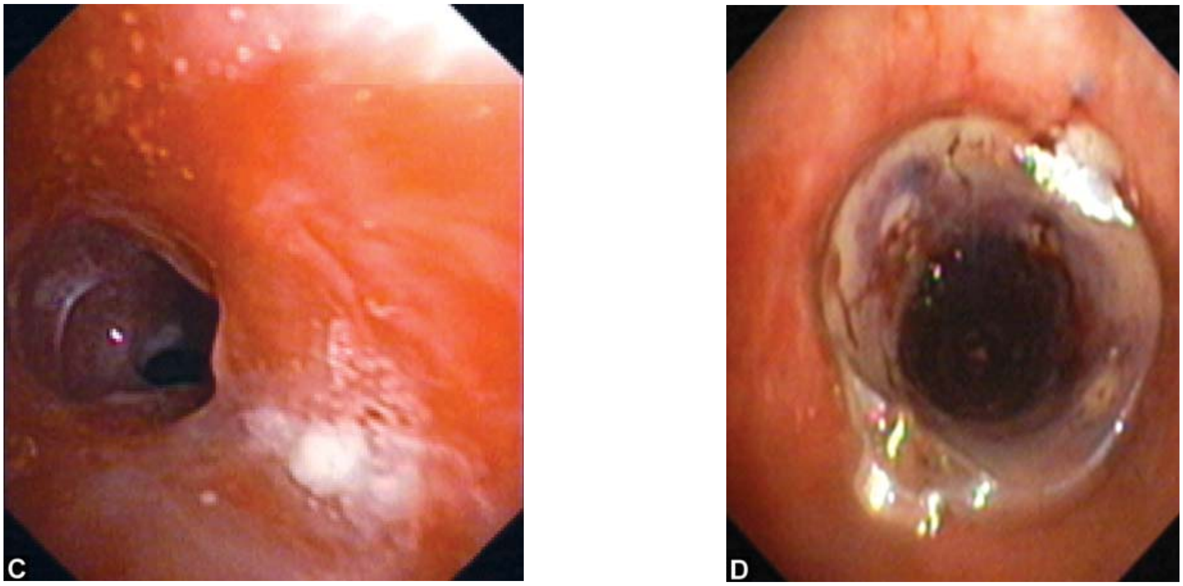


Fig. 90.7B: Example of pseudoglottis stenosis. There is a remarkable resemblance to vocal cords



Figs 90.7C and D: Complex stenosis. A complex stenosis involving more than one cartilage, managed.These patients are typically managed by dilatation followed by silicone stenting.

(*Courtesy:* Dr Ravindra Mehta, Bengaluru)

membranous type of stenosis or to the cartilage damage and weakening causing a complex stenosis.

Stenosis usually develops at the site of the cuff, though the distal end of the tube, because of the repetitive injury, may also be involved. In post-tracheostomy stenosis, stoma of the tracheostomy is an additional site for stenosis. Stenosis caused by percutaneous tracheostomy occurs earlier and subglottic in nature when compared to that caused by surgical tracheostomy.[56]

Management

Management of tracheal stenosis depends on the type of stenosis, presence of comorbidities, functional status of the patient, and the length of the stenosis. While surgical tracheal sleeve resection is a permanent solution considered the gold standard, it carries 3% mortality in trained hands. A multidisciplinary approach incorporating both surgical and bronchoscopic techniques is preferably employed.[60]

Bronchoscopic Management

Bronchoscopic management is sufficient in a majority of cases of membranous stenosis and can be very useful as either a stand-alone therapy or as a bridge to surgery in very sick patients. Bronchoscopy is used both for achieving and maintaining an effective lumen. Some of procedures to tackle membranous stenosis can be done with a flexible bronchoscope, but it is important that the bronchoscopist is trained in rigid bronchoscopy as well. Better ventilation, better control of secretions and of bleeding during the procedure and more importantly, the option of deploying silicone stents makes rigid bronchoscopy the procedure of choice.

The general recommendation by the FDA is to avoid metallic stents for such benign causes of tracheal obstruction.[61] Since the stent placement for benign lesions (PITS being the prototype) is usually temporary, it is customary to remove the stent and assess after 12 to 18 months of deployment to see the tracheal function effectively without the stent. Deploying metal stents is easy, can be done through flexible scope and can be done with little training, hence very popular. However, removal of stent after it is deployed is a messy affair. It cannot be removed in toto, needs trained physician with rigid bronchoscopy skills. Hence, a silicone stent is the standard choice for supporting stenosis secondary to cartilage weakness.

In membranous stenosis, stent is not required after dilatation since the cartilage is not involved, and the stability of airway is not affected. In complex stenosis, however, the underlying cartilage is damaged and collapsible. Therefore, despite achieving a good lumen by bronchoscopic means, it has to be followed by leaving a stent at the end of procedure.

Managing patients with tracheal stenosis is all about two important components: (i) to achieve an effective lumen, and (ii) to maintain the lumen:

i. *Achieving effective lumen:* Many techniques are described, which are broadly classified as mechanical or thermal. Dilatation using rigid bronchoscope-barrels of increasing diameters, dilators, balloon dilatation and making nicks in the membrane using rigid scissors are some of the techniques. Laser and electrocautery can be used to cut the membranes with Mercedes Benz incisions, which are mucosa sparing. They prove to be curative in about 65% cases when repeated up to three times.[62]
ii. *Maintaining the lumen:* For membranous stenosis, achieving an effective lumen would suffice. However, in complex stenosis, because of cartilaginous weakness, achieving effective lumen shall usually be followed by silicone stenting.

It is important to realize the importance of being gentle with the airways since the best approach to tracheal stenosis is to prevent its occurrence. Using appropriate cuff pressures and using noninvasive ventilation when indicated are important considerations. Newer endotracheal tubes that do not have cuffs and have ability to mould to the shape of the intratracheal airways have been tested in animals and show good promise in reducing tracheal injury.[63]

Idiopathic Tracheal Stenosis

Idiopathic tracheal stenosis is a rare condition. It is seen almost exclusively in females, involves the upper trachea, predominantly, the immediate subglottic portion.[64] Many causes have been proposed, it may represent some form of fibromatosis.[64] Immunohistochemical staining for estrogen receptors is usually positive. Gastroesophageal reflux disease is seen in about a third of cases. Usual treatment consists of dilatation, tracheostomy or if feasible, resection of the involved cartilage.

Extrinsic Compression

Extrinsic compression of trachea occurs from the enlargement of structures nearby such as the malignant lymph nodes, thyroid enlargement (both benign and malignant), esophageal tumors and occasionally vascular problems. Vascular problems may more often cause tracheomalacia secondary to a long-standing pressure effect than anatomical obstruction. In a patient with esophageal malignancy for whom surgery is not done due to any reason, stenting the esophagus is a popular intervention. However, in the presence of partial tracheal obstruction, stenting the esophagus may precipitate severe airway obstruction. In such a situation, trachea is stented first, followed by esophageal stenting (Fig. 90.8).

Both benign and malignant disorders of thyroid can cause UAO. Airway obstruction is an indication for surgery in both benign and malignant thyroid problems. Mechanisms of airway obstruction include extrinsic tracheal compression (e.g. benign intrathoracic or substernal goitre), tracheal invasion by a growth, vocal cord paralysis (e.g. recurrent nerve paralysis after

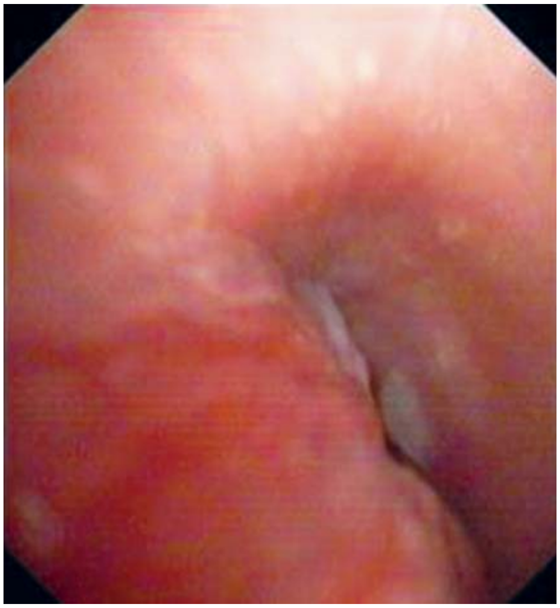


Fig. 90.8: A 60-year-old lady with esophageal malignancy causing near total occlusion at subglottic region

thyroidectomy), or a combination of the above (Fig. 90.9).[65] In a series of 30 patients with thyroid disorders causing UAO who were also not candidates for surgery due to various reasons, there is a great utility of rigid bronchoscopy and laser application in providing both immediate and long-term benefits.

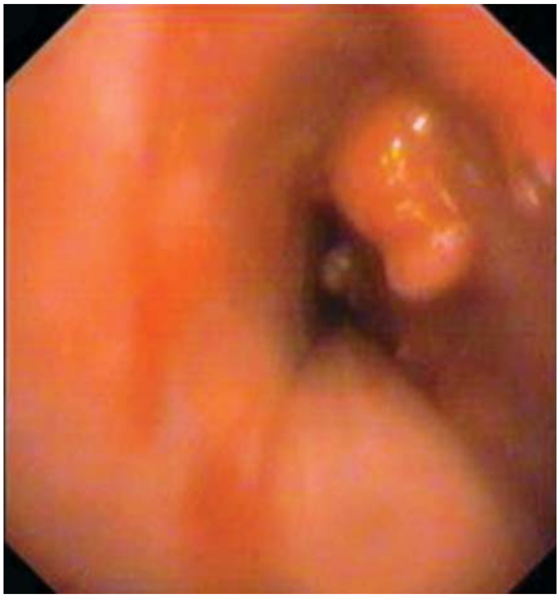


Fig. 90.9: Elderly lady with thyroid malignancy causing both extrinsic compression and tumor infiltration of upper trachea

Wegener's Granulomatosis

Upper Airways are commonly involved in Wegener's granulomatosis most of the times. Nasal and oral ulcerations, granulomatous inflammation, epistaxis, sinusitis and otitis, are common manifestations.[66,67] Usual features are ulceration of larynx and trachea. However, a rare but a significant airway problem is subglottis stenosis. This has been reported to develop during treatment with steroid and cyclophosphamide.[68] It is typically dealt by interventional techniques like laser application[68] or dilatation.[69] Recently, intralesional long-acting corticosteroids have found to be effective.[70]

Tumors

Primary tracheal tumors are very rare, seen in about 0.2 per 100,000 persons[71] of whom about 80% are malignant. Primary tracheal tumors can arise from the respiratory epithelium, salivary glands, and mesenchymal structures of the trachea.[72] Squamous and adenoid cystic carcinoma account for about two-thirds of tumors from trachea. The other malignant tumors are mucoepidermoid carcinoma, arising from the submucosal glands. Neuroendocrine neoplasm are seen more in bronchi than in trachea and include typical and atypical carcinoids, large cell neuroendocrine tumors and small cell carcinoma. The difference between the primary tracheal tumors and the bronchogenic malignancies is that the tracheal tumors have a better long-term prognosis and need more aggressive approach in providing good palliation or a cure.[73] Benign tumors of the trachea include tumors from surface epithelium like papilloma, papillomatosis, tumors from glands (like pleomorphic adenoma, mucous gland adenoma, myoepithelioma and oncocytoma) and tumors from mesenchymal structures (like fibroma, benign fibrous histiocytoma, hemangioma, paraganglioma (chemodectoma), hemangiopericytoma, glomus tumour, chondroma, lipoma, and leiomyoma granular cell tumors.[72]

Endotracheal metastases are much less common than endobronchial metastasis. Endobronchial metastasis commonly arise from renal, colon, or bronchogenic malignancy, melanoma and osteosarcoma. Presentation of metastases as UAO is very rare.

Other Causes

Bilateral vocal cord palsy can happen secondary to thyroid malignancy or thyroid surgery. Others include the neurological diseases or idiopathic causes. Cases of bilateral vocal cord palsy have been reported following nasogastric tube, systemic lupus erythematosus (SLE) and esophageal surgeries.[74-76] Other rare and diverse causes of UAO have been described as anecdotal case reports.[77-83]

THERAPEUTIC CONSIDERATIONS

As is true with many other conditions in medicine, treating the primary cause of the UAO is important. However it is also important to manage the obstruction. Obstruction can occur due to intrinsic pathology as in the case of tumors or tracheal stenosis, extrinsic compression as in compression from thyroid swelling or esophageal cancer. Functional obstruction without significant anatomic narrowing can happen secondary to tracheomalacia. In cases where surgery is feasible, especially in short segment complex stenosis or tracheal tumors, it should be offered. Several other interventional approaches provide a good quality of life in most of the conditions.

In the cases of intramural pathology, achieving a patent lumen is accomplished by techniques like rigid bronchoscopy, laser, electrocautery, and argon plasma coagulation, while airway stenting is necessary for extramural compression or tracheomalacia where maintaining lumen is the key issue. Silicone stents are preferred over metallic stents because the latter are difficult to remove after deployment. A recent study shows that most of the cases of UAO secondary to tracheal stenosis could be managed using flexible bronchoscopy, for balloon dilatation, laser application, stent placement and brachytherapy.[84] But rigid bronchoscopy is generally preferred because of a better control of airway, ventilation and for deployment of silicone stents.

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Bronchiolar and Bullous Lung Diseases

Gyanendra Agrawal, Dheeraj Gupta

INTRODUCTION

In addition to Chronic Obstructive Pulmonary Disease (COPD), asthma and cystic fibrosis, the "obstructive pulmonary disorders" include an important group of diseases—small airway diseases. The first part of this chapter focuses on the clinical approach to bronchiolar disorders. It also includes discussion on the bullous lung disease, highlighting its key differentiating features with bullous emphysema, in the later part.

BRONCHIOLITIS

The term "small airways" refers to airways less than 3 mm in diameter.[1,2] This definition includes small bronchi, bronchioles and respiratory bronchioles. Bronchioles are small airways less than 2 mm in diameter without cartilage or submucosal glands. This includes terminal bronchioles, whose principal role is to conduct air to the respiratory bronchioles. The latter contain alveoli, which are the site of air conduction and gas exchange. Although not strictly synonymous, the terms "bronchioles" and "small airways" are here used interchangeably.

Bronchiolitis is nonspecific inflammation of the respiratory bronchioles and peribronchiolar alveolar sacs of variable causes, clinical manifestations and evolution. The diseases affecting bronchioles can be classified into primary bronchiolar disorders—those diseases in which the pathologic process is centered in the bronchioles—and those disorders in which the bronchioles are secondarily involved by a pathologic process that is centered in the lung parenchyma or proximal large airways[3] (Table 91.1). In this chapter, the general features and the approach to only "primary" bronchiolar disorders are discussed.

No single classification scheme for bronchiolar disorders has been widely accepted. Classification schemes have been proposed based on causes and underlying diseases, radiologic features, histopathologic findings, or some combination of these parameters. Unavoidable overlaps exist, no matter which classification scheme is chosen.

TABLE 91.1: Classification of bronchiolar disorders*

Primary bronchiolar disorders

1. Constrictive bronchiolitis (bronchiolitis obliterans)
2. Diffuse panbronchiolitis
3. Respiratory bronchiolitis
4. Acute bronchiolitis
5. Mineral dust airway disease
6. Follicular bronchiolitis
7. Others (diffuse aspiration bronchiolitis, lymphocytic bronchiolitis)

Parenchymal disorders with prominent bronchiolar involvement

1. RB-ILD and DIP
2. Hypersensitivity pneumonitis (HP)
3. Cryptogenic organising pneumonia (idiopathic BOOP)
4. Others (PLCH, sarcoidosis)

Large airway diseases with bronchiolar involvement

1. Bronchiectasis
2. Chronic bronchitis
3. Asthma

RB-ILD: Respiratory bronchiolitis–associated interstitial lung disease; DIP: desquamative interstitial pneumonia; BOOP: bronchiolitis obliterans organizing pneumonia; PLCH: Pulmonary Langerhan's cell histiocytosis

* Modified from reference 3.

TABLE 91.2: Clinical classification of bronchiolitis

1. **Infectious bronchiolitis** Respiratory syncytial virus Mycoplasma pneumoniae Parainfluenza Adenovirus Measles Rubella Rubeola	2. **Drug Induced bronchiolitis** D-penicillamine, Gold, sulfasalazine, Amiodarone, interferon, phenytoin Cocaine, minocycline, nitrofurantoin, Carmustine, bleomycin, busulfan, *Sauropus androgynus,* Paraquat
3. **Inhalational Injury** Toxic fumes and gases Mineral dusts Organic dusts Volatile flavoring agents Flock worker's lung (fine nylon fiber) Grain dusts Fire smoke (World Trade Center lung)	4. **Post-transplant** Bone marrow Heart-lung Lung
5. **Connective tissue diseases** Rheumatoid arthritis Sjögren's syndrome Systemic lupus erythematosus Polymyositis, dermatomyositis	6. **Idiopathic** Cryptogenic adult bronchiolitis Respiratory bronchiolitis Diffuse panbronchiolitis Cryptogenic organizing pneumonia Diffuse aspiration bronchiolitis
7. **Systemic diseases** Ulcerative colitis Chronic eosinophilic pneumonia Wegener's granulomatosis Chronic thyroiditis Ataxia-telangiectasia Immunoglobulin A (IgA) nephropathy	8. **Other rare** Eosinophilic bronchiolitis Lymphocytic bronchiolitis Radiation pneumonitis Primary diffuse hyperplasia of pulmonary neuroendocrine cells

The clinical classification is primarily based on the proved or presumed etiology, related systemic diseases or other associations[4] (Table 91.2). An etiologic classification is useful for reminding the physician when to suspect the presence of bronchiolitis.

General Features of Bronchiolar Disorders

Bronchiolitis, a cellular and mesenchymal inflammatory reaction that follows damage to the bronchiolar epithelium of small conducting airways, is the most common form of disease affecting small airways. This entity is relatively uncommon in adults. Neutrophils which accumulate at the site of injury causes further damage to the airway epithelium and matrix by the release of inflammatory mediators. Depending on the disease stage, the repair process may cause narrowing and distortion of small airways (constrictive bronchiolitis) or complete obliteration (bronchiolitis obliterans).

Clinical Presentations

Most commonly, the patients present with slowly progressive exertional dyspnea and dry cough. Onset of symptoms is relatively acute in bronchiolitis from infections, inhalational injury or drugs; subacute in organizing pneumonia; and indolent and chronic in patients with post-transplant bronchiolitis. Cough with copious expectoration may be seen in infectious bronchiolitis and Diffuse Panbronchiolitis (DPB). Fever and constitutional symptoms are mainly seen in infectious bronchiolitis and collagen vascular diseases. Some patients may even present with pulmonary hypertension and respiratory failure in advanced stages. Due to extensive air trapping, the physiologic dead space gradually increases to the extent insufficient to washout normal carbon dioxide from the lungs, ultimately leading to hypercapnic respiratory failure.

Chest X-ray Findings

Chest radiography in bronchiolar disorders may be normal or demonstrate nonspecific findings like hyperinflation and peripheral attenuation of vascular markings in purely obstructive bronchiolar lesions such as constrictive bronchiolitis. In other primary bronchiolar disorders, small nodules or reticulonodular infiltrates may be observed. Increased bronchial wall thickening may also be seen. In distal acinar interstitial diseases with secondary bronchiolar involvement, chest radiography usually demonstrates features of the underlying parenchymal disease process such as cryptogenic organizing pneumonia (COP) or hypersensitivity pneumonitis.

Pulmonary Function Tests (PFT)

Depending on the predominant physiology, PFTs may yield variable results. Most of the primary bronchiolar disorders and large airway diseases are associated with obstructive physiologic defects. In contrast, most of the distal acinar interstitial diseases with secondary bronchiolar involvement show restrictive or mixed pattern. Abnormal values for Forced Expiratory Flow $(FEF)_{25-75\%}$, in conjunction with normal values for Forced Vital Capacity (FVC) and Forced Expiratory Volume in One Second $(FEV_{1)}$, are often useful in identifying small airway disease. Primary bronchiolar disorders often show nonreversibility with inhaled bronchodilators. In addition, these patients also demonstrate reduced diffusion capacity. The obstruction of small airways results in abnormal distribution of ventilation to peripheral lung units. This principle forms the basis of two tests: Frequency dependence of dynamic compliance and closing volumes. The tests of small airway function (Table 91.3), however, are rarely performed in clinical practice.

High Resolution Computed Tomography (HRCT) Findings

High resolution computed tomography is perhaps the most important tool in the diagnostic evaluation of bronchiolitis.[5] Normal bronchioles cannot be seen on Computed Tomography (CT) scans, as airways less than 2 mm in diameter are not visible on CT. However, diseased bronchioles with dilated lumen (>2 mm in diameter) or thickened walls can be visualized. High resolution computed tomography scan abnormalities that reflect bronchiolar diseases can be categorized into direct and indirect signs (Table 91.4).

TABLE 91.3: Tests of small airway function

Increase in mid-expiratory flow rate
Frequency dependence of dynamic compliance
Increase in closing volume
Increased volume of isoflow

TABLE 91.4: HRCT signs of bronchiolar disorders

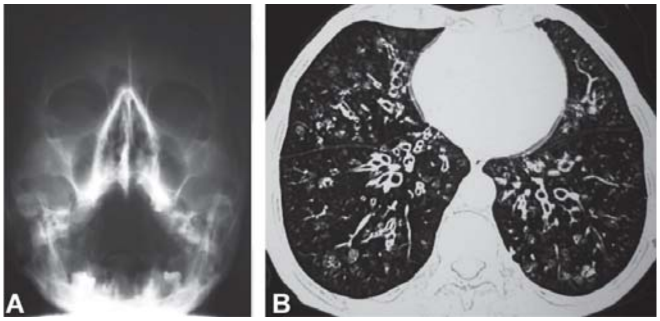
Direct signs	Indirect signs
• Bronchiolar wall thickening: inflammation/ fibrosis - Bronchiolectasis - Bronchiolar luminal impaction: Centrilobular nodules ± tree in bud appearance	- Mosaic attenuation - Subsegmental atelectasis

Bronchiolar wall thickening may occur due to inflammation and fibrosis, with or without dilatation (bronciolectasis). Bronchiolar luminal impaction manifests as 2 to 4 mm nodular and linear branching centrilobular opacities on CT. The "tree-in-bud" pattern represents a form of bronchiolar impaction in which branching linear structures have more than one contiguous branching site. Apart from direct signs, the most important indirect sign is the finding of mosaic attenuation, which occurs due to air trapping. However, this sign is not specific for bronchiolitis. In bronchiolar diseases, the mosaic pattern is caused by the hypoventilation of alveoli distal to bronchiolar obstruction, which leads to secondary vasoconstriction and is seen on CT scans as the areas of decreased attenuation. Paired CT scans performed in inspiration and expiration are useful for distinguishing bronchiolar disease from pulmonary vascular disease and some diffuse infiltrative diseases that may also cause a mosaic pattern.

Based on the radiologic features, bronchiolar diseases have been classified into four dominant CT patterns[2] (Table 91.5). "Centrilobular opacities with tree-in-bud" pattern is seen in infectious bronchiolitis, diffuse panbronchiolitis (Figs 91.1A and B), Diffuse Aspiration Bronchiolitis (DAB) and immunodeficiency syndromes. Centrilobular opacities appearing as ill-defined ground-glass nodules in the absence of a tree-in-bud pattern are associated with respiratory bronchiolitis, hypersensitivity pneumonitis and follicular bronchiolitis. "Ground-glass

TABLE 91.5: Radiologic classification of bronchiolar diseases

Centrilobular nodules with/without tree in bud
Ground-glass attenuation and alveolar consolidation
Mosaic perfusion
Mixed or different pictures



Figs 91.1A and B: A case of diffuse panbronchiolitis. X-ray paranasal sinuses (A) shows sinusitis and the HRCT scan (B) shows centrilobular nodules with bronchiectasis

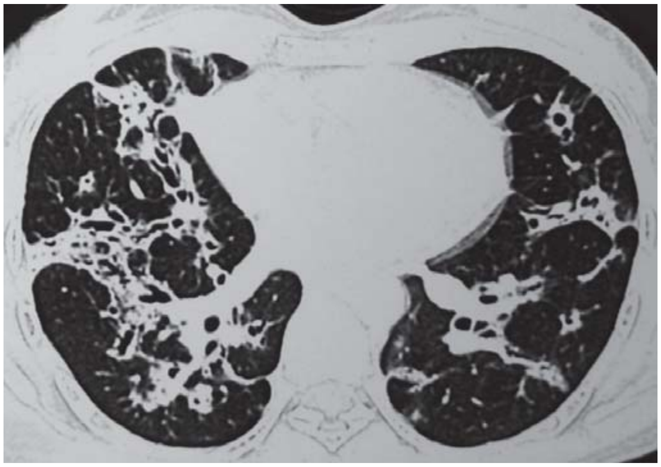


Fig. 91.2: A case of biopsy proven bronchiolitis obliterans organizing pneumonia showing diffuse patchy consolidations and ground-glass opacities

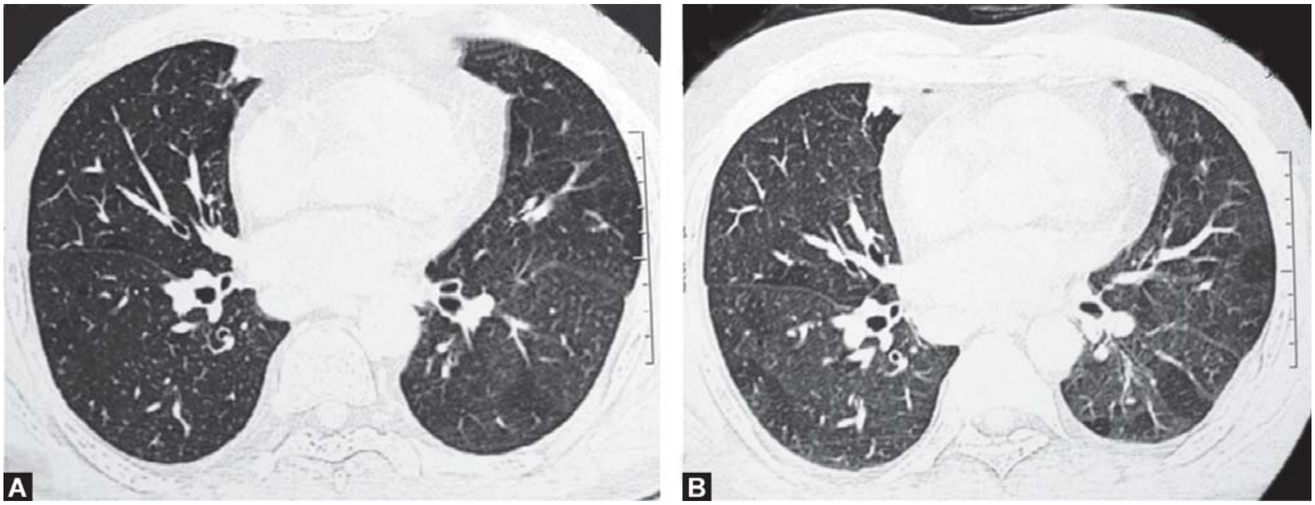
attenuation" or consolidation is due mainly to alveolar filling that occurs in Bronchiolitis Obliterans Organizing Pneumonia (BOOP) (Fig. 91.2) or in Respiratory Bronchiolitis-Interstitial Lung Disease (RB-ILD). The prototype of the third type of CT pattern, "mosaic lung attenuation," is constrictive bronchiolitis (Figs 91.3A and B). Other conditions resulting in a pattern of mosaic attenuation include connective tissue disorders, bone marrow and lung transplantation, toxic fume inhalation and drugs. Quite often many diseases will have a "mixed pattern" on HRCT. Association of tree in bud with mosaic perfusion can be seen in different entities, such as bronchiectasis and acute bronchopulmonary infections. The combination of mosaic perfusion and ground-glass opacities in the same patient, referred to as the "headcheese sign" is very suggestive of HP.[5]

Histologic Findings

Histologically, bronchiolitis can have a wide variety of patterns (Table 91.6). However, most morphological

TABLE 91.6: Histologic patterns of bronchiolitis

- Cellular bronchiolitis
  - Follicular bronchiolitis
  - Respiratory bronchiolitis
  - Diffuse panbronchiolitis
- Organizing pneumonia/ bronchiolitis obliterans with intraluminal polyps
- Constrictive bronchiolitis
- Peribronchiolar metaplasia and fibrosis



Figs 91.3A and B: Paired inspiratory (A) and expiratory (B) HRCT scans in bronchiolitis, mosaic attenuation and air trapping becomes more apparent on expiratory scans

abnormalities of the bronchioles are not specific, since bronchiolitis arises from a variety of sources of injury that result in the diversity of clinical, radiological and functional patterns. Bronchiolar changes should not be ascribed etiology or pathogenesis based solely on histologic features. Nevertheless, the histologic patterns generally show a better correlation with the radiological manifestations, the natural history of the disease, and the response to therapy.[6] In general, cellular bronchiolitis and Bronchiolitis Obliterans (BO) appear to be common "early" lesions that may resolve completely or partly, and are corticosteroid-responsive. As opposed to constrictive bronchiolitis which is relatively corticosteroid unresponsive and is usually progressive with the development of irreversible airflow obstruction and air trapping.

Since it is difficult to recognize and classify bronchiolitis in transbronchial biopsies because of the limited sampling size, the surgical biopsy is preferred. It is important to obtain wedge biopsies from multiple lobes because the bronchiolar pathology is often patchy. However, in certain clinical settings, such as those in post-transplant settings, transbronchial biopsies may be sufficient for diagnosis. It is recommended to obtain at least five pieces of well-expanded alveolar parenchyma with transbronchial biopsies.[7] The severity of clinical manifestations frequently exceeds that of histologic changes seen on lung biopsy.

In "cellular bronchiolitis," the bronchiole's structures show an increased number of inflammatory cells. It can further be characterized as acute or chronic based on the type of inflammatory cell type. It is a common pattern seen in many clinicopathologic settings like infectious bronchiolitis, inhalational injury, connective tissue diseases and aspiration. "Follicular bronchiolitis" represents hyperplasia of the Mucosa-Associated Lymphatic Tissue (MALT) and chronic peribronchiolar infiltrate along with secondary germinal centers. This pattern is associated with congenital or Acquired Immunodeficiency Syndromes (AIDS), including Human Immunodeficiency Virus (HIV) infection; collagen vascular diseases, especially rheumatoid arthritis and Sjögren's syndrome; and lymphoproliferative diseases. "Respiratory bronchiolitis" is a mild inflammatory reaction to cigarette smoke,[8] which consists of slight fibrosis, smooth muscle hypertrophy, and a characteristic presence of pigmented macrophages within the lumen of respiratory bronchioles, alveolar ducts and sacs. Respiratory bronchiolitis-associated interstitial lung disease is thought to be an exaggeration of respiratory bronchiolitis reaction sufficient to cause clinical disease. Respiratory bronchiolitis and RB-ILD often have accompanying emphysema.

"Diffuse panbronchiolitis" is a peculiar morphological form of cellular bronchiolitis largely restricted to the adult individuals of Japanese heritage. Its histologic hallmark is the presence of an interstitial inflammatory infiltrate containing foamy macrophages around respiratory bronchioles. Polyps of granulation tissue may partially occlude adjacent bronchiolar or alveolar lumina. When the histology of diffuse panbronchiolitis is encountered in an individual not of Asian descent, the possibility of inflammatory bowel disease-related bronchiolitis should be considered.

As the name suggests, "bronchiolitis obliterans" with "intraluminal polyps" is characterized, by intrabronchiolar polypoid protrusions of connective tissue that partially fill bronchiolar lumens. These polypoid proliferations usually extend distally in the alveolar ducts and alveoli, a pattern known as "organizing pneumonia." This combination of changes is referred to as BOOP pattern. The airway lumen appears to be occluded from within, as opposed to the concentric narrowing seen in constrictive bronchiolitis. Bronchiolitis obliterans organizing pneumonia is a very common tissue reaction pattern that occurs in a variety of settings. However, in many cases the cause cannot be ascertained, which is referred as cryptogenic organizing pneumonia (idiopathic BOOP). The common secondary causes of BOOP pattern are those associated with a variety of infections; connective tissue diseases and vasculitis like Systemic Lupus Erythematosus (SLE), rheumatoid arthritis, systemic sclerosis, inflammatory myopathies; post-transplant; inhalational injury like silo-filler's lung, paint aerosols, paraquat poisoning; drugs, radiation therapy and haematological malignancies.

"Constrictive bronchiolitis" refers to luminal narrowing by scarring that ranges from very subtle abnormalities to complete luminal obliteration. The hallmark of this type of bronchiolitis is mural thickening by submucosal collagenous fibrosis with progressive concentric narrowing associated with luminal distortion, mucus stasis and chronic inflammation. Bronchiolar dilatation with mucus impaction and smooth muscle hypertrophy may also be seen. There are many conditions and disorders which are associated with this type of bronchiolitis (Table 91.7); some specific ones are post-transplant bronchiolitis, bronchiolitis associated with rheumatoid arthritis and World Trade Center lung.[9]

"Peribronchiolar fibrosis" and "bronchiolar metaplasia" is a rare condition characterized by the growth of bronchiolar epithelium into the adjacent fibrotic alveolar walls (so-called lambertosis).[10] Inflammatory cells are scanty and usually present in the bronchiolar lumen. It represents a manifestation of previous

TABLE 91.7: Disorders associated with constrictive bronchiolitis

- Postinfectious
  - Viruses: Respiratory syncytial virus, influenza, parainfluenza, adenovirus, HIV
  - Bacteria: Mycoplasma, Chlamydia
  - Parasites: *Plasmodium vivax*
  - Fungi: *Pneumocystis jiroveci,* Cryptococcus
- Connective tissue diseases
  - Rheumatoid arthritis, SLE
- Inhalational Injury (toxic fumes or smoke)
  Phosgene, hot gases, nitrogen dioxide, sulfur dioxide, ammonia, chlorine
- Drugs
  - Penicillamine, lomustine, gold, amiodarone, interferon, nitrofurantoin, etc.
- Post-transplant
  Bone marrow, heart-lung or lung, graft versus host disease
- Idiopathic
- Others
  - Radiation, cocaine abuse, inflammatory bowel disease

HIV: Human immunodeficiency virus; SLE: Systemic lupus erythematosus

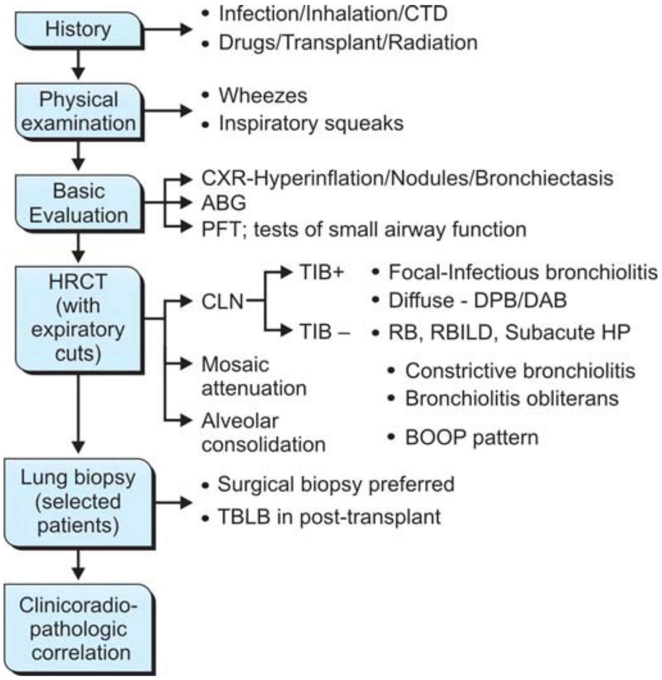
bronchiolar injury/scarring such as viral bronchiolitis or extrinsic allergic alveolitis.

Practical Approach for Diagnosis of Bronchiolar Disorders

The broad clinical spectrum of bronchiolar inflammatory disorders in adults can be diagnosed with the help of a practical algorithmic approach (Fig. 91.4).

A detailed history of symptoms suggestive of connective tissue disease, as well as exposure to inhalational irritants and radiation, should be elicited in order to identify a possible cause. A potential relationship with drug intake should be investigated in depth and taken into account in combination with the underlying disease. On auscultation, the presence of wheezing, inspiratory squeaks, or crackles should point to the bronchioles as the likely anatomic site involved. After history and physical examination, posteroanterior and lateral chest radiographs (CXRs) and PFTs are typically obtained. These tests are of limited value in directing the diagnostic workup of primary bronchiolar disorders as they rarely establish specific diagnoses. However, they are important to exclude large airway diseases in which secondary bronchiolar changes may be seen.

As both CXR and PFT findings are frequently nonspecific, a high index of clinical suspicion should be maintained in order to diagnose and/or exclude bronchiolar disease. High resolution computed tomography scanning (inspiratory and expiratory) may play a critical role in both suggesting the specific causes of bronchiolar disease and directing optimal management. In select cases, the diagnosis may be made solely using HRCT scans in combination with the history and clinical presentation, thus obviating more invasive diagnostic testing. However, in patients where the diagnosis of bronchiolitis and its cause is not clear, the clinical relevance of a bronchiolar lesion is best determined by identifying the underlying histopathologic pattern and assessing the correlative clinico–physiologic–radiologic context. Thus, the intimate interdependence of clinical, radiological and pathologic findings in assessing the significance of bronchiolar lesions and the necessity of a multidisciplinary (clinical-radiological-pathologic)[4] approach cannot be overemphasized (Table 91.8).


History
• Infection/Inhalation/CTD
• Drugs/Transplant/Radiation
Physical examination
• Wheezes
• Inspiratory squeaks
Basic Evaluation
CXR-Hyperinflation/Nodules/Bronchiectasis
ABG
PFT; tests of small airway function
HRCT (with expiratory cuts)
CLN
TIB+
• Focal-Infectious bronchiolitis
• Diffuse - DPB/DAB
TIB –
• RB, RBILD, Subacute HP
Mosaic attenuation
• Constrictive bronchiolitis
• Bronchiolitis obliterans
Alveolar consolidation
• BOOP pattern
Lung biopsy (selected patients)
• Surgical biopsy preferred
• TBLB in post-transplant
Clinicoradio-pathologic correlation

ABG: arterial blood gases; BOOP: bronchiolitis obliterans with organizing pneumonia; CLN: centrilobular nodules; CTD: connective tissue diseases; CXR: chest X-ray; DAB: diffuse aspiration bronchiolitis; DPB: diffuse panbronchiolitis; HP: hypersensitivity pneumonitis; PFT: pulmonary function tests; RB: respiratory bronchiolitis; RB-ILD: respiratory bronchiolitis interstitial lung disease; TBLB: transbronchial lung biopsy; TIB: tree-in-bud.

Fig. 91.4: Algorithm for practical approach to patients with supposed bronchiolitis

TABLE 91.8: Clinicoradiological-pathological correlation of bronchiolitis*

Histopathologic findings	*Radiological findings*	*Common clinical conditions*
Cellular bronchiolitis	CL nodules, TIB	Respiratory bronchiolitis
	Mixed pattern	Infectious bronchiolitis
		DPB, DAB
		Collagen vascular diseases
		Post-transplant
		Immunodeficiency
Bronchiolitis with intraluminal polyps	CL nodules	COP
	Mosaic oligemia	Drug induced bronchiolitis
	Air trapping on expiratory CT	Collagen vascular diseases
	Mixed pattern	Post- transplant
Constrictive bronchiolitis	Mosaic oligemia	
	Air trapping on expiratory CT	Postinfectious (MacLeod's syndrome)
		Inhalational injury
		Collagen vascular diseases
		Idiopathic
Peribronchiolar metaplasia and fibrosis	CL areas of increased attenuation	Chronic hypersensitivity pneumonitis

* Modified from reference 4.

CL: centrilobular; TIB: tree-in-bud; CT: computed tomography scan; DPB: diffuse panbronchiolitis; DAB: diffuse aspiration bronchiolitis; COP: cryptogenic organizing pneumonia

Specific Forms of Bronchiolitis

Infectious Causes of Bronchiolitis

Infection is the most common cause of acute bronchiolitis, mostly seen in children of less than 1 year of age, especially during the winter season. Respiratory syncytial virus (RSV) is the etiologic agent in the majority of these patients, but other viruses (adenovirus, influenza, parainfluenza) and nonviral pathogens (mycoplasma, chlamydia) can cause a similar syndrome.[3] Symptomatic acute bronchiolitis in adults is relatively rare, but can be caused by infectious agents such as *M. Pneumonia* and RSV. No systematic study has been reported; therefore, the clinical presentation of infectious bronchiolitis in adults is ill defined.[11]

Most patients with acute viral bronchiolitis can be managed at home with supportive care since respiratory symptoms are generally mild. Although bronchodilators, epinephrine and corticosteroids have been commonly used in more severe cases of acute viral bronchiolitis, there is considerable disagreement regarding optimal treatment strategies. Beyond the use of supportive care and supplemental oxygen, there is little evidence to support a routine role for any of these drugs.[12,13]

One of the long-term complications of postinfectious constrictive bronchiolitis occurring in childhood is the development of the Swyer-James (or MacLeod's) syndrome, that is, unilateral hyperlucent lung with the evidence of air trapping and decreased vascularity especially after adenoviral infection occurring in infancy.

Inhalational Lung Injury

Several irritant gases like sulfur dioxide, chlorine gas, ammonia, nitrogen dioxide (NO_2), phosgene, photochemical air pollutants, and ozone have been occasionally associated with bronchitis or bronchiolitis. Two distinct and uncommon types of airway processes can follow exposure to noxious fumes, gases or mists: Reactive Airway Dysfunction Syndrome (RADS) and constrictive bronchiolitis. Reactive airway dysfunction syndrome is defined as the development of respiratory symptoms in the minutes or hours after a single accidental inhalation of high concentrations of irritant gas and aerosol. These symptoms are followed by asthma-like symptoms and airway hyper-responsiveness.

Mineral dust airways disease occurs because of the inhalation of a number of inorganic dusts, including asbestos, iron oxide, aluminum oxide, talc, mica, silica and coal. Inflammatory response induced by the dust likely leads to the local production of fibrogenic factors and morphogenesis of the bronchiolar lesion. Poorly defined centrilobular opacities can be seen on HRCT scans early in the course of the disease; these predominate posteriorly and at the lung bases owing to the gravitational effects of fiber deposition. Peribronchial infiltration of dust-laden macrophages is often noted on microscopy. Inhalations of "organic dusts" are associated with the development of hypersensitivity pneumonitis. Interstitial pneumonitis with granulomas are seen in most of the patients on lung biopsy.

Volatile flavoring agents used in the microwave popcorn industry can cause a respiratory illness resembling bronchiolitis obliterans, especially in workers who worked nearest the mixing tank. Lung function testing shows severe airflow obstruction, which does not recover after removal from exposure. However, there does not appear to be any risk to the general population who use microwave popcorn products.

Bronchiolitis Associated with Connective Tissue Diseases

A wide spectrum of inflammatory and fibrotic disorders involving the small airways may complicate Connective Tissue Diseases (CTDs) and include COP; constrictive (obliterative) bronchiolitis; small airways disease; cellular or follicular bronchiolitis; and bronchiectasis (most often seen in late rheumatoid arthritis). In addition, medications used to treat CTDs, penicillamine, methotrexate and gold can cause histologic abnormalities similar to those seen in the primary disease. Small airway diseases are most commonly seen in the following CTDs: Rheumatoid arthritis, Sjögren's syndrome, SLE, systemic sclerosis and polymyositis-dermatomyositis.[14] Corticosteroids are highly efficacious for COP, but therapeutic options for constrictive bronchiolitis are disappointing. Prophylactic antibiotics and good pulmonary hygiene remains the mainstay of therapy for patients with bronchiectasis.

Idiopathic

Cryptogenic adult bronchiolitis is a rare entity, the diagnosis of which is largely of exclusion. Most patients are middle-aged women with symptoms usually of 6 to 24 months' duration. Lung biopsies show cellular constrictive bronchiolitis, often quite subtle. Early treatment with corticosteroids might be of benefit in some patients.[15-18]

Respiratory bronchiolitis is a specific form of smoking-related small airway disease. Respiratory bronchiolitis usually occurs without symptoms or physiologic evidence of lung disease.[8] In some patients, however, respiratory bronchiolitis can cause symptomatic diffuse parenchymal lung infiltrates, a syndrome referred to as RB-ILD. Respiratory bronchiolitis per say does not require any treatment other than smoking cessation. Most studies suggest a favorable response to steroids in RB-ILD.

Diffuse aspiration bronchiolitis is a term used to define a clinical entity characterized by the chronic inflammation of bronchioles caused by recurrent aspiration of foreign particles.[19] Most previously described patients with this disorder have been elderly and bedridden.[19] However, this disorder can be seen in the adults of varying ages with gastroesophageal reflux disease that may be clinically occult.[20]

Drug-Induced Bronchiolitis

Several drugs have been reported to have an association with the development of bronchiolitis, usually with organizing pneumonia. However, a definite "cause and effect" relationship between these drugs and the development of BO is uncertain, because most reports are of single cases or small case series. Pure bronchiolitis obliterans, with airflow obstruction, has been associated with gold therapy.[21] However, it is difficult to state that these cases resulted from gold-induced airway injury, because patients with rheumatoid arthritis also are prone to develop pure bronchiolitis obliterans. Pulmonary complications of penicillamine therapy are uncommon, but may include BO and diffuse interstitial infiltrates.[22,23] This form of BO may be characterized by a rapidly deteriorating course and pulmonary insufficiency. Up to 25% cases of amiodarone lung disease may develop organizing pneumonia (BOOP pattern), which mimic an infectious pneumonitis. Treatment primarily consists of stopping the offending drug, and corticosteroid therapy (prednisone 40 to 60 mg a day, tapering over 2 to 6 months) can be life saving in severe cases.

In Taiwan, an outbreak of rapidly progressive respiratory distress associated with consumption of uncooked *Sauropus androgynus,* a vegetable, claimed to be effective in weight control, has been reported. No effective treatment has been reported and the clinical response to prednisolone was limited.[24]

Bronchiolitis Associated with Organ Transplantation

Patients with bone marrow transplantation, heart-lung transplantation, or lung transplantation may develop BO as a chronic rejection phenomenon. This type of bronchiolitis remains the most common form of chronic rejection in patients with lung transplants, occurring in up to 50% of patients.[25] Constrictive bronchiolitis is also seen as a manifestation of graft versus host disease in 10% of people who have received allogeneic bone marrow transplants.[26] This problem is a major threat to long-term survival in these transplant recipients and is the leading cause of late death after lung transplantation.[27]

Three major kinds of airway injury may be seen in allograft recipients: Acute (cellular) rejection, bronchiolitis obliterans, and lymphocytic bronchitis. The lesions of BO are characterized by the features of constrictive bronchiolitis. Ultimately, smooth muscle cells, myofibroblasts, and mature collagen obliterate the airways ("vanishing airways disease").[28,29] Occasionally, classic BOOP, with patchy organizing pneumonia and granulation tissue plugs extending into the alveolar ducts, is observed as the predominant lesion.

The pathogenesis of post-transplant bronchiolitis is a finely orchestrated process involving multiple events. Alloreactive injury to the bronchial epithelium is considered as the key pathogenetic mechanism. Other possible mechanisms like recurrent, persistent bacterial or viral infections; graft-versus-host disease or transplant rejection; impaired repair of injured airways due to bronchial artery ligation; altered mucociliary clearance; and recurrent aspiration also contribute to the development of BO.

Because of the patchy distribution of lesions and difficulties in obtaining adequate samples of bronchioles, confirming the diagnosis of constrictive bronchiolitis in transplant recipients by transbronchial lung biopsies is problematic. Thus, the phenomenon of progressive airway obstruction in lung transplant recipients is termed "Bronchiolitis Obliterans Syndrome (BOS)," a clinical diagnosis, and is defined physiologically by a decrement in FEV_1 of 20% or more below a stable baseline.[27,30]

Most patients with BO progress to respiratory failure, and some patients develop bronchiectasis with frequent bacterial exacerbations. Aggressive therapy results in improvement of lung function in only 8% to 20% of patients.[31] Intensification of immunosuppressive therapy is the mainstay of therapy. The maintenance therapy with macrolides have demonstrated significant functional improvement in BOS,[32] and is used as an adjunct to immunosuppressive regimen.

Diffuse Panbronchiolitis

Diffuse panbronchiolitis (DPB) is a progressive inflammatory disease characterized by chronic sinusitis, bronchiolitis and progressive obstructive airway disease that rapidly progresses to bronchiectasis, respiratory failure and death. While DPB is prevalent in Asian countries especially Japan, it has been rarely described among non-Asian patients.[33,34] It has a strong genetic predisposition with HLA-B54 common among the Japanese.[33] However, the precise etiology is unknown. It usually affects people in the second to fifth decade. If DPB is left untreated, only 12% to 25% of patients survive for up to 10 years.

The plain CXR film reveals bilateral, diffuse, small nodular shadows predominantly in the lower field of the lung with hyperinflation. In advanced cases, ring shaped or tram-line shadows indicating bronchiectasis appear. High resolution computed tomography is extremely useful for the detection of characteristic pulmonary lesions of DPB (Fig. 91.1). In fact a system for grading these HRCT scan changes has been described.[35] Stage I is characterized by multiple centrilobular nodules usually less than 5 mm in diameter, which are present at the end of bronchovascular branching structures. In stage II, these centrilobular nodules are seen connected to distal branching bronchovascular structures in a Y-shaped configuration, which provides the tree-in-bud appearance. Early-stage bronchiectasis is seen in stage III, while the presence of large cysts makes it stage IV. The diagnosis of DPB is often made on clinicoradiologic grounds by demonstrating its distinctive features and excluding other sinobronchial disorders. Lung biopsy shows transmural and peribronchiolar infiltration with lymphocytes and plasma cells. However, it is usually not necessary in countries where the disease is of high prevalence. (Table 91.9)

Erythromycin therapy has been shown to improve symptoms, lung functions, CT scan changes and survival rates in the patients of DPB. Most patients are treated for more than 2 years and until the resolution of symptoms and the disappearance of centrilobular nodules. Treatment should be resumed if symptoms reappear after the cessation. Other members of the macrolide family are also efficacious in treating patients with DPB. An immune system modulating effect is more

TABLE 91.9: Diagnostic criteria for diffuse panbronchiolitis*

Major
1. Persistent cough, sputum and exertional dyspnea
2. History suggestive of chronic paranasal sinusitis
3. Bilateral small nodular shadows on plain chest radiograph or centrilobular nodules on HRCT

Minor
1. Coarse crackles
2. $FEV_1/FVC < 70\%$ and $PaO_2 < 80$ mm Hg
3. Cold hemagglutinin titre ≥ 64

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PaO_2: arterial oxygen tension

Definite diagnosis made if all three major and two out of three minor criteria present.

*Modified from reference 34.

likely than antibacterial activity, as the mechanism of erythromycin therapy. It has been demonstrated by the ability of erythromycin to reduce neutrophil influx by decreasing levels of interleukins that are chemoattractants.[36]

Other Rare Forms of Primary Bronchiolar Disorders

A relatively new entity termed "eosinophilic bronchiolitis" have been described wherein the lung biopsy specimen demonstrated peri- and transmural bronchiolar infiltration by massive numbers of eosinophils along with plasma cells and degenerating eosinophils with Charcot-Leyden crystals within bronchiolar lumina, with minimal alveolar involvement.[37] This disease responds fairly well to steroid therapy.

BULLOUS DISEASE OF THE LUNG

A "bulla" is an air-containing emphysematous space within the lungs that has a diameter of more than 1 cm in the distended state and that causes a local protrusion from the surface of the removed lung. The terminology "bullous lung disease" is reserved for an entity characterized by the presence of bullae in one or both the lung fields, with normal intervening lung.[38] This entity is different in etiology and pathogenesis from "bullous emphysema," a condition in which bullae occur in conjunction with the emphysematous changes in the nonbullous lung.[39-41] "Giant bullous lung disease" is said to be present if the bullae occupy at least one-third of the hemithorax and compress the surrounding lung parenchyma.[39]

It is important to differentiate between the terms bulla, bleb and cyst. "Bleb" is an accumulation of air between the two layers of visceral pleura and lined by the elastic lamina. Whereas, "bulla" is present deep to the internal elastic layer of the visceral pleura and is confined by connective tissue septa of the lung. In contrast, "cyst" is lined by epithelium and can be present in the lung parenchyma or mediastinum. Three types of bullae are recognized pathologically, which differ in location, size of neck, and amount of contained residual lung tissue; the clinical significance of which is unclear.

Pathogenesis

The pathogenesis of bullae formation is complex and poorly understood. Bulla arises from destruction, dilatation and confluence of airspaces distal to terminal bronchioles, the walls of which are composed of attenuated and compressed parenchyma. Of all the hypotheses, that of an underlying paraseptal emphysema is the most popular. The structural weakness of the interalveolar septa caused by elastolysis, which itself may be secondary either to a constitutional disorder or to enhanced proteolysis is the predominant mechanism for the development of paraseptal emphysema. Airspaces in paraseptal emphysema may become confluent and develop into bullae, which may be large. Airway obstruction caused either by the loss of airway support or by inflammatory changes in the walls of small airways, also, contribute to progressive enlargement of these airspaces; ultimately resulting in the formation of bullous emphysema.

However, in the patients of "bullous lung disease" with normal intervening lung, a mechanism different from that of bullae occurring in conjunction with emphysema is more likely. Several hypotheses have been proposed over the years, but none has been proved. Two hypotheses which have attracted most of the attention are "paper bag hypothesis" and a "ball valve mechanism" for bulla formation. Chronic inflammation of the airways especially terminal bronchioles causes airway obstruction, which acts as ball valve allowing air to enter during inspiration, leading to progressive air trapping and tension airspaces. However, this theory of bulla formation by positive pressure within the airspace has been refuted by the studies of dynamic computerized tomography and intrabulla pressure measurements. Moreover, in studies performed in subjects with bullae who are taken to altitudes of 18,500 feet (at an ascent rate of 1000 feet per minute), little increase in bulla volume is noted, probably reflecting good communication between bullae and airways and adequate pressure equalization.

The pressure in bullae is normally negative and same as that of pleural pressure.[42] The lung surrounding the bulla is less compliant than the bulla itself. Therefore, the pressure required to inflate the surrounding lung is greater than that necessary to inflate the bulla. During inspiration, when bullae and the adjacent lung parenchyma are subjected to same negative pleural pressure, bulla fills preferentially than the surrounding lung like a "paper bag." However, this "paper bag compliance" is seen up to a critical lung volume, after which they become stiff and much less compliant than lung.[43]

Bullae communicate with the rest of the bronchial tree, but air enters or leaves the bullae quite slowly. So bullae generally do not act as clinically important dead space. During tidal breathing PO_2 in bullae is higher than arterial PO_2.

Etiology

Bulla may originate in a variety of clinical and pathogenetic settings. Smoking and alpha 1-antitrypsin deficiency are the two most important risk factors for bullous emphysema. A hereditary predisposition to bullous emphysema is also suggested by its association with a variety of rare familial disorders, including Fabry's disease, cutis laxa, Ehlers-Danlos syndrome and Marfan's syndrome. Marijuana smoking has been implicated as the cause of large upper zone bullae in some individuals.[44] Upper zone "fibrobullous disease" is also reported in ankylosing spondylitis, usually seen in patients of long-standing disease of 15–20 years duration with marked spinal involvement. It is possible that some patients labeled as having giant bullous disease harbor an unusual condition like pulmonary sarcoidosis, Langerhans cell histiocytosis, idiopathic pulmonary fibrosis or progressive massive fibrosis. Post-tubercular fibrosis may sometimes present as bullous disease. The cause cannot be ascertained in a subset of patients with bullous disease, they are labeled as idiopathic bullous disease.

Clinical Presentation

As a rule, small bullae usually produce no symptoms, signs or discernible alterations in pulmonary function; and are detected during routine chest radiography. However, rupture of one or more bullae may lead to spontaneous pneumothorax.

The most common presenting symptom in bullous lung disease is of gradually progressive exertional dyspnea. Occasionally they may develop sudden severe increase in breathlessness either due to pneumothorax or overdistension due to air-trapping. Chest pain may occur in a patient with bullous lung disease. This is also due to overdistension of the large bullae or development of pneumothorax. Overdistension causes a diffuse dull aching type of chest pain, usually located retrosternally. Hemoptysis is an uncommon presentation, and usually indicates hemorrhage inside the bullae. Increase in cough and sputum production, in patients with known bullous disease, usually heralds the presence of infection in a bulla.

The findings on physical examination are usually dominated by the presence of associated disease. Occasionally, giant bullae may cause localized hyperresonant note and decreased breath sounds.

Radiologic Features

Small bullae rarely become visible on the chest radiograph, but they are usually easily visible by computed tomography. Apical bullae may sometimes be misinterpreted as cavitation on plain radiographs. They can be differentiated if it is remembered that cavities are centered within areas of consolidation and they do not merely overlap them.

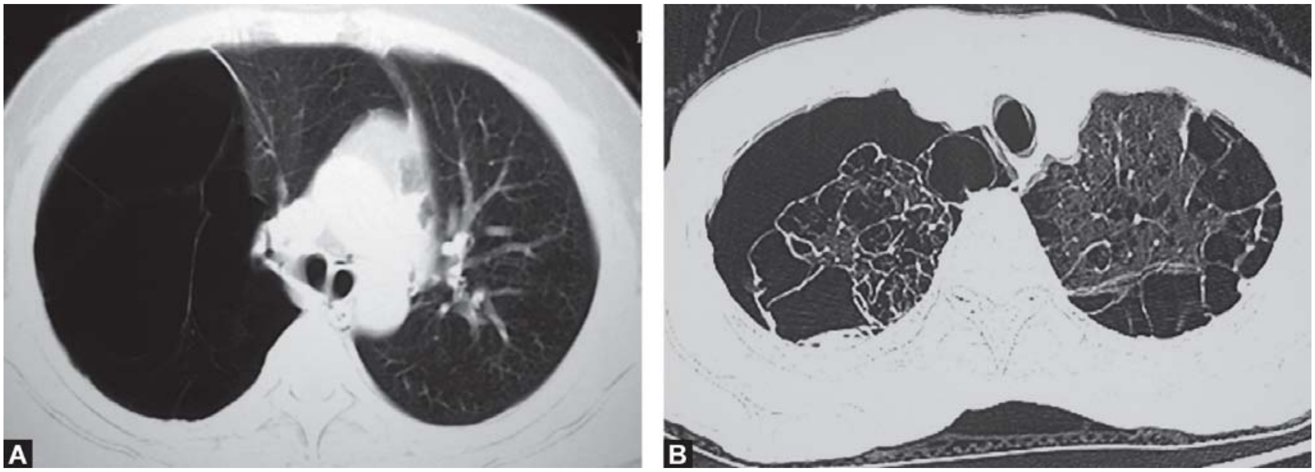
High resolution computed tomography is an important tool as it can locate the bullae with considerable accuracy, even when their presence is not suspected on the basis of clinical and radiographic data. It also helps in assessing the extent and localization of bullae and associated diffuse nonbullous emphysema. It also allows assessment of associated diseases such as bronchiectasis, infected cysts, pleural disease and pulmonary hypertension.[38] Computed tomography scans can help in differentiating bullous lung disease from bullous emphysema. The intervening lung parenchyma is normal in bullous lung disease as opposed to changes of emphysema seem in emphysematous bullae (Figs 91.5A and B).

The bulla is seen as an avascular transradiant area separated from the rest of the lung parenchyma by a thin curvilinear wall. The wall is usually of hairline thickness. They are of variable size ranging from 1 cm to almost half of the hemithorax. Bullae are much more common in the upper zones, especially those associated with paraseptal emphysema. The difficult distinction between bullous disease and pneumothorax can be made with CT through the "double-wall sign" (i.e. air visible on either side of the wall of bulla). CT has also been used to create 3-D reconstructions of bullae, which can then be used to calculate bullae volumes.

Pulmonary Function Tests

Detailed PFTs have an important place in the assessment of these conditions and to differentiate bullous disease from bullous emphysema. This distinction is important since the patients with bullous emphysema are in general poor surgical candidates as compared to patients with bullous lung disease. Pulmonary function tests can also help to make an objective assessment of the severity of the underlying disease, quantifying the size of bulla and monitor the response to treatment.

Spirometry done in patients with bullous lung disease usually shows restrictive defect, presumably as a result of the bulla compressing intervening normal lung; whereas a predominant obstructive defect is seen in patients having bullous emphysema. The diffusing capacity is reduced to a greater extent in bullous emphysema as compared to bullous lung disease, and this test correlates better with morphologic estimates of emphysema than do most other tests. The diffusing capacity fails to increase normally during exercise. With



Figs 91.5A and B: HRCT scan in bullous lung disease (A) and bulllous emphysema (B)

exercise, the arterial oxygenation, ratio of dead space to tidal volume and the alveolar-arterial difference in PaO_2 tend to remain normal or near normal in patients with a few circumscribed bullae and otherwise normal lungs, as compared to patients with bullous emphysema where they uniformly decrease, indicating progressive alveolar hypoventilation.

In patients with bullous lung disease, the lung volumes should be assessed by both the helium dilution technique and via body plethysmography. A known volume of gas and a trace amount of helium (an inert gas, very little of which absorbs into the pulmonary circulation) is breathed in and out of a reservoir in the helium dilution technique. The helium is diluted by the gas that was previously present in the lung. With the knowledge of the gas in the reservoir and the initial and final helium concentrations, the functional residual capacity and the Total Lung Capacity (TLC) can be calculated. However, because of inadequate time to equilibrate with slowly communicating and noncommunicating air spaces such as bullae, this technique may underestimate the TLC. So, lung volumes should also be measured with body plethysmography, which measures the total volume of the thorax. The difference in TLC measured by body plethysmography and that by the helium dilution technique approximates the volume of the bullae.[38]

Bullae volume = TLC by body plethysmography – TLC by helium dilution

In some patients with bullous emphysema respiratory muscle strength improves after bullectomy, as assessed by the measurements of maximal inspiratory and transdiaphragmatic pressures.[45] In patients with bullous emphysema, due to reduction in the pulmonary vascular bed, the resting pulmonary artery pressures are increased which further exaggerate during exercise. However, isolated bullae act like amputated segments of the lung and resting pulmonary arterial pressure and blood flow are within normal limits.

Natural History

Systematic long-term studies on the natural history of bullous lung disease are lacking. Patients with bullous disease should be monitored by chest radiography at regular intervals to ensure that the disease is stable. Bullae usually enlarge over months and years with a variable rate. And the period of stability may be followed by a sudden expansion. In some patients, often young men, there may be the inexorable progression of idiopathic giant bullous disease. The alternative name given for the devastating nature of this condition is "vanishing lung syndrome." In some patients bulla may disappear either spontaneously[46,47] or following infection and hemorrhage,[47] or with medical therapy alone.[48]

Complications

The main complications of bullae are pneumothorax, infection or hemorrhage. When infected, bullae usually contain fluid and develop an air-fluid level. Fluid may be frequently resorbed, and cause complete resolution of the bulla.[47] The hair-line wall often becomes thickened, and indeed this may be the only sign of infection. An infected bulla differs from an abscess in that the patient is less ill, the wall of the ring shadow is thinner and has a sharp margin, and there is less adjacent pneumonitis. Sometimes, a fungus colonizes a bulla and may form a mycetoma or fungal ball. Hemorrhage inside the bulla is a less common complication and it manifests as hemoptysis or decrease in hemoglobin level.[49] As with infection, bulla may disappear after bleeding occurs. Pneumothorax may occur due to the rupture of the bulla in pleural cavity or as a complication of paraseptal emphysema. Patients tend to have a prolonged air-leak in such cases.[50]

Isolated cases of carcinomas arising in bullous lung diseases have been reported during the past 40 years. The majority of lung cancers associated with bullous disease are non-small-cell tumors. The frequency of lung cancer in subjects with bullous disease is approximately 32 times higher than in those without these abnormalities.[51] High resolution computed tomography signs which could suggest the presence of carcinoma include mural nodule, mural thickening, fluid within bulla and change in bulla diameter.[52,53] The possible carcinogenic mechanism of bullous disease remains uncertain. The proposed mechanisms are: (1) carcinogens may inhibit antielastase enzymes, resulting in interalveolar-septal destruction with subsequent bulla formation; (2) constitutional or congenital factors may cause bullous disease and simultaneously may also predispose to lung cancer; and (3) impaired ventilation of bullae may facilitate the deposition of carcinogens.

Treatment

An asymptomatic patient diagnosed to have bullous lung disease should be reassured and educated about the disease. All attempts should be made to quit smoking. The patients should be asked to avoid the activities that promote rupture of bulla like “scuba-diving.” Appropriate treatment for the associated disease like asthma or COPD should be given. There are case reports of the spontaneous resolution of progressively enlarging giant bullous emphysema after medical therapy for COPD was instituted.[48] Appropriate antibiotics and chest physiotherapy should be started as soon as the diagnosis of infected bullae is established.

Because of the impairment of respiratory function, and the higher incidence of coexisting infection and cancer, the giant bulla should be resected in all patients, even if they are asymptomatic. Enlarging bullae causing incapacitating dyspnea or chest pain or impending respiratory insufficiency also need to be resected. Any lung mass associated with bullae should be considered an indication for surgery. Other indications of bullectomy include infected bullae and that causing recurrent pneumothorax (Table 91.10).

TABLE 91.10: Indications of bullectomy

- Giant bullae
- Symptomatic bullous lung disease
    - Incapacitating dyspnea
    - Chest pain
- Complications
    - Infection
    - Recurrent pneumothorax
    - Cancer

Even in bullectomy cases without the evidence of parenchymal lesions, the surgical resection should be as complete as possible and accurate pathological examination of the resected specimen should be performed because of the suspected existing occult or small sized lung cancer. Bullectomy can be done either via video-thoracoscopy (using a stapling device) or conventional thoracotomy. Mortality and complication rates are usually lower with thoracoscopy than with other surgical approaches.

Bullectomy is different from Lung Volume Reduction Surgery (LVRS), which is the surgical removal of 20% to 30% of nonbullous emphysematous lung from each side. The greatest benefit from surgery is seen in patients with a large bulla (occupying 50% or more of hemithorax), a moderate reduction in FEV_1, a rapid onset of dyspnea and no evidence of generalized emphysema.[54] The physiologic basis of functional improvement after bullectomy is similar to that following LVRS.[55]

Other treatment approaches for giant bullae include reduction pneumoplasty and Brompton’s procedure (endocavitary aspiration with sclerosis and pleurodesis); the latter is preferred in patients with poor pulmonary function.[56]

Distinction between widespread obstructive airways disease with concomitant bullae and bullous lung disease has practical significance, since surgical lung resection in generalized emphysema offers a less certain therapeutic response than does resection of giant bullae in the absence of widespread obstructive lung disease. As a rule, surgical intervention is avoided in bullae associated with either obstructive or fibrotic lung disease, unless life-threatening complication arises.

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Immunomodulators in Respiratory Diseases

Agam Vora

INTRODUCTION

Immunomodulation is a process that can alter immune system by interfering with its function, which results in the suppression or augmentation of immunological reactivity.[1-3] Apart from specific suppressive or stimulative activity, certain agents can normalize or modulate the pathophysiological process. It involves homeostasis between Th1 (cell mediated) and Th2 (humoral) immunity. Also, it leads to the fine tuning of inhibitors, activators and regulatory signals ensuring immunostasis (Tables 92.1 and 92.2). Agents which restore this balance are classified as Immunomodulators.

Immunomodulator is a broad term, it practically involves all environmental insults that can alter body's internal milieu and hence from cigarettes to antibiotics, to simple pain killer or may be a multivitamin could be an Immunomodulator. In practice it may be more appropriate to restrict the use of the term, to molecules or interventions altering host immune reactions to boost immunity. There are several pharmacological agents and approaches used to enhance/modulate immunity (Table 92.3).

TABLE 92.1: The major goals of immunomodulator and immune-based therapies

- Potentiating the host's immune system to better control of insult/infection.
- Strengthening the patient's native immunity against a variety of opportunistic infections.
- Oppose the biological effects of the bacilli on the host by:
  - Inducing the production of beneficial cytokines and amplifying their biological effects.
  - Inhibiting the production and biological effects of harmful proinflammatory cytokines.
  - Stimulating the overall generation and activity of immune cells by stimulating the bone marrow thymus axis.

TABLE 92.2: Uses of immunomodulators

- Preventing infections proceeding to disease state
- Preventing the occurrence of secondary infections
- Achieving early control of infection/disease in conjunction with specific chemotherapy.
- Achieve early clinical response in terms of weight gain and reduction in toxemia

TABLE 92.3: Immunomodulators agents[4]

- Levamisole
- Immunoglobulins–IgG
  - Polyclonal
  - Monoclonal
- Herbomineral drugs
- *Mycobacterium welchii* vaccine
- Vaccine approach (Bacterial lysates)
- Cytokines (Interferons and Interleukins 2)/Leukotriene
- Donor lymphocyte infusion
- Synergic bone marrow transplant
- Granulocyte macrophage colony stimulating factors and granulocyte colony stimulating factors

Of these various immunomodulators which are currently available, cytokines, bone marrow transplantation (allogeneic or syngeneic) or donor lymphocyte infusions are generally beyond the reach of most of our patients. The herbomineral drugs, bacterial lysates or polyclonal immunoglobulins may prove to be cheaper options.

Levamisole

Levamisole is primarily an antiparasitic drug, which possesses immunomodulatory property. It is known to restore depressed immune function as an immunoadjuvant. Its effect on the immune system depends in part on the presence of antigenic stimulation. Levamisole can stimulate antibody formation to various antigens, enhance T-cell responses by stimulating T-cell activation and proliferation, potentiate monocyte and macrophage functions, including phagocytosis, chemotaxis and increase motility, adherence and chemotaxis. Levamisole can stimulate a normal and a depressed immune system, often classified as both an immunoregulator and immunostimulant. Levamisole affects T-cells to a greater degree than the B-cells, leading to cutaneous reactivity to delayed-type hypersensitivity antigens and improvement in helper, suppressor and cytotoxic T-cell functions.

Immunoglobulins

Immunoglobulins are proteins produced by cells of the B-lymphocyte lineage that are the major effector molecules of the humoral immune system. Immunoglobulin molecules are antibodies that react with specific antigens. Immunoglobulin preparations from human blood were first used in clinical medicine in 1952 to treat immune deficiency conditions. At that time, the available preparations required Intramuscular Immunoglobulin (IMIG) administration. In the past two decades, several immunoglobulin preparations for intravenous administration have become available. Although initially used for immune deficiency states, Intravenous Immunoglobulin (IVIG) has also been utilized as a prophylactic and therapeutic reagent in a variety of other conditions. The use of IVIG has undergone tremendous growth in the past several years. This rapid growth in use is the result of improvements in the preparations of IVIG, which have led to reduced morbidity and reports of its benefits in a number of unexpected circumstances. IVIG has been used in such diverse diseases as primary immunodeficiency, pediatric AIDS, infections in low birth weight infants, bone marrow transplantation, chronic lymphocytic leukemia, idiopathic thrombocytopenic purpura, Kawasaki syndrome and demyelinating polyneuropathies.

There are various mechanisms of importance in the different therapeutic uses of IVIG: (1) replacement therapy for primary and secondary immunodeficiencies, (2) specific passive immunotherapy, and (3) management of specific inflammatory and/or immunologic disorders. In our own experience, patients of Multidrug-Resistant Tuberculosis (MDR-TB) as well as those with HIV infection, who had received immunoglobulins along with antituberculosis therapy had sputum conversion along with quicker clinical improvements. Also, they had significantly lower opportunistic infections. We have used this treatment for a variety of disorders like chronic persistent asthma, burnt out Interstitial Lung Disease (ILD), MDR-TB, bronchiectasis and Chronic Obstructive Pulmonary Disease (COPD) requiring frequent hospitalizations for repeated infective exacerbations.[4]

Mycobacterium welchii (MW)

Mycobacterium Welchii is a nonpathogenic, rapidly growing organism. It was identified as an unique organism as an immunomodulator for leprosy. Multibacillary leprosy is associated with anergy to *Mycobacterium leprae* antigen. The anergy is very specific to *M. leprae* antigen. Even when patients are cured for leprosy using Multidrug Therapy (MDT), anergy to *M. leprae* antigen persists, to poor Th1 type response.

In search of a potent immunomodulator to enhance Th1 response, different mycobacteria were evaluated. All were evaluated for their ability to enhance Th1 response (human) as determined by blast cell transformation as well as for lymphoproliferative response. *Mycobacterium welchii,* was found to be the most potent, so it was selected for further evaluation and clinical application. *Mycobacterium welchii* also shares antigens (particularly 13 KDa protein), which are specific for immunity with *Mycobacterium tuberculosis.* This antigen sharing may result to provide protection against tuberculosis and drug-resistant tuberculosis.

Herbo Mineral Preparations

From the time immemorial, we have been using herbomineral preparations as immunomodulators in ayurvedic medicine. These herbs have been shown to differentially modulate the cytokine profile, inducing and amplifying the effects of certain cytokines while at the same time inhibiting others. With the advent of Human Immunodeficiency Virus (HIV) and with increased prevalence of MDR-TB, there is resurgence of interest in the traditional medicine of Chinese and Indian origin, to use these drugs as adjuvants to potentiate the immunity of host.

Bacterial Lysates

Bacterial lysates are constituted by a mixture of bacterial antigens derived from different bacterial species, according to the considered extract. The more often included species are: *Staphylococcus aureus*, *Streptococcus viridans*, *Streptococcus pneumoniae* (6 strains), *Streptococcus pyogenes, Klebsiella pneumoniae, Klebsiella ozenae, Moraxella catarrhalis* and *Hemophilus influenzae.*

Bacterial lysate is both a specific and nonspecific immunostimulating agent, indicated for both the prevention and treatment of respiratory infections, including sequelae to common cold and influenza. In particular, it is useful for the treatment of acute and chronic bronchitis, tonsillitis, pharyngitis, laryngitis, rhinitis, sinusitis and otitis. It can also be used for infections resistant to common antibiotics and for the sequelae of bacterial and viral infections.

The rationale for oral immunization strategies is solely based upon the communication between different mucosal tissues. Dissemination of lymphoid cells from the gut-associated lymphoid tissue to distant mucosa-associated effector sites, such as the respiratory tract, the genitourinary tract and various excretory glands, where these cells proliferate and differentiate into effector cells, is observed on the application of oral antigens.

Local immune protection due to oral vaccination is a result of increased production of antigen-specific secretory Immunoglobulin A (IgA). Oral application of bacterial antigens enhanced peripheral polymorphonuclear leukocyte functions, as reflected by a significantly increased oxidative burst activity. Significant reduction of intrapulmonary inflammatory reactions to infection with *S. pneumoniae* and an enhancement of pulmonary defense mechanisms mediated by increased gamma interferon production have been reported.[5]

Bacterial lysates are powerful inducers of a specific locoregional immune response that significantly enhance the concentration of antibodies directed to antigenic structures of bacteria, most commonly observed during infections of the upper respiratory tract. Those antibodies have the capability of opsonizing living bacteria, thus allowing the engulfment and killing mediated by human phagocytes, such as the granulocytes. This activity is linked to the capacity of inducing a significant reduction (or a complete disappearance) of signs and symptoms related to respiratory infections.

Interferons

Interferons (IFNs) are small proteins that inhibit viral replication and promote the cellular (T-cell) immune response. Interferon use for cancer treatment was limited until the late 1970s, when technological advances enabled mass production of IFN. There are three major types of IFNs: alpha, beta and gamma. Each type has similar but distinctive capabilities for altering biological responses.

Interleukin-2

Interleukin-2 (IL-2) is a substance produced by lymphocytes. In addition to being an essential factor for the growth of T cells, IL-2 augments various T-cell functions and enhances NK cell function. IL-2 also activates Lymphokine-Activated Killer (LAK) cells, which are a type of killer T cell produced when lymphocytes are incubated with IL-2. Lymphokine-activated killer cells destroy tumor cells and improve the recovery of immune function in certain immunodeficiency states. Patients with renal cell cancer, melanoma and non-Hodgkin's lymphoma have demonstrated responses to IL-2 therapy.

Colony-Stimulating Factors

Colony Stimulating Factors (CSFs) are growth factors which mediate the proliferation, maturation, regulation, and activation of granulocytes, macrophages, lymphocytes, monocytes, erythrocytes and platelets. Many types of CSFs have been produced synthetically. Some have been approved for use and some are in various stages of clinical trials. Generally, CSFs have been named for the major cell lineage they affect: Granulocyte-Macrophage CSF (GM-CSF) affects both granulocyte and macrophage lineage; Granulocyte CSF (G-CSF) targets only granulocytes. These hemopoietic factors have mainly been used to improve immune response to variety of adverse reactions seen with immunosuppressive therapy.

Tumor Necrosis Factor

Tumor Necrosis Factor (TNF) is a substance naturally secreted by macrophages. When activated by endotoxins, the macrophages release TNF, which then binds to receptors on cell membranes. Once bound to the cell membrane, TNF initiates cellular activity and is possibly cytotoxic to that cell.

The experience with these TNF, CSF, interleukin and interferon is mainly limited to oncology practice.

Biological Response Modifiers (BRM)

These are the substances of biological origin, which can modify immune function. Therapeutic enzymes work together with body enzymes as immune stimulants and are considered important BRMs. Enzymes have a central importance in ensuring the equilibrium between activation and inhibition of reactions of the immune system, which leads to tissue damage in almost every disease. Mechanism of action in these conditions is by enzymatic interruption of the complement cascade, breakdown of pathogenic immune complexes and activation of macrophages.

Lysozyme: Lysozyme is an enzyme found in egg white, tears and other secretions. It is responsible for breaking down the polysaccharide walls of many kinds of bacteria and thus it provides protection against infection. Lysozyme is an antimicrobial, innate immune molecule, which hydrolyzes the 1,4-beta-links between N-acetylmuramic acid and N-acetylglucosamine, thus cleaving an important polymer of the cell walls of many bacteria (degrading peptidoglycan of the bacterial cell wall).

Synergism of the antimicrobial effect in the presence of lysozyme is variable for the drugs differing in the mechanism of their action and depends on the pathogen species. The most pronounced synergistic effect is observed with respect to gram-positive bacteria with the use of many drugs. Combination of lysozyme with aminoglycosides results in increasing antimicrobial effect with respect to practically all the microbial cultures tested. The clinical trials of the efficient combinations of the antibiotics and lysozyme studies experimentally prove their high efficacy in combined therapy of patients with pneumonia and pyelonephritis of bacterial genesis.

Lysozyme protects from the ever-present danger of bacterial infection. It is a small enzyme that attacks the protective cell walls of bacteria. Bacteria build a tough skin of carbohydrate chains, interlocked by short peptide strands, that braces their delicate membrane against the cell's high osmotic pressure. Lysozyme breaks these carbohydrate chains destroying the structural integrity of the cell wall. The bacteria burst under their own internal pressure.

Lactoferrin: Lactoferrin is a globular multifunctional protein with antimicrobial activity (bactericidal, fungicidal), is part of the innate defense, mainly at mucosa. Lactoferrin is found in milk and many mucosal secretions such as the tears and the saliva. Lactoferrin is also present in secondary granules of Polymorphonuclear Leukocytes (PMN) and also secreted by some canard cells. Lactoferrin can be purified from milk or produced recombinantly. Human colostrum has the highest concentration, followed by human then cow milk.

Over the past three decades, various laboratories have identified lactoferrin as an antimicrobial agent. The occurrence of lactoferrin in saliva has initiated many studies on antimicrobial activity against oral streptococci and control of caries.

Bioenhancers

Bioenhancers increase the bioavailability of an orally administered pharmaceutical compound through the inhibition of P-glycoprotein transport activity in the gut, like piperine. They enhance the effect of other molecules taken together, but have no effect on their own.

Place in Therapy

Immunomodulators may be considered for patients with advanced immunocompromised disease state; patients with multiple comorbidities; patients on immunosuppressant and for patient not showing satisfactory clinical response in spite of being on adequate therapy. Large scale studies or randomized controlled trials of their use in various respiratory diseases are not yet available.

Immunomodulators are likely to form the central part of the treatment modality of this decade. Helping the host to modulate the immune system for a favorable outcome in an otherwise high-risk situation holds the key to a successful management plan.

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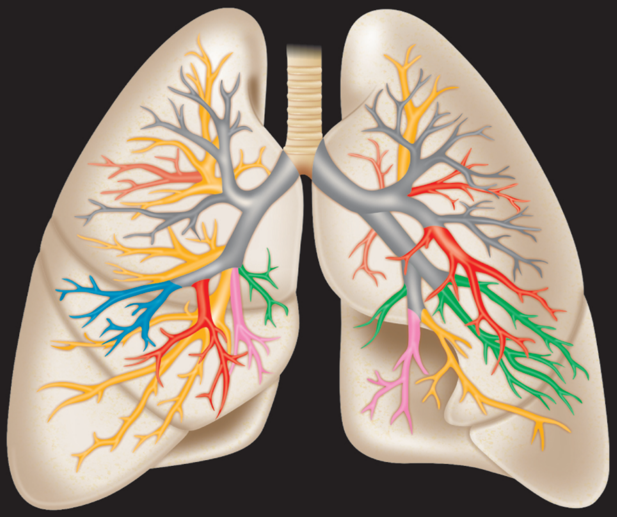

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Volume 1

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Foreword

In reading through the *Textbook of Pulmonary and Critical Care Medicine* edited by Professor SK Jindal of the Postgraduate Institute of Medical Education and Research, Chandigarh, my thoughts drifted to a recent best-selling book authored by Thomas Friedman, titled, *The World is Flat: A Brief History of the Twenty-first Century*. The author argues that the world is shrinking from a size small to a size tiny and this has been accompanied by a flattening of the playing field. The dynamic forces of recent globalization give a unique quality to our flat world today—the power of individuals to collaborate and compete globally. Using this 21st century power and the tools of the flat world, namely the personal computer, the fiberoptic cable, and modern publishing house software, Professor Jindal has fostered an outstanding collaboration among experts spanning several continents. He has also produced a practical, authoritative and comprehensive resource for students, physicians in training and seasoned clinicians alike, that rivals any standard textbook on this subject and can compete on equal footing with other educational tools.

However, as globalization flattens the playing field, and countries leap to industrialization, cultural beliefs, natural resources, climate and geography have slowed the pace of development in many parts of the world. Poverty leads to malnutrition, homelessness, lack of education, and poor access to health care. Overcrowded cities and rural underdevelopment are other challenges that impact health in the various parts of the world. Moreover, epidemics of HIV, drug abuse and smoking addiction take a greater toll on the population. Yes, the world is flat, but the terrain is filled with mountains and valleys and local problems demand local solutions. And these local problems need to be explored and presented with a scholarly perspective. The *Textbook of Pulmonary and Critical Care Medicine* has successfully incorporated these sociodemographic factors into the subject matter.

The text is well-written and the chapters are carefully referenced with subjects found in all traditional pulmonary and critical care textbooks, e.g. airway diseases, interstitial lung disease, pleural disease, pulmonary neoplasia, pulmonary infection, sleep and critical care. There are several nontraditional sections as well that are practical and especially helpful to the practicing physician. These include a section on the symptom approach to lung disease, an overview of the pharmacologic agents used to treat lung disease, and a comprehensive review of methods in lung diagnosis from the simple history and physical examination to the latest complex tools of interventional pulmonology. The textbook is especially unique because of the abundance of illustrations, flow charts and tables. Their clarity and at times simplicity make them especially valuable for the novice. There are many radiographic and pathologic reproductions that are especially helpful.

The textbook also offers a unique exposure to the problems in many parts of the world. Tuberculosis, the "number one" treatable condition has been extensively covered; and special topics such as multi-drug resistance, directly observed therapy, TB prevention, nonpharmacologic approaches and extapulmonary tuberculosis are particularly relevant. Many countries are facing a growing burden of noncommunicable respiratory diseases. They have become the second leading cause of death after injuries, and their impact on indirect costs such as loss of work and home productivity is enormous. These problems are addressed and measures of prevention such as smoking cessation are included. Other special challenges including topics such as indoor and outdoor air pollution, climate change, poisoning with pesticides, snakebite toxicity, pulmonary manifestations of tropical infections and industrial accidents such as the tragedy seen in Bhopal, Madhya Pradesh, with methyl isocyanate, have been well covered.

What is most impressive about this textbook is how comprehensive and practical it is for the reader. Topics range from the history of respiratory medicine to the approach to end-of-life issues with critically ill patients. It is hard to think of a topic that is missing. While this textbook will have a special appeal and value to the physicians of the South-Asian continent, clinicians around the globe will benefit from Professor Jindal's extensive efforts.

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Preface

It was merely a quarter of a century ago when the specialty of Pulmonary Medicine was factually recognized as an important division of Medicine. Until then, the lung diseases were generally dismissed as tuberculosis, or nondescriptive pneumonias and infections. Most of the nontuberculous lung diseases remained either undiagnosed or unknown. Of course, several stalwarts of the sixties and seventies had clearly identified this deficiency and made efforts to define the pulmonary problems and plan their solutions.

It was in 1989 that the first independent, postdoctoral DM Fellowship Program in Pulmonary Medicine was started at Chandigarh. Subsequently, the program was expanded to include the Critical Care as an essential component of the DM training. In addition, there were several postgraduate MD and/or diploma courses in tuberculosis and chest diseases, and/or respiratory diseases at different medical colleges. Unfortunately, most of the postgraduate programs lacked in their curricula especially for nontuberculous diseases and other systemic disorders. Moreover, the on-hand training in diagnostic and treatment modalities had been highly inadequate in the postgraduate courses. It is rather enigmatic that we still continue to lack the dedicated thoracic surgery courses and texts in the various countries.

The increased importance and scope of respiratory and critical care medicine had also necessitated the need to develop the indigenous teaching and training materials including the texts with incorporation of local problems and possible solutions. Undeniably, the science is the same all over the world, but the experiences are different. Excellent texts and reference materials on the subject are available for long which continues to guide the students, the teachers and the practicing physicians. In the present literature, quite a few textbooks of pulmonary medicine have been published and continue to remain available. Ours is one more attempt in this direction to add to the existing literature on lung diseases available worldwide. This book contains contributions by approximately hundred international esteemed pulmonary medicine consultants and teachers.

There are, however, a few important additions in the present textbook. It is fairly comprehensive with contributions from several internationally eminent authors. It includes the basic principles as well as the recent advances related to different subjects. We have also attempted to incorporate allied clinical sciences relevant to the practice of the pulmonologist. A classical example is the critical care which forms an integral component of pulmonary medicine. It also incorporates tuberculosis, other pulmonary infections, environmental and occupational medicines, sleep disorders and general systemic diseases affecting the respiratory system in one or the other way. Although the critical care is relevant to most of the medical and surgical specialties, the pulmonologists have a more vested interest than other specialists. Assisted respiration which forms the core of most critical care lies in the primary domain of pulmonologists.

We have taken care not to forget the need to push forward and meet the goals of excellence in health care. The real test of merit of a book lies in its readership by the students and adoption of its recommendations in clinical practice. Hopefully, the material in the text will benefit a diverse category of people including internists, general physicians, pulmonologists, pediatricians, intensivists, anesthesiologists and others who need to handle patients with respiratory diseases and critical care.

SK Jindal

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My faculty colleagues, Drs D Behera, Dheeraj, Ashutosh, Ritesh and Navneet, Senior Residents and Pulmonary-Fellows had remained a constant source of assistance. I greatly pay my sincerest appreciation to all of them. Ms Manju Aggarwal, my Secretary had done a remarkable job of refining and typing the manuscripts. I also owe a great deal of gratitude to my wife Umesh and children who have borne with my being busy and helping me in sorting out difficult matters.

Nothing could have been accomplished without the efficient editing and publishing by M/s Jaypee Brothers Medical Publishers (P) Ltd, Delhi who have done an excellent job. Shri Jitendar P Vij, CEO, had taken his personal interest in this publication. Dr Naren Aggarwal and Dr Richa Saxena deserve my special thanks for coordinating the process of publication.

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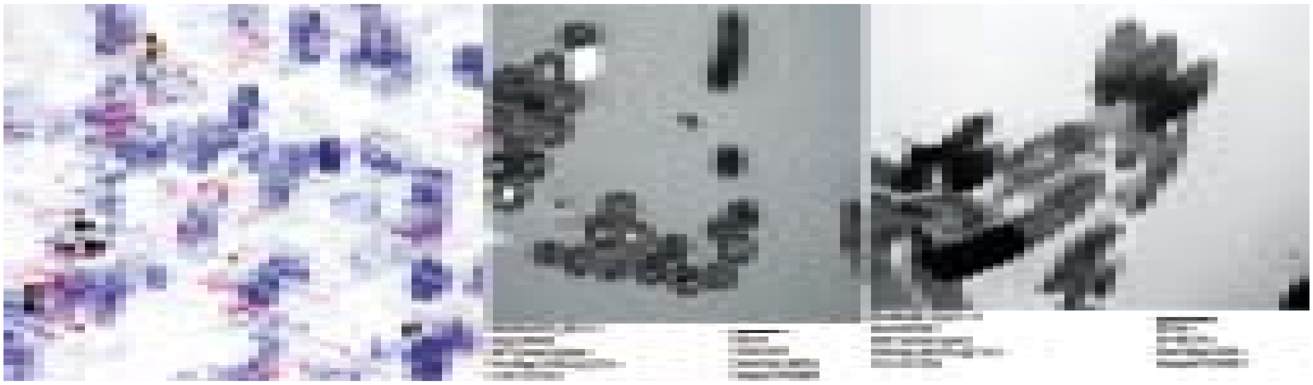

Fig. 1: Mycobacteria in the granuloma, engulfed by macrophages and its ultramicroscopic structure

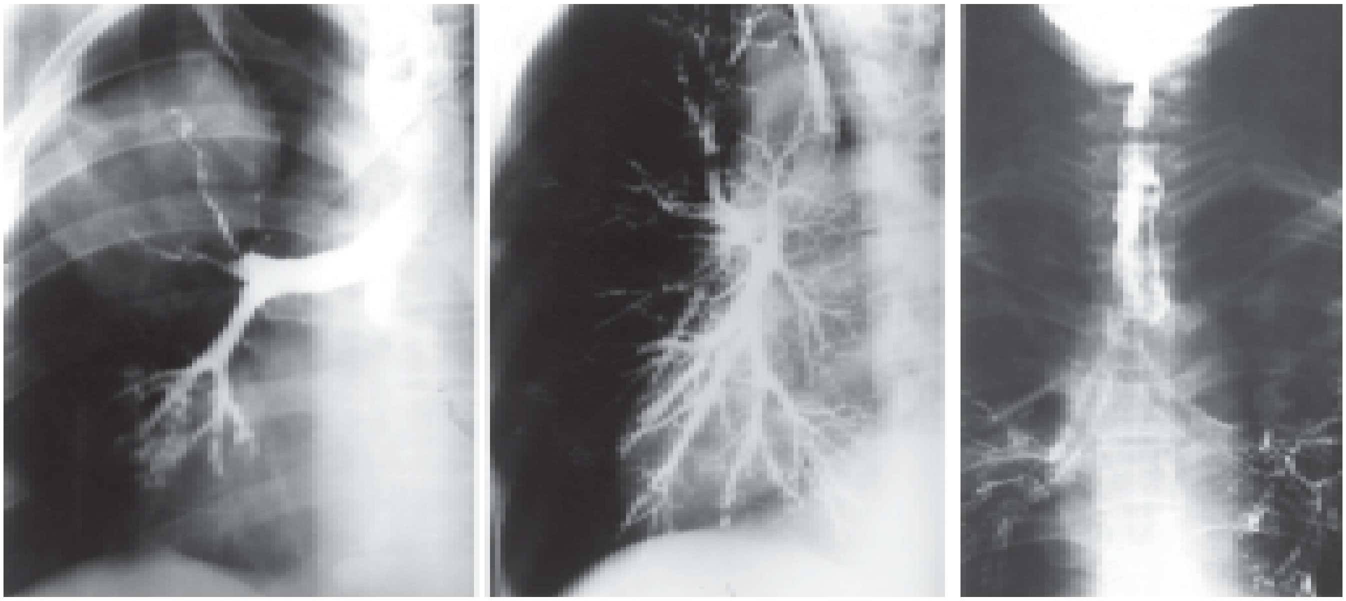

Fig. 2: Bronchography with instillation of a radiopaque dye (Dionosyl) with the help of a catheter was a common procedure to delineate the bronchial tree and diagnose lesions such as bronchial masses, bronchiectasis, fistulae and pouches. Endoscopic and scanning procedures have done away with old, gold-standard

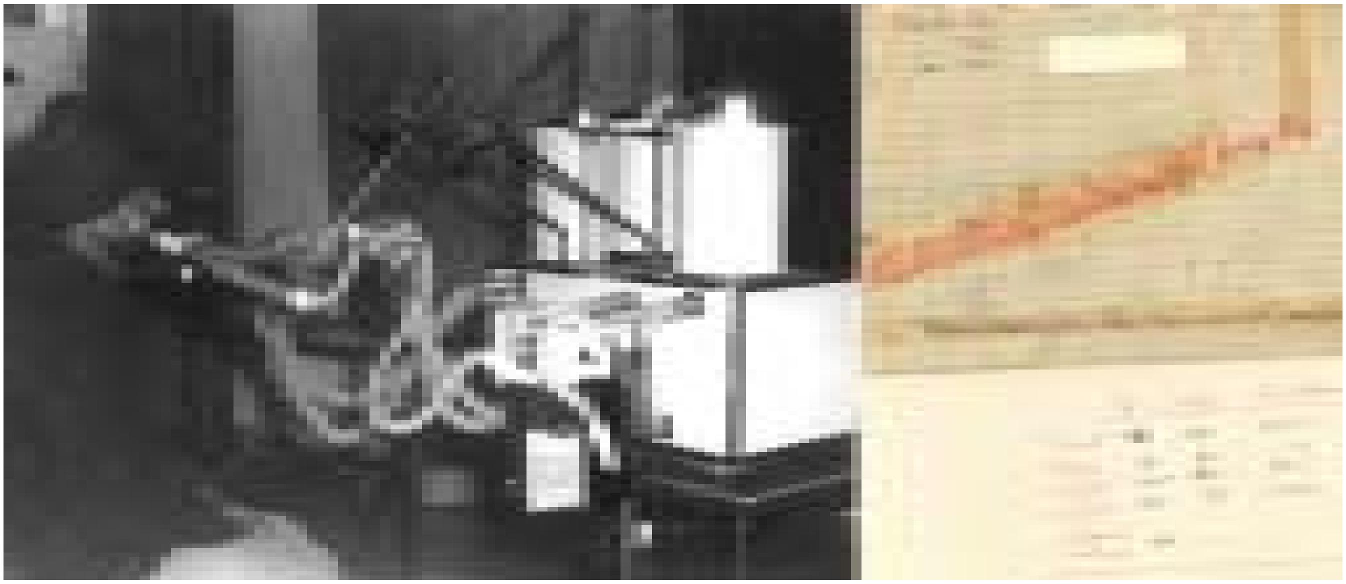

Fig. 3: Differential spirometry was used to assess the function of each lung separately. The figure demonstrates the nonfunctional left lung (Right). This was generally performed with the help of a double barrel, volume displacement spirometer (Left)

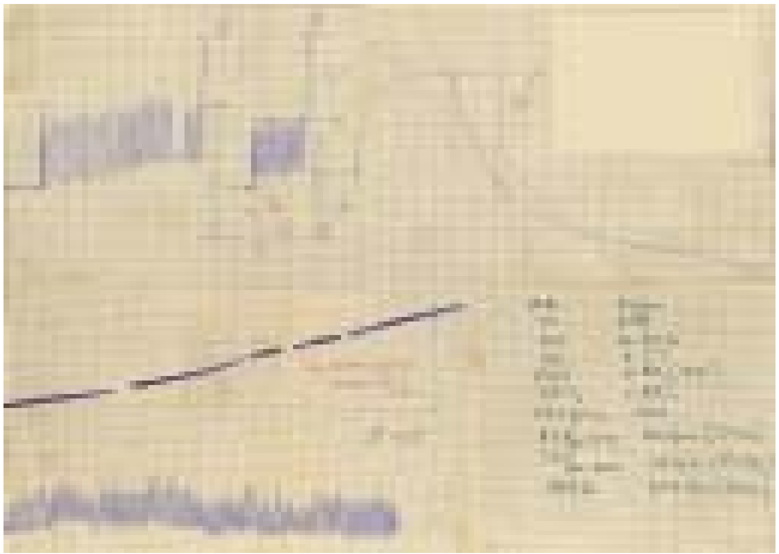

Fig. 4: Oxygen consumption obtained with the help of a spirometer by measuring the amount of oxygen required to replace the consumed volume, after absorption of CO_2 from the exhaled air using the formula:

$$\text{Oxygen consumption} = VC \times FiO_2 - FeO_2$$

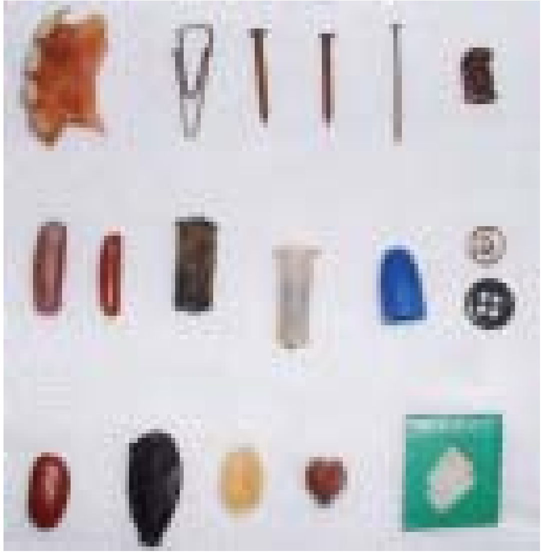

Fig. 5: Some of the foreign bodies recovered from the tracheobronchial tree (mostly, with the help of fiberoptic bronchoscopy)

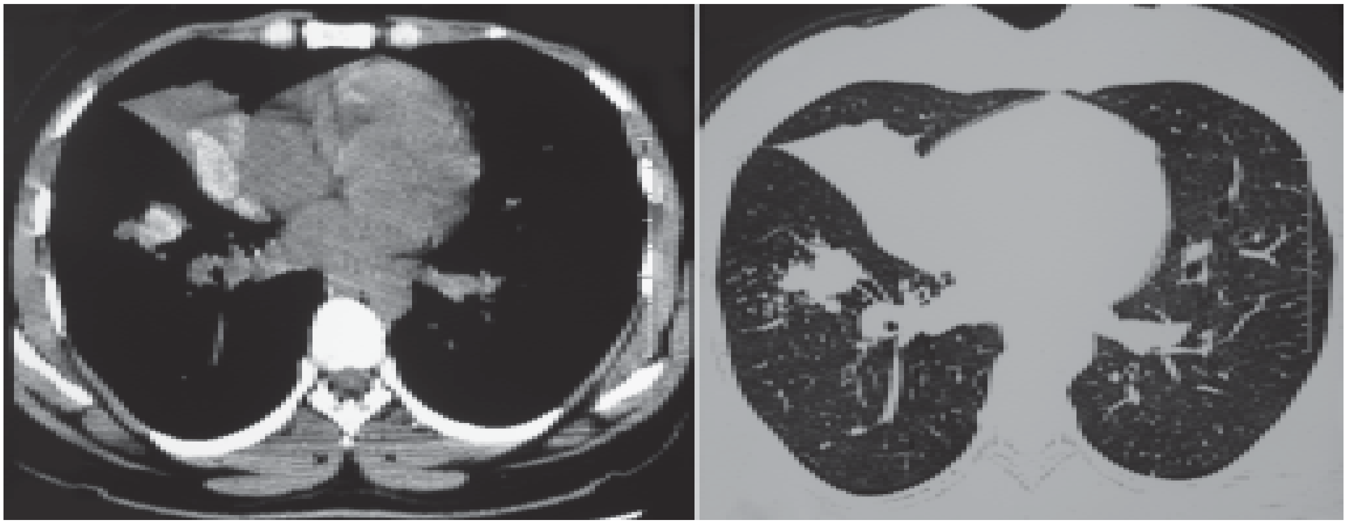

Fig. 6: Presence of high attenuation mucus in a patient with allergic bronchopulmonary aspergillosis. The mucus is denser than the paraspinal skeletal muscle

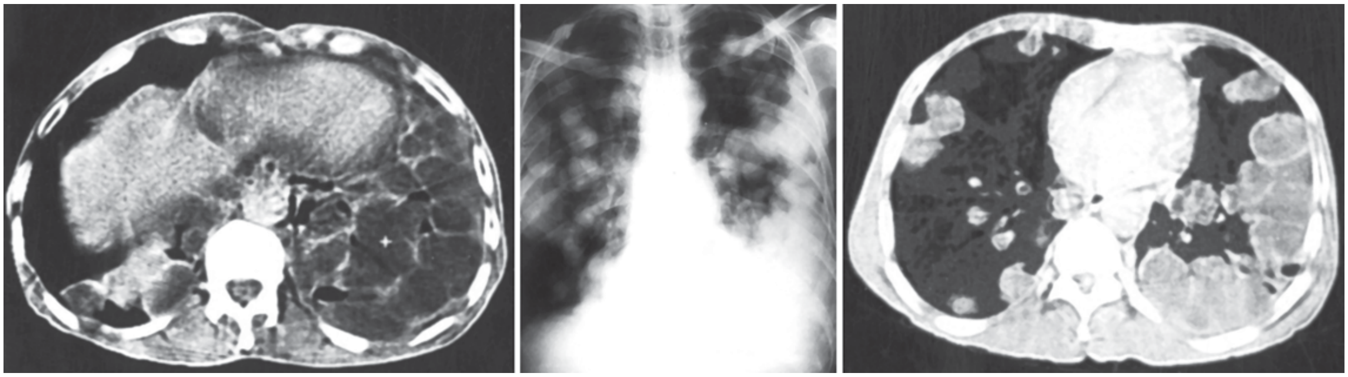

Fig. 7: Radiography in a patient with multiple hydatid cysts

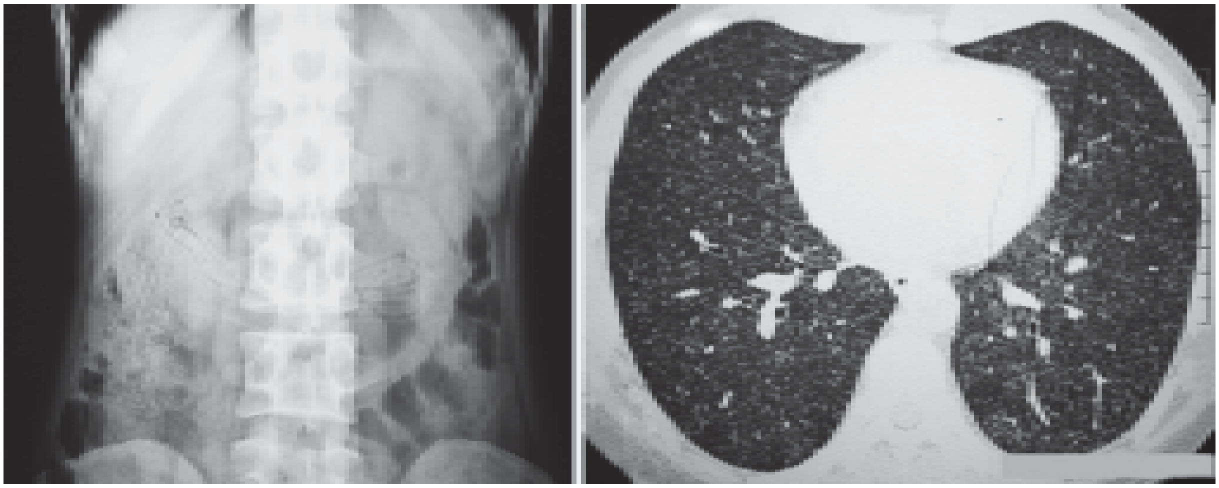

Fig. 8: A case of Loeffler's syndrome caused by intestinal round worms. Abdominal X-ray shows the presence of intra-abdominal worms. High-resolution CT of the chest demonstrates ground glass opacities and centrilobular nodules secondary to eosinophilic pneumonia

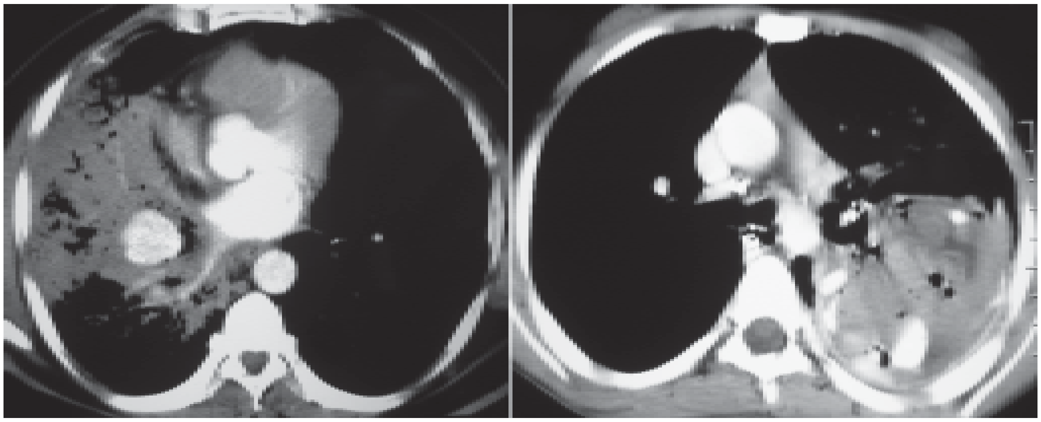

Fig. 9: Contrast-enhanced CTs of two different patients with community acquired necrotizing pneumonia demonstrating an uncommon but potentially life-threatening complication of infective pulmonary aneurysm. The CT films show the presence of contrast enhanced densities within the areas of consolidation consistent with the presence of vascular aneurysm

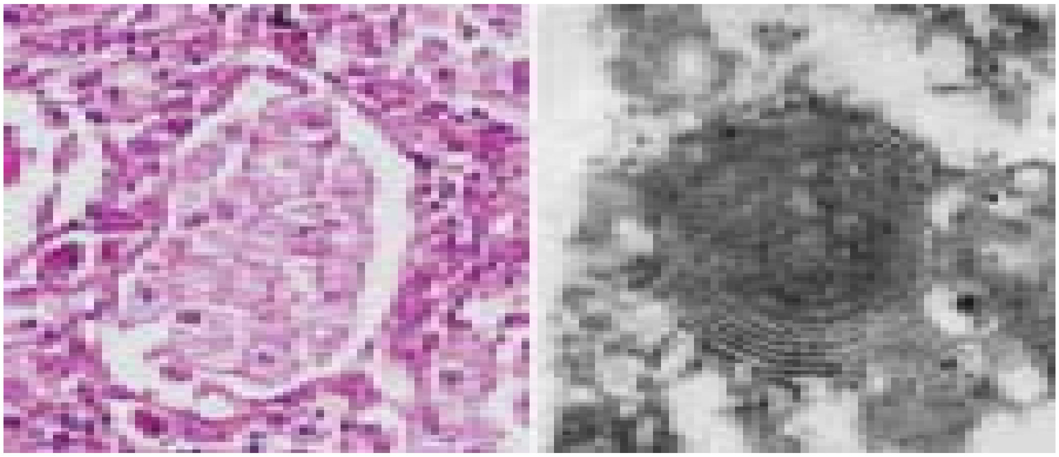

Fig. 10: Figure showing foamy macrophage with intracytoplasmic granular material in a case of pulmonary alveolar proteinosis (Hematoxylin and eosin, x200). Electron microscopic image of the same patient showing whorled lamellated surfactant bodies (x6450)

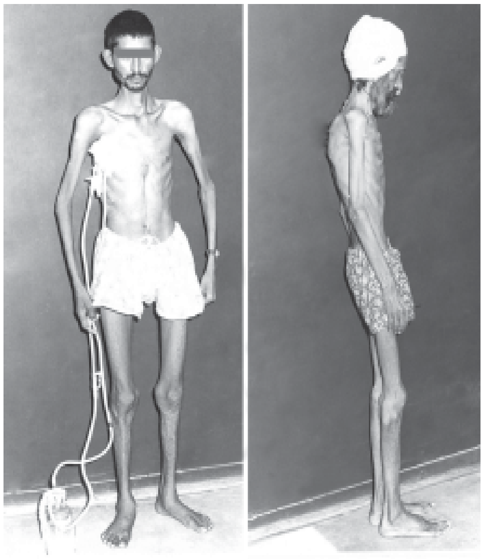

Fig. 11: Extreme wasting from tuberculosis (justifying the older terminology of consumption) was common to see in the TB-wards, even in the sixties and seventies. Fortunately, this degree of severity has become rare with the advent of effective chemotherapy and TB Control Programmes

Section

11

INTERSTITIAL LUNG DISEASE

Dheeraj Gupta

93

Approach to Diagnosis of Interstitial Lung Disease

Dheeraj Gupta

INTRODUCTION

Diffuse Interstitial Lung Disease (ILD) encompasses a group of disorders of diverse etiologies with the common feature of generalized involvement of the lung interstitium. It is a heterogeneous group of diseases and includes over 200 different diseases, which in spite of their heterogenous nature have several common clinical, radiological and histological manifestations. The presenting symptoms of cough and dyspnea are nonspecific and the diagnosis is often delayed unless the examining physician has a high level of suspicion. Diagnosis comes from a thoughtful history/physical examination coupled with specific laboratory and radiological investigations. The etiology may be further clarified by lung biopsy, however it is not essential. Depending on the etiology, therapy may include immunosuppression, trigger avoidance or observation. The prognosis is closely tied to the etiology. Overall, early diagnosis is critical for best patient outcomes and is dependent on physician's awareness of this often deadly disease.

ETIOLOGY AND CLASSIFICATION

The classification of ILD is confusing and still evolving. Several terminologies and classifications have been used to describe the same clinicopathological disease. ILD is broadly grouped as (a) Primary, when the cause is unknown, and (b) Secondary, when there is an identifiable disease responsible for the interstitial involvement (Table 93.1).

Primary ILD

Primary ILD is idiopathic in origin. No secondary cause or association is identifiable. It was also known in the past as cryptogenic fibrosing alveolitis or Idiopathic Pulmonary Fibrosis (IPF) or "lone IPF". This group of Idiopathic Interstitial Pneumonias (IIP) based on clinicoradiological and pathological features, is now classified into seven distinct types:[1] UIP, DIP, LIP, NSIP, AIP or DAD, and COP. Some of these IIPs such as the DIP, NSIP and RBILD are characteristically associated with the smoking history (See Chapter 95).

Secondary ILDs

Most forms of secondary ILDs have either a known etiological cause or an association with another disease of known (or unknown) etiology (Table 93.1). An ILD secondary to another illness factually represents the pulmonary involvement of the primary disease than a separate entity. There are more than 200 conditions/ exposures known to be associated with ILD. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) International Consensus Statement on ILD categorized ILDs into three broad groups: (1) DPLD with known cause [e.g. connective tissue disease (CTD), hypersensitivity pneumonia, toxins, infections, inherited, malignancy, pneumoconiosis]; (2) Granulomatous DPLD (e.g. sarcoidosis) and (3) Other Diffuse Parenchymal Lung Diseases (DPLDs) [e.g. lymphangioleiomyomatosis (LAM), histiocytosis, esosinophilic lung diseases, etc.] Unfortunately, the etiology of a given ILD more often falls into the idiopathic

TABLE 93.1: Important causes of interstitial lung disease

I. Primary or Idiopathic Interstitial Pneumonias
  1. Usual Interstitial Pneumonia (UIP), i.e. Idiopathic Pulmonary Fibrosis
  2. Nonspecific Interstitial Pneumonia (NSIP)
  3. Cryptogenic Organizing Pneumonia (COP)
  4. Respiratory Bronchiolitis associated ILD (RBILD)
  5. Acute Interstitial Pneumonia (AIP) / Diffuse Alveolar Damage (DAD)
  6. Desquamative Interstitial Pneumonia (DIP)
  7. Lymphocytic Interstitial Pneumonia (LIP)

II. Secondary
  A. *Known Causes*
    1. Infections
      - Tuberculosis
      - Bacterial
      - Fungal
      - Parasitic
      - Viral
    2. *Noninfectious causes*
      - Hypersensitivity pneumonitis
      - Pneumoconiosis
      - Drug induced
      - Radiation induced
      - Malignancies
      - Systemic vasculitides
  B. *Association with Diseases of Inflammatory or Unknown Etiology*
    1. *Sarcoidosis*
    2. *Connective tissue disorders*
      - Systemic sclerosis
      - Rheumatoid arthritis
      - Polymyositis/dermatomyositis
      - Systemic lupus erythematosus
    3. *Chronic eosinophilic pneumonia*
    4. *Miscellaneous*
      - Histiocytosis
      - Eosinophilic granuloma
      - Lymphangioleiomyomatosis
      - Tuberous sclerosis

category. Even in cases of ILD with a defined etiology, the mechanisms of lung injury and fibrosis are largely undefined.

Connective Tissue Diseases

The most important association of ILD is seen with different connective tissue disorders (CTDs). Pulmonary Fibrosis is most prevalent in Systemic Sclerosis (SSc-PF), forming part of the American Rheumatism Association minor diagnostic criteria for SSc.[2] Clinically significant pulmonary fibrosis occurs in approximately 30% of patients with SSc and polymyositis/dermatomyositis (PM/DM), 10% with Sjögren's syndrome (SS), and in less than 5% with Systemic Lupus Erythematosus (SLE) or Rheumatoid Arthritis (RA).[3] Studies of lung function and High Resolution Computed Tomography (HRCT) scanning suggest a much higher prevalence of subclinical disease in all of these disorders.[4-7] Ankylosing Spondylitis (AS) is frequently associated with limited nonspecific HRCT abnormalities, but clinically significant upper zone fibrobullous disease is relatively uncommon.[8] There is a great degree of overlap between idiopathic pulmonary fibrosis and fibrosis associated with different CTDs.

Occupational and Environmental Exposures

Occupational exposure to different inorganic and metal dusts is another important cause. Silica dust causes progressive fibrosis, massive progressive fibrosis can occur in a much shorter period of a few weeks to a few months in case of a heavy exposure. Asbestosis and anthracosis are also associated with pulmonary fibrosis. Inhalation of toxic gases and fumes, such as methyl isocyanate and nitrogen dioxide can cause interstitial involvement. In view of a shorter exposure, it is generally self-limiting, but chronic pulmonary involvement from inhalational exposure is also possible.

Drugs (See Chapter 114)

Several drugs are known to cause ILD. Pneumotox® (www.pneumotox.com) provides free and updated information on drug-induced respiratory disease. Drugs and drug classes which more often cause ILD include amiodarone, chemo agents [bleomycin, busulfan, chlorambucil, cyclophosphamide, gemcitabine, imatinib, methotrexate, mitomycin C, nitrosoureas (BCNU, CCNU and newer nitrosoureas), rituximab, trastuzumab and taxanes], disease-modifying anti-rheumatic drugs (methotrexate, anti-TNF-alpha antibody therapy), interferon, minocycline, nitrofurantoin, nonsteroidal anti-inflammatory drugs (NSAIDs), and rapamycin.[9] Drugs given by almost any route of administration [oral, parenteral, inhaled, topical (ophthalmic, dermal, intranasal), intrathecal, intracavitary and intra-arterial] can cause ILD. However, the vast majority of cases results from oral or parenteral administration of drugs. The incidence rate of drug-induced ILD varies with the specific drug and among studies and is between 1/100,000 and 1/5,000 treatment courses for nitrofurantoin, to 1 to 5% of patients exposed to the regular doses of amiodarone long term, 17 to 36% of patients treated with rapamycin and congeners[10] and greater than 30% in patients exposed to high-dose amiodarone (>1,200 mg/day).[11]

Radiation

Radiation administered for thoracic malignancies, especially when used in a higher dose, is another iatrogenic cause of ILD.[12] Radiation can induce both pulmonary and mediastinal fibrosis. Radiation lung injury can manifest during weeks, months or years after radiation therapy for lung cancer, breast carcinoma, Hodgkin's or non-Hodgkin's lymphomas, or following total body irradiation in recipients of bone marrow or stem cell transplant. Radiation induced changes may involve the pleura, heart, pulmonary veins, mediastinum, lymphatic vessels and nerves in addition to the lung, creating manifold possibilities and patterns of involvement.

Hypersensitivity Pneumonias (See Chapter 112)

Hypersensitivity pneumonias (extrinsic allergic alveolitis) of acute, subacute or chronic onset, which occur on exposure to known environmental or occupational antigens, include farmer's lung, byssinosis, air-conditioner lung, bird-fancier's disease and mushroom picker's disease. They may also occur in individuals working with different chemicals, drugs, pharmaceutical agents and laboratory animals. This is especially so in the industrial workers engaged in the manufacturing/processing of rubber foam, azo-dyes, tetracyclines, ampicillin, antihypertensive drugs and others.[13]

EPIDEMIOLOGY

Although the exact incidence and prevalence of ILD is not known, patients with this disease comprise about 15% of a pulmonary physician's practice.[14,15] Mortality from cryptogenic fibrosing alveolitis continues to increase in many countries.[16] In India, this was earlier considered to be a rare disease. In 1979, Jindal et al. published their data on 61 cases of DPLD seen over a period of five years.[17] However, the scenario is different now and the disease is no longer rare or uncommon. Recently the same center published data on 76 patients with IPF diagnosed over a 16-month period showing a definite increase in the frequency of diagnosis.[18] A number of other publications from India have described various aspects of the disease.[19-31] The increase in the number of studies from India may be a true reflection of the increase in the incidence or may be apparent because of increased awareness of the condition or due to better availability of diagnostic facilities like HRCT and fibreoptic bronchoscopy.

Globally, also the incidence and prevalence of ILD is unclear, as it is often found incidentally and can be the result of innumerable insults. Idiopathic pulmonary fibrosis, is the most common and best studied ILD. The prevalence of this disease was studied in Bernalillo County, New Mexico, and was estimated to be 13.2 to 20.2 per 100,000, with an annual incidence of 7.4 to 10.7 per 100,000 cases per year.[15] Since IPF accounts for 60% of the ILD cases, one can estimate the true incidence of ILD in the general population is much greater.[15] Furthermore, the prevalence of IPF in individuals older than 75 years of age has been estimated to be as high as 175 per 100,000.[15] This is of importance given that two-thirds of patients with IPF are over 60 years of age at diagnosis and globally the population is ageing, ILD will be encountered with increasing frequency.[32] In a recent population-based study from Olmsted County, Minnesota, from 1997 to 2005, the age- and sex-adjusted incidence was 8.8/100,000 and 17.4/100,000 person-years, using narrow or broad criteria respectively. The age-adjusted incidence was higher in men than in women, and among patients aged 70 to 79 years and had shown a significant decline during the study period.[33]

PATHOLOGY

As is implied in the name the primary site of pathology is in the pulmonary interstitium. The diverse etiologies lead to pulmonary inflammation and/or fibrosis as the final common pathways to lung damage. Hence, the ILDs are often referred to collectively as "pulmonary fibrosis." The normal pulmonary interstitium comprises of the anatomical space between the alveolar and the capillary basement membranes. In a normal lung, this space is occupied by a single cell layer, only 10 microns in width, allowing passive diffusion of oxygen between the alveolus and blood in the capillaries. It also contains mesenchymal and connective tissue cells, and extracellular matrix composed of collagen, elastin and proteoglycans. Characteristically, there is cellular infiltration and thickening of pulmonary interstitium and of alveolar walls, as well as spillage of mononuclear cells in the alveolar lumen. The cellular exudate comprises primarily of alveolar macrophages, but lymphocytes, neutrophils, eosinophils and plasma cells are also present.

Although the total collagen component of lungs remains normal, the ratio of type I to type III collagen is increased. The interstitial involvement progressively encroaches the alveolar spaces, the terminal bronchioles and also the overlying pleura. It is for this reason the ILDs are also referred to as "Diffuse Parenchymal Lung Diseases" (DPLDs). The advanced-stage disease is characterized by extensive fibrosis, obliteration of the lumen of alveoli and formation of multiple cysts, also called as the honeycomb lung. The ILDs are distinct from diseases predominantly affecting the airways and blood vessels.

PATHOGENESIS

There is no clear understanding of disease-pathogenesis. Chronic inflammation, recurrent epithelial injury and impaired wound repair are some of the possible reasons of pulmonary fibrosis.[34] Several new mechanisms of pulmonary fibrosis have evolved in the last decade. Pulmonary fibrosis is considered to result from an aberrant defense reaction with failure of mechanisms which are normally responsible for repair. It is now recognized that there is persistence and/or repetitive injury responsible for inflammation followed by recruitment of a host of inflammatory cells.[35]

Recently an interesting perspective has proposed that ILD (IPF) should be considered as a neoproliferative disorder of the lung. Genetic alterations, response to growth and inhibitory signals, resistance to apoptosis, myofibroblast origin and behavior, altered cellular communications, and intracellular signaling pathways are all fundamental pathogenic hallmarks of both IPF and cancer and IPF is associated with a poor prognosis, like the cancers.[36]

Several pathobiological processes have been identified or proposed, some of which have been outlined below (Fig. 93.1), a detailed account being out of preview of this chapter.

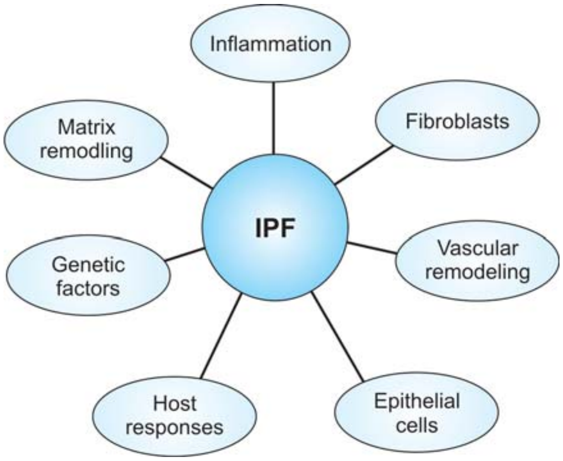

Fig. 93.1: Proposed mechanisms for development of pulmonary fibrosis

Inflammatory Hypothesis

Inflammation as the central mechanism causing IPF was largely derived from the observation that bronchoalveolar lavage fluid from patients with IPF had increased numbers of inflammatory cells (mostly neutrophils and eosinophils) relative to normal individuals. Therapies were therefore directed at abrogating inflammation with corticosteroids. However, lack of response to corticosteroids has lead to the belief that inflammation may be a result, rather than a cause of the fibrosis. This was supported by the studies showing increased levels of the CXC chemokine IL-8/CXCL8, a potent chemotactic cytokine for neutrophils in lung tissue.[37]

Vascular Hypothesis

Increased angiogenesis has been suggested to play an important role in the progression of pulmonary fibrosis in both animal models and clinical specimens.[38,39] This increased angiogenic activity has been attributed to an imbalance of pro-angiogenic chemokines (IL-8, ENA-78) and anti-angiogenic CXC chemokines (IP-10/CXCL10).[40,41] In contrast, recent reports have shown decreased expression of Vascular Endothelial Growth Factor (VEGF) and endothelial cell proliferation in IPF.[40-42] It is likely that angiogenesis may be enhanced in the earlier stages of the development of UIP, while there is a loss of blood vessels in the more advanced stages. Pulmonary hypertension is becoming recognized as an important clinical component of progressive IPF in some patients.[21,43]

Alveolar Epithelial Cells

Abnormalities in alveolar type II cell injury and repair may be a critical feature in the pathogenesis of pulmonary fibrosis. Ultrastructural studies have demonstrated alveolar type II cell injury and apoptosis in lung biopsies from IPF patients. Studies have demonstrated increased expression of proapoptotic proteins in alveolar epithelial cells and in Broncho-alveolar Lavage (BAL) from IPF patients. More recent data have suggested that there is increased oxidative stress in alveolar epithelium in IPF patients.[44-49]

Matrix Remodeling

There is an imbalance between the production and degradation of extracellular matrix, which leads to excessive production of extracellular matrix molecules including collagens, tenascin, proteoglycans and glycosaminoglycans.[50] TGF-beta promotes matrix production and inhibits inhibitors of matrix degradation (TIMPs) and thus could be a key mediator in this process.[51,52]

Fibroblast Activation and Dysfunction

A variety of growth factors that influence fibroblast and myofibroblast functions have been shown to be produced in the lung tissue of IPF patients. These include Th2 cytokines (IL-4, IL-5 and IL-13), growth factors such as TGF-β, IGF-1[53], PDGF A or B and CTGF.[54] Also the fibroblasts in IPF may have unique phenotype that can have different growth rates.[55,56] Recent studies suggest that myofibroblasts may also have an important role in mediating lung fibrosis.[46,57,58]

DIAGNOSTIC APPROACH

Diagnosis of ILD is generally suspected on history and clinical examination. However, a comprehensive evaluation is required to narrow down the possible predisposing factor in the secondary ILD or to assign it to one of the known categories of idiopathic varieties. This exercise is important as there are important treatment and prognostic implications to a proper diagnosis. The final diagnosis of ILDs essentially rest on the evaluation of ***C***linical, ***R***adiological and ***P***athological data in unison and is also referred to as ***C-R-P*** diagnosis. In approaching the ILD several actions are required, which include:

- A methodical history to include demographics, family history, and occupational/environmental exposures
- Physical examination
- Chest radiographs
- High resolution computed tomographic scans
- Blood tests
- Fiberoptic bronchoscopy with BAL or transbronchial lung biopsies (selected patients)
- Surgical lung biopsy (selected patients)

Clinical History

The clinical signs and symptoms of ILD are generally not specific to a diagnosis of ILD. Individuals present with progressive dyspnea on exertion and dry cough. Symptoms are usually progressive. Since two-thirds of patients with ILD are over 60 years of age at diagnosis, the initial symptoms may be attributed to cardiac disease, deconditioning or advancing age, thus delaying the ultimate diagnosis and treatment.[26] A thoughtful assessment of the course and progression of the illness (weeks, months, years) provides some suggestions regarding etiology. A long history over many years is a good hint for idiopathic pulmonary fibrosis. Clinical data may be used to predict a diagnosis of IPF over other IIPs.[59] A patient with a much more fulminant presentation is suggestive of COP or AIP. Occasionally, additional symptoms, may suggest a potential etiology for the ILD (Table 93.2). Connective tissue disease-associated ILD (CT-ILD) often presents in previously diagnosed CTD, although ILD may predate other manifestations of CTD. In these patients, specific symptoms related to various CTDs provide a critical clue to the etiology of the lung disease. An increased incidence of ILD has been noted in certain families. These cases of “familial idiopathic pulmonary fibrosis” are thought to account for less than 3% of all cases and may be associated with a defect in surfactant protein C.[60] Careful history of drug and tobacco use is also important.[61,62]

Physical Examination

Physical examination is helpful in suggesting interstitial involvement, but rarely it leads to a specific diagnosis (Table 93.2). The bibasal dry, end-inspiratory “velcro” crackles are quite characteristically heard in most patients of IPF. These crackles are attributed to the snap opening up of collapsed alveoli when equalization of pressure occurs between the alveolar spaces and the proximal bronchiole during inspiration.[1,63] Finger-clubbing is present in about one-third of patients. Hypertrophic osteoarthropathy is rarely seen. Cyanosis is generally absent at rest but desaturation occurs and cyanosis appears after even mild exercise. Cyanosis may be present even at rest in an advanced disease. Physical examination of the chest may reveal tachypnea, reduced chest expansion and intercostal retractions. Breath sounds are vesicular and quite distinct. Bronchovesicular or bronchial breathing is heard in the presence of a consolidation, a cavity or an advanced disease.

Patients with secondary ILD may also show symptoms and signs of the underlying disease. Patients with CREST syndrome (calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly and telangiectasia) may present with pulmonary hypertension as a primary manifestation. Pulmonary hypertension and chronic cor pulmonale, chronic congestive failure develops in a long-standing disease.[64,65]

Chest Radiography

A diffusely abnormal chest radiograph often is the first leading clue to a diagnosis of ILD, however, a normal chest X-ray does not exclude ILD.[1] The interstitial infiltrates are seen as discrete linear, nodular or

TABLE 93.2: Clinical clues to specific diagnosis of ILD[66]

Clinical clue	*Diagnostic possibilities*
A. History	
• Age 60 years	IPF
Younger (20-40)	CTD
• Gender	LAM exclusively in women
• Acute onset, fever	Infections, AIP, CTD (acute lupus), AEP, COP, HP, drugs
• History of smoking	RB-ILD, DIP, UIP, PLCH, Goodpasteur's syndrome, less in HP
• Specific exposures	Occupational ILD, pneumoconiosis, HP
• Hemoptysis	Alveolar hemorrhage syndromes, LAM
• Arthralgia	IPF, CTD (arthritis with morning stiffness)
• Skin rash, dysphagia, Raynaud's, skin tightness, dryness	CTD
B. Physical examination	
• Typical 'velcro' crepts	IPF, crepts frequently absent in sarcoidosis
• Inspiratory squeaks	COP
• Clubbing	IPF, DIP, IBD
• Skin involvement	Sarcoidosis, CTD, Vasculitis, Tuberous sclerosis
• Arthritis	CTD, sarcoidosis
• Eye changes (uveitis, conjunctivitis)	Sarcoidosis, CTD
• Muscle weakness	Polymyositis, dermatomyositis
• Neuropathy	Sarcoidosis, CTD
• Lymphadenopathy	Sarcoidosis, CTD

Adapted from reference 66

IPF: idiopathic pulmonary fibrosis: CTD: connective tissue diseases: LAM: lymphangioleiomyomatosis: API: acute interstitial pneumonia: AEP: acute eosinophilic pneumonia: COP: cryptogenic organizing pneumonia: HP: hypersensitivity pneumonitis: RB-ILD: respiratory bronchiolitis associated ILD: DIP: desquamative: UIP: usual interstitial pneumonia: PLCH: pulmonary Langherhan's cell histiocytosis: IBD: inflammatory bowel disease

reticulonodular shadows diffusely distributed in both the lungs. The individual nodular shadows are usually of less than 2 mm in diameter. They may also coalesce and form larger nodules. The shadows are generally bibasilar in distribution in early stages. In later stages, diffuse involvement occurs all over the lungs. Upper lobe involvement suggests diseases such as pneumoconiosis, sarcoidosis and hypersensitivity pneumonias. The abnormalities on chest radiograph often provide useful clues and are a good starting point in narrowing the differential diagnoses (Table 93.3).

Presence of diffuse mottling or ground-glass appearances may suggest an active stage of diffuse alveolitis. Miliary distribution throughout the lung fields is characteristically seen in tuberculosis, pneumoconiosis, and sometimes in sarcoidosis. Occasionally, fluffy alveolar shadows may be present due to the coalescence of interstitial shadows or a complicating infection. In advanced disease, when fibrosis is extensive, the lungs get shrunken and reduced in volume. Small, uniform sized, quadrangular cystic spaces, representing patent bronchioles, give the typical appearances of a honeycomb lung.

High Resolution Computed Tomography

High resolution computed tomographic scanning offers a much better view of lung parenchymal involvement.[67] The classical picture of bibasilar reticular and/or nodular infiltrates, honeycombing and absence of lymphadenopathy support the diagnosis of idiopathic pulmonary fibrosis.[68] Pathology is considered uncertain if radiographic findings are atypical, lung involvement is mild or patchy and/or there is presence of hilar or mediastinal lymphadenopathy. The HRCT scan is of great use in classifying IPF.[59,69,70] The HRCT features of subpleural septal thickening, traction bronchiectasis and ground glass attenuation can be considered as definite UIP and lung biopsy avoided.[71,72] Diseases such as sarcoidosis, histiocytosis and lymphangitis have more characteristic patterns.[66] High resolution computed tomography is also of some help in making a quantitative assessment of pulmonary fibrosis.[73] Spiral CT scan gives an even better resolution, especially in a patient with tachypnea who cannot hold his breath.

Pulmonary Function Tests (PFT)

Most ILDs demonstrate a restrictive defect on spirometry and PFT cannot help in differential diagnosis. They are important however for functional assessment and to monitor therapy. Tidal volumes are generally small and both the vital capacity and the total lung capacity are reduced.[74,75] Expiratory flows are normal or even "supranormal". Airway obstruction, characterized by reduced Forced Vital Capacity (FVC) and forced expiratory flows, can occur in patients with hypersensitivity pneumonias, and in smokers. Reduced diffusing capacity (DLCO) and arterial hypoxemia (reduced PaO_2) may not be present in the early stages. Some degree of arterial hypoxemia on exercise is almost always demonstrable.

Measurements of pulmonary compliance can pick up early lung involvement in CT-ILDs.[6,7]

Bronchoalveolar Lavage

Assessment of cellular response in the BAL fluid, although nonconclusive, may help in the differential diagnosis.[76] BAL may be adequate to diagnose specific infections (e.g. tuberculosis, histoplasmosis, coccidioidomycosis, endemic fungal infections) and selected non-infectious diseases (e.g. PLCH[77]or LAM[78]). Increases in BAL lymphocytes suggest sarcoidosis, HP, or other granulomatous processes. When BAL lymphocytes exceed 50%, HP is likely.[76] Presence of eosinophils (>25%) may suggest acute or chronic eosinophilic pneumonia.[79] However, mild increases in lymphocytes or eosinophils have no diagnostic value.[80] Increase in neutrophils can be seen in a wide array of fibrotic disorders.[81] The interstitial lung diseases differ in the pattern of cytokines expressed in BAL and thus the measurement of cytokine levels could be diagnostically useful.[82] Infective microorganisms such as the *Mycobacteria*, fungi or *Pneumocystis jiroveci* can be isolated from BAL fluid. Presence of lymphocytosis in the BAL fluid is shown to predict a better response to corticosteroid therapy. An increase in the alkaline phosphatase/albumin ratio in BAL fluid on a repeat study reflects progression of fibrosis.[83]

Other Investigations

Although nonspecific, hematological investigations provide useful information. A high Erythrocyte Sedimentation Rate (ESR) of more than 50 mm in the first hour occurs in connective tissue disorders, malignancies, infections and systemic vasculitides. Unexplained anemia is seen in diffuse alveolar hemorrhage and connective tissue diseases. Mild-to-moderate leukocytosis is common in both primary and secondary ILDs. Eosinophilia is more characteristically seen in eosinophilic and hypersensitivity pneumonias, vasculitides, sarcoidosis and drug induced lung disease. Occasionally, there is leukopenia and/or thrombocytopenia.

Abnormal liver or renal function tests suggest the involvement of these organs. Elevated calcium may be seen in sarcoidosis and malignancies. Increased enzymes such as creatinine phosphokinase and aldolase are present in polymyositis and dermatomyositis. Increased Serum Angiotensin Converting Enzyme (SACE) in sarcoidois is quite characteristic but may be seen in silicosis, hypersensitivity pneumonias and other diseases.

A number of immunological parameters are described in connective tissue disorders and other ILDs. Hypergammaglobulinemia, positive serum autoantibodies (e.g. the antinuclear factor) and circulating immune complexes may be seen. Anti-basement membrane antibodies in Goodpasture’s syndrome, Antineutrophil Cytoplasmic Antibody (C-ANCA) in Wegener’s granulomatosis, Churg-Strauss syndrome and systemic necrotizing vasculitis, and anti-Jo-1 antibody in polymyositis-dermatomyositis are generally considered characteristic.

Radionuclide scanning using Gallium-67,[84-85] and Position Emission Tomography (PET) scans[86-87] with glucose Fluorodeoxyglucose (FDG) isotope have a place to identify disease-activity and to predict response to therapy. Similarly, the clearance of aerosolized technetium-99m Diethylene Triamine Penta-acetic Acid (DTPA) is markedly increased in patients with inflammatory lung diseases including sarcoidosis.[88]

Lung Biopsy

Diagnosis of IIPs is fairly specific on clinical features and roentgenographic characteristics seen on HRCT scanning. Lung biopsy is required only when the findings are atypical, to exclude an infection, vasculitis or some other undiagnosed cause of ILD is suspected. It may also help to predict the response to treatment and prognosis of a patient.[89] Patients with usual interstitial pneumonia do worse than those with other histological subsets of IIP. Transbronchial Lung Biopsy (TBLB) with the help of fiberoptic bronchoscopy is less rewarding especially in patients with IPF. In sarcoidosis, the positivity rates of TBLB may be as high as 70 to 80%. Many a patient of IPF cannot be subjected to TBLB in view of an inadequate biopsy size and risks involved with fiberoptic bronchoscopy. Transthoracic or open surgical approach provides a better option to obtain lung tissue.[90,91] Surgical lung biopsy achieves three purposes: (1) establishes a precise diagnosis; (2) assesses the extent of inflammation and fibrosis; (3) identifies a histopathological pattern for IIPs.[92,93]

MANAGEMENT

Treatment options for ILD are limited and traditionally are not successful, especially in the case of IPF. Establishing a clear diagnosis of ILD and identifying a potential etiology is critical in determining appropriate therapeutic interventions. The management of ILD should follow an algorithmic approach (Fig. 93.2). In the absence of a satisfactory, definitive treatment of IPF, most objectives (Table 93.4) are achieved with supportive and symptomatic therapy.[63] Several different groups of drugs are employed in its treatment (Table 93.5). Supportive

TABLE 93.3: Some important clues to specific diagnoses in ILD on investigations

Investigation	*Diagnostic possibilities*
A. Chest radiographs	
• Normal	Sarcoidosis, CTD, RB-ILD
• Increased or preserved lung volumes	RB-ILD, CPFE, LAM, AHP
• Upper lobe predominance	Sarcoidosis, HP, Pneumoconiosis, AS
• Lower lobe predominance	IPF, CTD
• Peripheral (Reverse pulmonary edema)	CEP
• Honeycombing	IPF, CTD, chronic HP
• Spontaneous Pneumothorax	LAM, PLCH,
• Pleural effusions	CTD, asbestosis, sarcoidosis
• Fleeting infiltrates	COP, HP
• Miliary pattern	Infections, HP, Sarcoidosis
B. High resolution CT scans	
• Interlobular and intralobular septal thickening, honeycombing, traction bronchiectasis	CTD, IPF, Asbestosis
• Alveolar shadows, ground glassing	COP, AIP, PAP, AEP
• Nodules	Sarcoidosis, Pneumoconiosis, RA
• Cystic ILD	LAM, PLCH, LIP
C. Laboratory investigations	
• Eosinophilia	AEP, CEP
• Iron deficiency anemia	DAH
• Leukopenia/thrombocytopenia	CTD
• Creatinine kinase, Jo-1 antibody	Polymyositis
• ANA, RF	CTD, IPF (low titers)
• Serum precipitins to specific antigens	HP
• ANCA, Anti-GBM antibodies	Vasculitides, Goodpasture's syndrome

Adapted from Raghu and Brown:[66] Abbreviations: CTD: connective tissue diseases: RB-ILD: respiratory bronchiolitis associated ILD: CPEF: combine pulmonary fibrosis and emphysema: LAM: lymphangioleiomyomatosis: AHP: acute hypersensitivity pneumonitis: AS: ankylosing spondylitis: IPF: idiopathic pulmonary fibrosis: AIP: acute interstitial pneumonia: AEP: acute eosinophilic pneumonia: COP: cryptogenic organizing pneumonia: HP: hypersensitivity pneumonitis: PLCH: pulmonary Langherhan's cell histiocytosis

TABLE 93.4: Treatment objectives in ILD

1. Provide symptom-relief
2. Slow down disease progression
3. Prevent complications
4. Improve quality of life
5. Prolong survival
6. Prevent treatment-complications
7. End-of-Life care and palliative treatment

TABLE 93.5: List of drugs used in the treatment of ILD

Treatment of Primary ILD

1. Anti-inflammatory drugs
    - Corticosteroids
    - Azathioprine
    - Cyclophosphamide
2. Anti-fibrotic agents
    - Colchicine
    - Pirfenidone
    - Pentoxifylline
    - D-Penicillamine
    - TGF beta antagonist
    - Interferon-gamma
3. Anti-oxidant agents
    - N-Acetyl Cysteine
    - Nitric Oxide Synthase inhibition
4. Receptor antagonists
5. Anti-Apoptosis agents
6. Anti-Angiogenesis agents

Supportive and symptomatic drugs

1. Oxygen
2. Pulmonary vasodilators
3. Diuretics
4. Antibiotics (if infection)

Rehabilitation

1. Nutrition and dietary supplements
2. Graded, regulated exercises

treatment is provided for respiratory failure, pulmonary hypertension, cor pulmonale and congestive cardiac failure, wherever indicated. Long-term pulmonary vasodilators are not shown to prevent the development of pulmonary hypertension. An acute increase in symptoms and presence of fever with or without mucopurulent expectoration raise the suspicion of a respiratory infection necessitating treatment with antibiotics. To assess the response to therapy and monitor

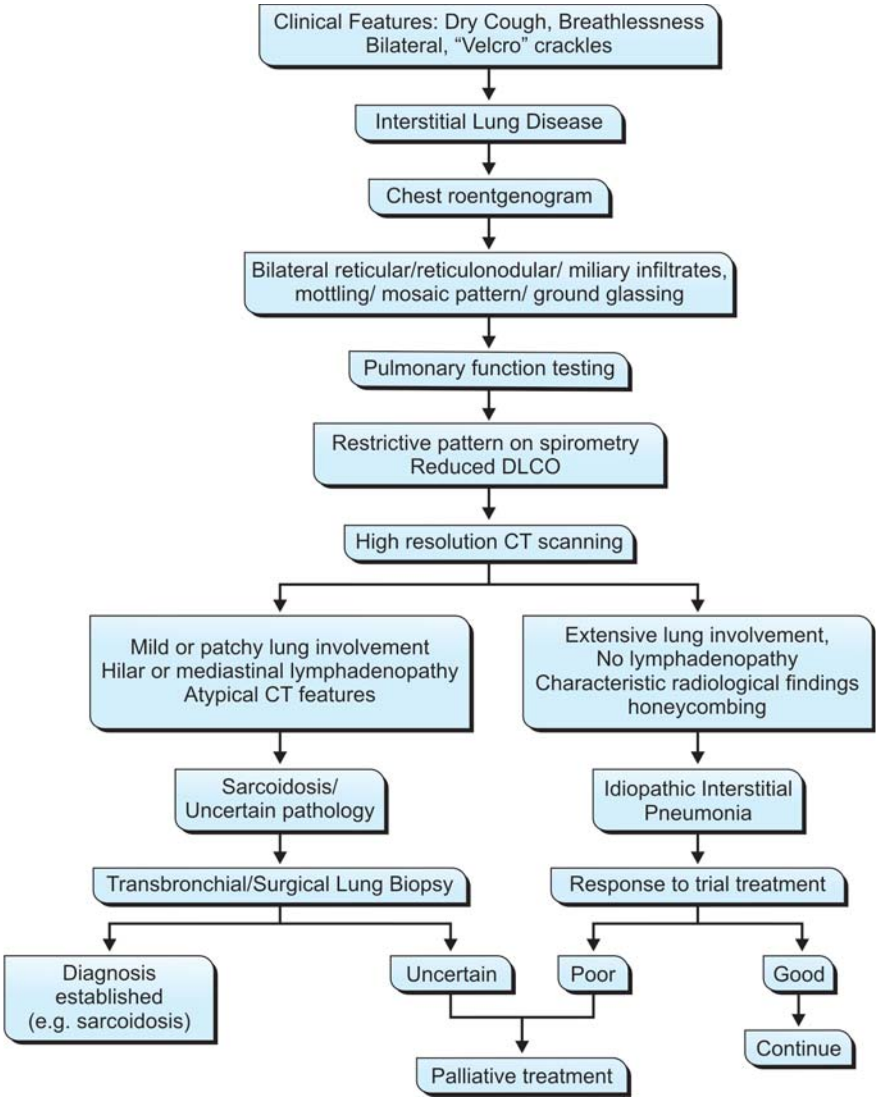
Clinical Features: Dry Cough, Breathlessness
Bilateral, "Velcro" crackles
Interstitial Lung Disease
Chest roentgenogram
Bilateral reticular/reticulonodular/ miliary infiltrates, mottling/ mosaic pattern/ ground glassing
Pulmonary function testing
Restrictive pattern on spirometry
Reduced DLCO
High resolution CT scanning
Mild or patchy lung involvement
Hilar or mediastinal lymphadenopathy
Atypical CT features
Extensive lung involvement,
No lymphadenopathy
Characteristic radiological findings
honeycombing
Sarcoidosis/
Uncertain pathology
Idiopathic Interstitial
Pneumonia
Transbronchial/Surgical Lung Biopsy
Response to trial treatment
Diagnosis
established
(e.g. sarcoidosis)
Uncertain
Poor
Good
Continue
Palliative treatment

Fig. 93.2: Algorithm for diagnosis and management of interstitial lung disease

its progress a Clinical, Roentgenological and Physiological (CRP) score has been used in the past. It is difficult to frequently repeat invasive investigations such as the bronchoalveolar lavage or lung biopsy. It is generally adequate to rely on clinical picture, simple spirometry and a plain chest roentgenogram. The American Thoracic Society has published therapeutic guidelines for specific subtypes of ILD.[1] Broad approaches are discussed here:

Anti-Inflammatory Therapy

Anti-inflammatory therapy has remained the mainstay of treatment. Minimal to significant improvement is reported with the use of anti-inflammatory agents. But their efficacy remains unproven and the toxicities are substantial. The commonly used criteria to start anti-inflammatory treatment include the presence of severe or worsening clinical symptoms, younger age of the patient and shorter duration of illness.

Despite their widespread use only 10 to 30% of patients with IPF improve on quantitative assessment when treated with corticosteroids.[94] Forty percent respond on the basis of subjective or undefined assessment criteria (because of placebo effects or mood-enhancing effects of corticosteroids). Responses are usually partial and transient. If responses are to occur with corticosteroids, improvement is usually noted within three months. Prednisolone is administered in a dose of 1 to 1.5 mg/kg for a period of about 6 to 12 weeks. Maintenance dose of about 15 to 20 mg daily is continued for one to two years, or more. High-dose intravenous pulse methylprednisolone has no proven advantage over oral corticosteroids.[95]

Treatment with corticosteroids alone is now considered inappropriate. Corticosteroids should be used in conjunction with cytotoxic agents.[96] Other immunosuppressive agents such as azathioprine or cyclophosphamide administered along with prednisolone are shown to do better. In one prospective double blind randomized placebo controlled study with 27 patients, combination of azathioprine and prednisolone had a marginally significant survival advantage.[97] Intravenous cyclophosphamide used as intermittent pulse therapy (1 to 1.3 gm/month) is shown to provide some relief.[98] The role of anti-inflammatory therapy is limited to patients with predominant inflammation. The risks especially of prolonged corticosteroid and other immunosuppressants often outweigh the benefits of therapy. A recent study suggested that combined corticosteroid and cyclophosphamide therapy has no impact on survival in patients with IPF.[99]

Anti-Fibrotic Agents

There is a greater trend to rely on antifibrotic drugs for the treatment. Of the several antifibrotic agents which had been tried, colchicine is considered the safest alternative. It is recommended in a dose of 0.6 to 1.2 mg/day for a period of at least 6 to 12 months. Colchicine inhibits collagen formation and modulates the extracellular milieu and suppresses the release of alveolar macrophage-derived growth factor and fibronectin.[100] Efficacy appears similar to corticosteroids and side effects with colchicine are rarely severe. Initial studies were encouraging with trend towards improved outcome.[101] However subsequent studies have failed to demonstrate any benefit of treatment with colchicine over no treatment at all.[102,103] D-penicillamine and pirfenidone are other drugs which have been tried with variable results.[103,104]

Interferon (IF)-γ inhibits the proliferation of lung fibroblasts in a dose-dependent manner and reduces the synthesis of protein in fibroblasts.[56] This had generated great interest in IF as the magic cure for IPF but subsequent studies dampened the hopes.[105] In a large double-blinded trial with 330 patients with IPF who did not respond to corticosteroid therapy, it was found that IF-γ-1b did not affect progression-free survival, pulmonary function, or the quality of life over 58 weeks. However a trend toward enhanced survival was seen in those who received IF (an absolute reduction in the risk of death of 7% and a relative reduction in the risk of 41%).[106] Increased levels of Interleukin-18 in the induced sputum of patients with IPF have been found to decrease after treatment with IF-γ.[107] A recent meta-analysis showed that IF-γ-1b therapy is associated with reduced mortality.[108] More studies are currently underway to exactly define the safety and efficacy of this form of therapy.[109]

Other Treatments

Antioxidants such as N-acetyl cysteine to reduce oxidative stress are shown to offer some clinical advantage when used along with anti-fibrotic agents. A recent double-blind, randomized, placebo-controlled multicenter study assessed the effectiveness over one year of a high oral dose of acetylcysteine (600 mg three times daily) added to standard therapy with prednisone plus azathioprine.[110] This landmark trial showed that acetylcysteine slowed the deterioration of vital capacity and DLCO at 12 months without significant differences in the type or severity of adverse events.

Drugs targeted to prevent or reduce apoptosis, angiogenesis and coagulant activity may find some use in the future. Presently, no drug from these groups is available for clinical use. It is a better option to resort to symptomatic palliative therapy and withdraw immunosuppressive drugs in case there is no response in the initial three to six months of use and for end-stage disease.

Lung Transplantation

Lung transplantation is the only hope for the advanced, end-stage disease.[111] Single lung transplantation is recommended in most patients. Five years survival is reported in up to 40 to 60% of patients. The common posttransplant complications include the risk of resection, multiple opportunistic infections in an immunosuppressed host and organizing pneumonias. The lack of availability of organ for transplantation and very high costs involved in the procedure are the limited factors. Living-Donor Lobar Lung Transplantation (LDLLT) is a new and evolving option for patients with end-stage lung disease.[112]

Other Supportive Measures

The primary goal in managing a patient with IPF is to restore them to the highest possible functional state. Patients should be encouraged to enroll in a pulmonary physical rehabilitation program. Daily walks or use of a stationary bicycle are useful. Those with hypoxemia at rest or during exercise should be managed by supplemental oxygen. Higher flow rates than those needed in COPD may be frequently required. Dry cough may be controlled with anti-tussives. Low dose opioids are effective and safe in the palliative management of dyspnea in terminally ill IPF patients.[113] Pulmonary hypertension, cor pulmonale and right heart failure, which complicate late stages of IPF, should be appropriately managed. In randomized controlled, open-label trial a phosphodiesterase type 5-inhibitor sildenafil causes preferential pulmonary vasodilatation and improves gas exchange in patients with severe lung fibrosis and secondary pulmonary hypertension.[114]

ACUTE EXACERBATION OF ILD

Acute Exacerbation of Idiopathic Pulmonary Fibrosis (AE-IPF) is a clinical entity defined by the rapid deterioration of IPF during the course of the disease that is not due to infections, pulmonary embolism or heart failure. The condition needs to be differentiated from acute interstitial pneumonia (or Hamman-Rich syndrome), which occurs in patients with no underlying lung disease. The exact etiology and pathogenesis remain unknown, but the condition is characterized by diffuse alveolar damage (on a background of IPF) that probably occurs as a result of a massive lung injury due to some unknown etiologic agent. High-resolution computed tomography can help in prognostication and management of this condition. Once infections and other causes of worsening have been excluded, treatment involves enhanced immunosuppression with pulse doses of methylprednisolone and cytotoxic agents. A systematic review shows that the outcome, however, is poor, with one-month and three-month mortality around 60 and 67%, respectively. Few studies have shown beneficial effects of cyclosporine, pirfenidone, and anticoagulants in the management and prevention of AE-IPF.[115]

PROGNOSIS

Prognosis of ILDs, secondary to systemic diseases or other causes is determined by the natural course of the underlying disease. Prognosis of primary IIPs is variable. While NSIP, DIP and RBILD respond better, the IPF is progressive and fatal. The survival has not significantly improved in the last nearly 50 years or so from that reported in the 1960s. The median survival of IPF is about four years. Acute interstitial pneumonia and acute exacerbation of IPF are rapidly fatal, sometimes in a course of a few weeks or months.[116]

It is unclear how many ILD patients actually die of their lung disease.[15,117] Given the advanced age of many with ILD, patients are at risk for other age-related diseases and need close follow-up. Survival for ILD is worse if at time of diagnosis there is advanced age (>50), male gender, moderate/severe dyspnea on exertion, history of tobacco use, moderate loss of lung function (TLC <45%, DLCO <40%), neutrophilia/eosinophilia on bronchoalveolar lavage, honeycombing on HRCT, lack of a response to corticosteroids, or moderate/severe fibrosis and fibroblastic foci on histology.[118-119]

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94

Pathology of Interstitial Lung Disease

Amanjit Bal, Kusum Joshi

Interstitial Lung Disease (ILD) is a heterogeneous group and refers to a diverse range of acute, subacute and chronic diseases that cause inflammation and fibrosis of the alveoli, distal airways and septal interstitium of the lungs. The "interstitium" is a connective tissue framework, abundant around the airways and arteries in the center of the lobules and around the veins at the periphery. At the alveolar level, it includes the space between the epithelial and endothelial basement membranes. It consists of collagen and elastin fibers (fibroblasts and myofibroblasts), histiocytes, lymphocytes, dendritic cells, Langerhans cells and mast cells. Though ILD dominantly involves the interstitium, these disorders may affect the airspaces, peripheral airways and blood vessels along with their respective epithelial and endothelial linings. Hence, an alternative term of Diffuse Parenchymal Lung Disease (DPLD) has been used to define the same group of disorders (Table 94.1).

IDIOPATHIC INTERSTITIAL PNEUMONIA

The Idiopathic Interstitial Pneumonias (IIPs) are a group of diffuse parenchymal diseases of unknown etiology. The American Thoracic Society/European Respiratory Society (ATS/ERS) sponsored committee comprising of the clinicians, radiologists and pathologists developed a consensus classification system for IIPs.[1] This classification was based on the seven histopathologic patterns seen on surgical lung biopsies.

Pathogenesis of Idiopathic Interstitial Pneumonias

Despite intensive research, the etiology and pathogenesis of idiopathic interstitial pneumonias remain poorly understood. Increased number of inflammatory cells in Bronchoalveolar Lavage (BAL) in patients with IIPs, led to the prevailing hypothesis that disease process begins as an "alveolitis" and progresses to interstitial fibrosis. It is speculated that chronic inflammatory process injures the lung and modulates fibrogenesis, leading to the end-stage fibrotic scar. Tansforming Growth Factor-Beta

TABLE 94.1: Classification of Interstitial (Diffuse Parenchymal) Lung Disease

I. **Idiopathic Interstitial Pneumonias**
  - Usual Interstitial Pneumonia/Idiopathic Pulmonary Fibrosis (UIP/IPF)
  - Nonspecific Interstitial Pneumonia (NSIP)
  - Desquamative Interstitial Pneumonia (DIP)
  - Respiratory Bronchiolitis associated Interstitial Lung Disease (RB-ILD)
  - Acute Interstitial Pneumonia (AIP)
  - Lymphoid Interstitial Pneumonia (LIP)
  - Cryptogenic Organizing Pneumonia (COP)

II. **Multisystem Diseases**
  - Sarcoidosis
  - Connective tissue disorders
  - Drug Reactions

III. **Environmental and Occupational Diseases**
  - Pneumoconiosis
  - Hypersensitivity pneumonitis/Extrinsic allergic alveolitis

IV. **Rare Lung Diseases**
  - Lymphangioleiomyomatosis
  - Pulmonary alveolar proteinosis
  - Pulmonary Langerhans cell histiocytosis
  - Pulmonary eosinophilia
  - Idiopathic pulmonary hemosiderosis

(TGF-α) activation which is responsible for maintaining the mesenchymal cells and regulating Extracellular Matrix (ECM) synthesis and degradation is a proposed key element in promoting the progression of pulmonary fibrosis.[2] Though at present the inflammatory cells are the principle source for fibrogenic mediators, but there is evidence that supports the essential role of activation of alveolar epithelial cells after injury. Alveolar epithelial cells are being considered as the main source of Platelet-Derived Growth Factor (PDGF), TGF-β1, Tumor Necrosis Factor-Alpha (TNF-α), Endothelial (ET)-1 and Connective Tissue Growth Factor (CTGF); the mediators implicated in the pathogenesis of pulmonary fibrosis.

Utility of Bronchoalveolar Lavage (BAL) and Lung Biopsy

Bronchoalveolar lavage is useful for detecting infections as a cause of diffuse lung infiltrates. The method consists of instilling saline via a bronchoscope wedged in a segmental bronchus, which gets exposed to a large area of the parenchyma and then aspirating and collecting the same. Opportunistic infections in the immunosuppressed can be easily diagnosed. An excess of lymphocytes can be indicative of sarcoidosis; whereas, an increase in neutrophils and eosinophils is typically found in idiopathic pulmonary fibrosis. Rarely, langerhans cells can be identified in a case of langerhans' cell histiocytosis. Hemosiderin laden macrophages indicate old hemorrhage in pulmonary hemosiderosis, vasculitis or other causes.

Lung biopsy is often required to clinch the diagnosis. Although, lung biopsy is said to be the gold standard, it is limited by the fact that only a small tissue is being sampled in a disease which is heterogeneous from area to area. Transbronchial lung biopsy is usually inadequate for the diagnosis as it samples only centrilobular areas; however, it may be of value to diagnose organizing pneumonia, and RB-ILD and to exclude granulomatous lesions, neoplasms as well as infectious etiologies. Thus surgical lung biopsy is almost always required to determine the histological pattern in idiopathic interstitial pneumonias. It is important to avoid areas of end stage disease and biopsies from multiple sites provide diagnostic tissue and reduce sampling errors.

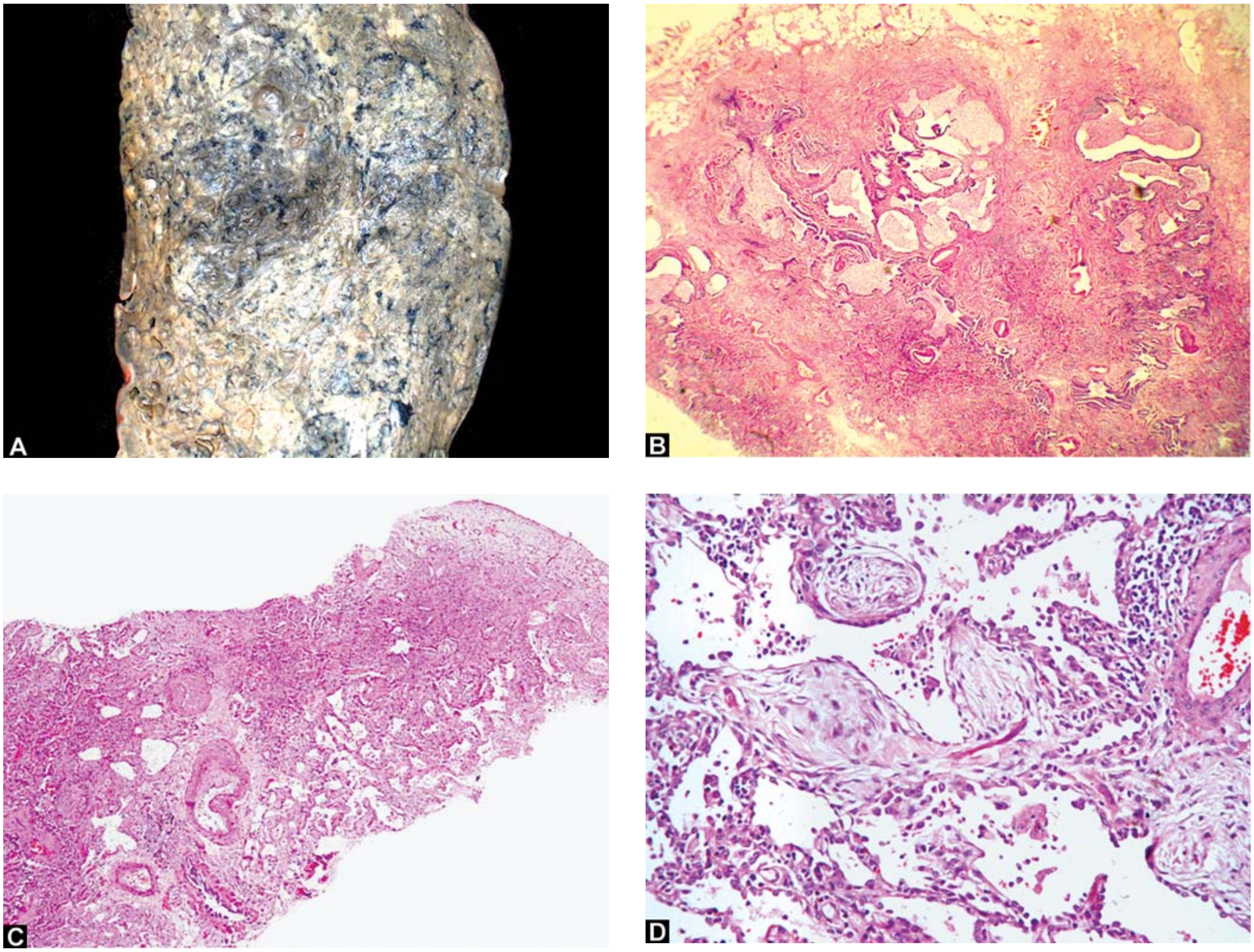
Usual Interstitial Pneumonia (UIP)

Usual interstitial pneumonia is the most common of idiopathic interstitial pneumonias. Idiopathic Pulmonary Fibrosis (IPF) and UIP are interchangeable terms; IPF being a chronic fibrosing interstitial pneumonia of unknown cause with a surgical lung biopsy showing a histologic pattern of UIP.[3] Patients with UIP usually present in the sixth or seventh decade of life with slowly progressive dyspnea and cough. Pulmonary function studies show restrictive abnormalities, and/or impaired gas exchange, decreased PaO_2 with rest or exercise, or decreased diffusing capacity of the lung for carbon monoxide. High Resolution Computed Tomography (HRCT) shows a characteristic combination of peripheral (subpleural), irregular, linear "reticular" opacities involving predominantly the lower lung zones with associated architectural distortion in the form of traction bronchiectasis and honeycomb change.

Histopathological features: UIP is a specific morphological entity defined by a combination of (i) fibrosis distributed in a heterogeneous fashion, (ii) fibroblastic foci, and (iii) honeycomb change and scars.[4] On examination at low magnification, UIP is characterized by "spatial heterogeneity" and nonuniform distribution of the inflammatory and fibrosing process (Fig. 94.1A). These morphological changes are sharply demarcated from the adjacent normal areas. The fibrosis is more marked at the periphery and paraseptal region in the lower lobes. The other cardinal feature of UIP is the presence of active fibroblastic foci which comprises of plump spindle cells with little intervening collagen (Fig. 94.1B). The other areas of fibrosis show poorly cellular foci with deeply eosinophilic hyalinized collagen. This variation in age of fibrosis is termed as "temporal heterogeneity." The inflammatory component in UIP is usually mild to moderate and is composed of lymphocytes and plasma cells with occasional aggregate formation. In advanced stages, fibrosis leads to distortion of the lung parenchyma and cystic dilatation of air spaces resulting in end stage lung or honeycomb change (Fig. 94.1C). The end stage lung shows bronchiolar metaplasia of alveoli, prominence of type II pneumocytes and smooth muscle hyperplasia (Fig. 94.1D). These end stage changes when florid has been termed as "muscular cirrhosis" of the lungs. Vascular changes in the scarred areas show intimal proliferation and medial hypertrophy resulting in endarteritis obliterans.

Nonspecific Interstitial Pneumonia (NSIP)

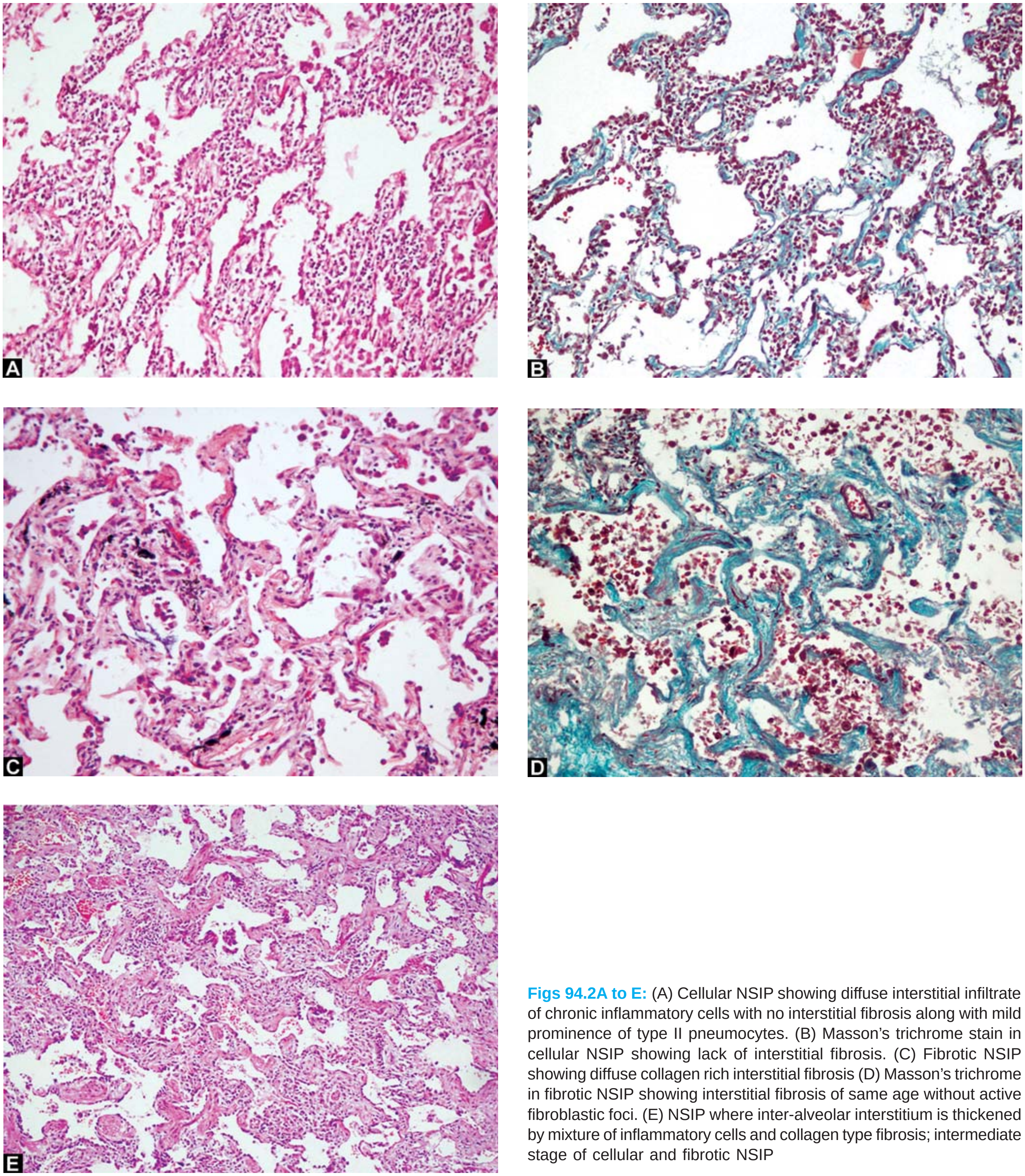
Nonspecific interstitial pneumonia is regarded as provisional in ATS/ERS consensus classification and is used for cases that do not fulfill the diagnostic criteria of UIP, DIP and RB-ILD. Nonspecific interstitial pneumonia is currently the second most common (after UIP) histopathological pattern of the idiopathic interstitial



Figs 94.1A to D: (A) Gross photograph of cut surface of the lung in usual interstitial pneumonia showing extensive peripheral honeycombing. (B) Photomicrograph of honeycomb change in UIP characterized by enlarged airspaces lined by bronchiolar type of epithelium, surrounded by dense fibrosis and lumen filled with mucin and inflammatory cells. (C) Patchy heterogeneous inflammation and fibrosis with subpleural localization, and alternating with normal lung parenchyma in a case of UIP. (D) Fibroblastic foci composed of plump spindle shaped fibroblasts in the interstitium and lifting the alveolar lining epithelial cells in UIP

pneumonias and is characterized by a temporally and spatially uniform pattern that suggests that the lesions are of the same age.

Histopathological features: Nonspecific interstitial pneumonia is characterized by "temporal homogeneity". Nonspecific interstitial pneumonia has three major subgroups based on the amount of inflammation and/or fibrosis in the lung biopsies: **Group I (Cellular NSIP):** Primarily with interstitial inflammation, **Group II**: With both inflammation and fibrosis, and **Group III (Fibrotic NSIP):** Primarily with fibrosis.[4] The cellular end of the spectrum has mild-to-moderate interstitial inflammation comprising of lymphocytes and plasma cells with minimal or no fibrosis (Fig. 94.2A and B). The fibrotic end of spectrum shows interstitial fibrosis composed of mature collagen and only a few fibroblasts (Fig. 94.2C and D). Intermediate stage of cellular and fibrotic NSIP shows mixture of inflammatory cells and collagen type fibrosis (Fig. 94.2E). The lung architecture may appear to be lost on examination of routine hematoxylin and eosin-stained sections, but is relatively preserved with elastic stains. NSIP lacks alveolar remodeling with honeycomb cyst formation and active fibroblastic foci distinguishing it from UIP.[5]

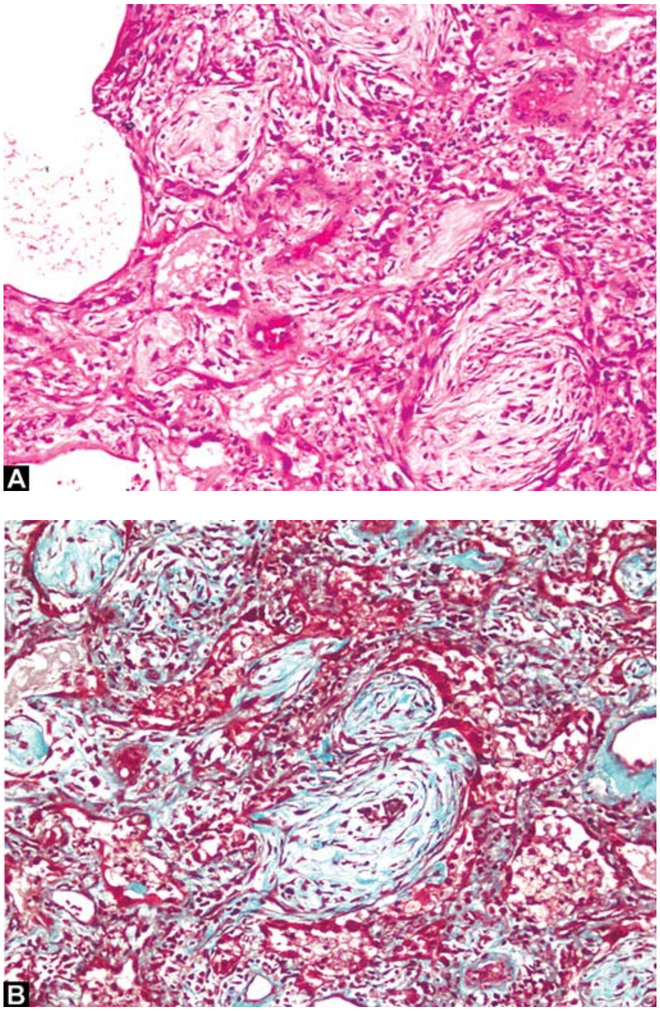


Figs 94.2A to E: (A) Cellular NSIP showing diffuse interstitial infiltrate of chronic inflammatory cells with no interstitial fibrosis along with mild prominence of type II pneumocytes. (B) Masson's trichrome stain in cellular NSIP showing lack of interstitial fibrosis. (C) Fibrotic NSIP showing diffuse collagen rich interstitial fibrosis (D) Masson's trichrome in fibrotic NSIP showing interstitial fibrosis of same age without active fibroblastic foci. (E) NSIP where inter-alveolar interstitium is thickened by mixture of inflammatory cells and collagen type fibrosis; intermediate stage of cellular and fibrotic NSIP

Cryptogenic Organizing Pneumonia (COP)

Organizing pneumonia is a histologic pattern of repair in response to injury. It is characterized by air space filling fibrosing process that involves distal bronchioles, alveolar ducts and peribronchiolar alveolar spaces. Different terminologies have been used for this lesion which includes; Bronchiolitis Obliterans-Organizing Pneumonia (BOOP) in cases where luminal fibrosis is seen in the bronchioles as well; Cryptogenic Organizing Pneumonia (COP), a preferred term for idiopathic disease. ATS/ERS consensus classification has proposed the term Organizing Pneumonia (OP) for the histologic pattern on biopsy. Bronchiolitis obliterans is not seen in every case, thus the terminology of OP reduces the emphasis of this finding, while COP is the clinical term for idiopathic form of this disease. Organizing pattern of ILD is seen secondary to various underlying etiologies like infections; bacterial, viral and fungal, collagen vascular diseases and drugs.

Histopathological features: Organizing pneumonia is characterized by patchy areas of loose fibroblastic intraluminal plugs involving alveolar ducts and alveolar spaces.[6] This process is centered on bronchioles and obliterative bronchiolitis may be seen in many cases. These intraluminal fibroblastic plugs called "Masson's bodies" are rich in mucopolysaccharides and assume the oval, elongated or serpiginous shapes of airspaces in which they are formed (Figs 94.3A and B). The adjoining inter-alveolar interstitium shows varying degrees of inflammatory infiltrate. In addition there is accumulation of foamy, lipid containing macrophages in the airspaces that represent postobstructive or endogenous lipoid pneumonia due to bronchiolar obstruction.

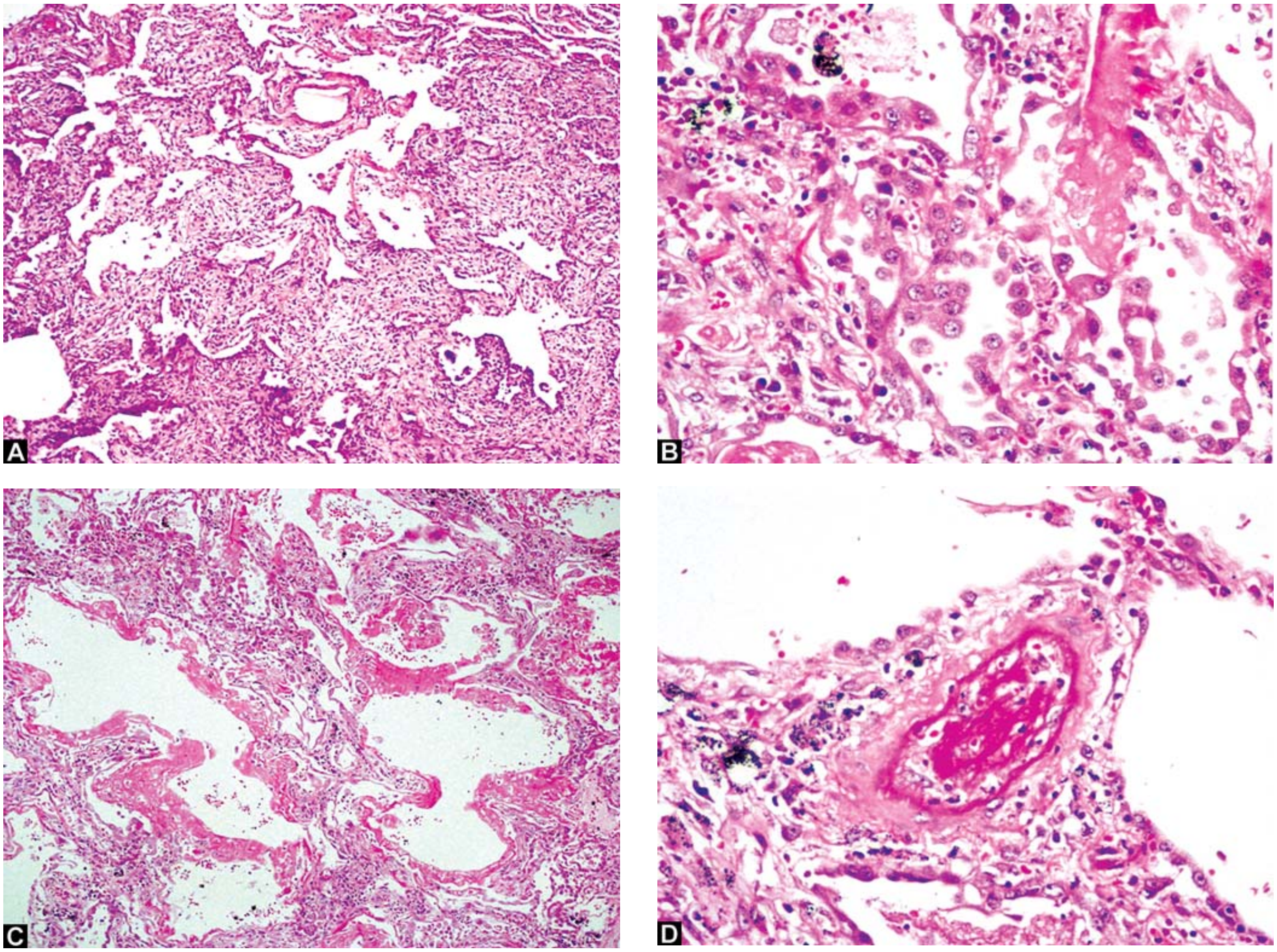


Figs 94.3A and B: (A) Loose plugs of fibroblastic tissue, "Masson's bodies" filling the alveolar spaces in organizing pneumonia. (B) Masson's trichrome highlighting the intraluminal fibroblastic plugs in organizing pneumonia

Acute Interstitial Pneumonia (AIP)

Acute interstitial pneumonia is a Diffuse Alveolar Damage (DAD) occurring in an idiopathic setting. It is a very aggressive form of ILD that may occur as an acute phase of acceleration of UIP and is as also termed as Hamman-Rich disease. AIP is the least common and rapidly progressive histologically distinct form of interstitial pneumonia analogous to Acute Respiratory Distress Syndrome (ARDS) caused by sepsis and shock.[7] Patients with AIP present with rapidly evolving shortness of breath and non-productive cough of one to three weeks duration preceded by a flu-like illness. Most patients are severely hypoxemic at the time of diagnosis and require hospitalization and mechanical ventilation. High resolution computed tomography shows ground glass attenuation and consolidation in a bilateral and symmetrical distribution.

Histopathological Features: Biopsy specimens from patients with AIP demonstrate DAD, usually in the late or organizing stage. The lung biopsy typically shows diffuse involvement, although there may be variation in the severity of the changes among different histologic fields. Alveolar septa are thickened and distorted by proliferating spindle cells (fibroblasts and myofibroblasts) within a pale-staining basophilic matrix (Fig. 94.4A). The uniformity of the findings contrasts sharply with the heterogeneous distribution of varying abnormalities in UIP. Fibroblast proliferation is



Figs 94.4A to D:(A) Organizing phase of acute interstitial pneumonia showing marked interstitial thickening by prominent fibroblast proliferation and scanty inflammatory infiltrate. (B) Proliferation and prominence of type 2 pneumocytes in acute interstitial pneumonia. The lining alveolar epithelial cells are hobnail shaped and have prominent nucleoli. (C) Exudative phase of acute interstitial pneumonia showing hyaline membranes lining alveolar ducts and alveolar spaces. The alveolar septa are thickened by interstitial edema. (D) Fibrin thrombi in small vessels in acute interstitial pneumonia

accompanied by marked hyperplasia of type II pneumocytes which may show cytological atypia characterized by nuclear enlargement and prominent nucleoli (Fig. 94.4B). Remnants of hyaline membranes may be present in some cases, but are often inconspicuous. Hyaline membranes are a histologic hallmark of DAD in early exudative phase and their presence is helpful in the distinction from the UIP, NSIP or organizing pneumonia patterns (Fig. 94.4C). Thrombi in small to medium-sized pulmonary arterioles and squamous metaplasia of bronchiolar epithelium which are features of acute lung injury can provide an important clue to the diagnosis (Fig. 94.4D).

No histological features can reliably distinguish DAD in the setting of AIP from DAD of other known causes. Therefore, before making a diagnosis of AIP all potential causes of DAD should be excluded. The presence of granulomas, viral inclusions, foci of necrosis or neutrophilic abscesses suggest infection.

Respiratory Bronchiolitis-associated Interstitial Lung Disease (RB-ILD)

Respiratory bronchiolitis-associated interstitial lung disease is the clinical manifestation of interstitial lung disease associated with the pathologic lesion of respiratory bronchiolitis. Respiratory bronchiolitis affects younger patients, with a mean age at diagnosis in the fourth or fifth decade of life. Nearly all patients have strong histories of cigarette smoking, thus RB-ILD is being considered as a smoking-related interstitial lung disease. It is rarely symptomatic and is usually associated with no more than minor small airway dysfunction. In rare cases the condition presents as a form of interstitial lung disease with significant pulmonary symptoms, abnormal pulmonary function and imaging abnormalities. It is then described as Respiratory Bronchiolitis-associated Interstitial Lung Disease (RB-ILD).[8] HRCT shows patchy ground glass opacities and centrilobular nodules often with a lower lung zone distribution, without fibrotic scars and honeycomb change.

Histopathological Features: In respiratory bronchiolitis the changes are patchy at low magnification and have a bronchiolocentric distribution. Respiratory bronchioles, alveolar ducts, and peribronchiolar alveolar spaces contain clusters of pigmented (smoker's) macrophages (Fig. 94.5). The macrophages have abundant cytoplasm containing finely granular dusty brown pigment that stains faintly with perls' stain. Mild peribronchiolar fibrosis is also seen that radiates to and expands contiguous alveolar septa, which are lined by hyperplastic Type II pneumocytes. It is also frequently associated with the presence of centrilobular emphysema and not uncommonly encountered as an incidental finding in the context of other forms of lung disease.

Desquamative Interstitial Pneumonia (DIP)

Desquamative interstitial pneumonia is a rare form of ILD that affects smokers and is characterized by the desquamation of alveolar macrophages with minimal fibrosis. Previously the intraalveolar cells were thought to represent alveolar epithelial cells that had desquamated from alveolar septa. This condition is considered by many to represent the end of a spectrum of RB-ILD in view of its similar pathology and almost invariable association with cigarette smoke.[9]

Histopathological Features: The DIP pattern is characterized by diffuse involvement of the lung by numerous macrophage accumulations within most of the distal airspaces (Fig. 94.6). The alveolar macrophages form loose clusters and have round nuclei with abundant eosinophilic cytoplasm containing golden brown pigment that stains weakly with perl's stain. The alveolar septa are thickened by a sparse inflammatory infiltrate that often includes plasma cells and occasional eosinophils, and they are lined by plump type II pneumocytes. The main feature that distinguishes DIP from RB-ILD is that the former affects the lung in a uniform diffuse manner and lacks the bronchiolocentric distribution seen in RB-ILD.

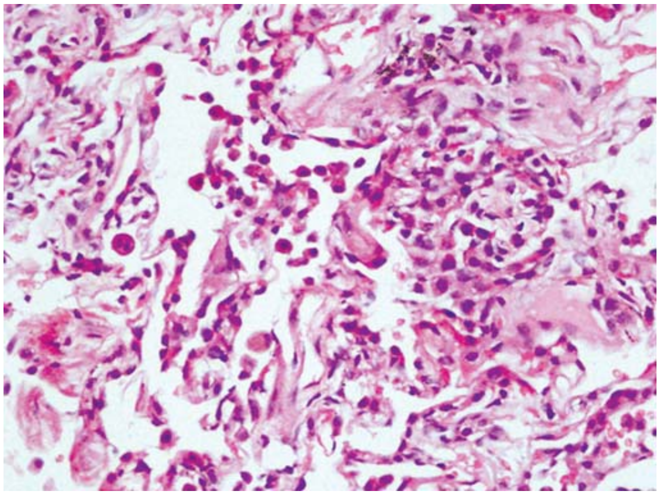


Fig. 94.5: Respiratory bronchiolitis associated interstitial lung disease showing collection of smoker's macrophages in respiratory bronchiole and adjoining alveolar spaces

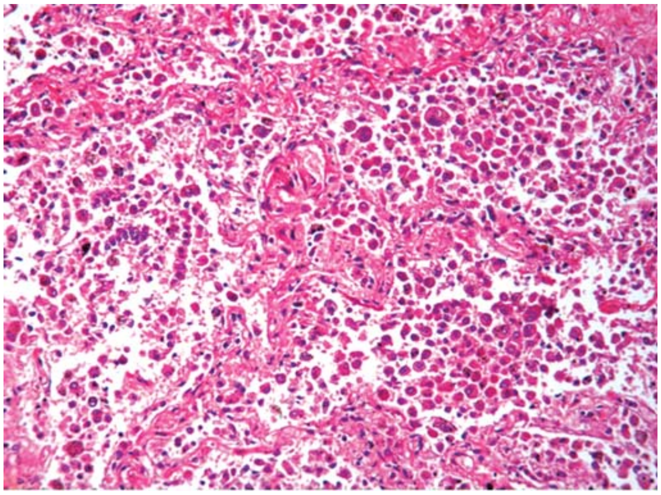


Fig. 94.6: Desquamative interstitial pneumonia showing diffuse distribution of macrophages in the alveolar spaces. Macrophages have abundant eosinophilic cytoplasm with granular brown pigment

DIP-like Reactions: Areas resembling RB-ILD and DIP are commonly seen as incidental findings in cigarette smokers with other lung diseases. No histological changes can reliably separate patients with RB-ILD/DIP from those with other lung diseases in whom RB and "DIP-like reactions" represent incidental findings. Thus RB-ILD/DIP should be diagnosed only when other forms of interstitial lung diseases have been excluded by careful examination of the surgical lung biopsy, clinical features and radiological findings.

Lymphoid Interstitial Pneumonia (LIP)

Lymphoid interstitial pneumonia is characterized by the expansion of the interstitium by sheets of lymphoid cells that are histologically benign and immunophenotypically polyclonal. It may be idiopathic in nature or occurs in association with connective tissue diseases, autoimmune diseases or Human Immunodeficiency Virus (HIV) infection. In a small number of cases LIP undergoes transformation to lymphoma. Lymphoid interstitial pneumonia is perhaps best regarded as a histologic variant of diffuse pulmonary lymphoid hyperplasia with predominant interstitial changes.

Histopathological features: Lymphoid interstitial pneumonia is defined as a dense and diffuse interstitial lymphoid infiltrate, comprising of lymphocytes, plasma cells and histiocytes (Fig. 94.7). The alveolar septa should be extensively infiltrated and lymphoid follicles including follicles with germinal centers are often present. Some architectural derangement (including honeycombing) and non-necrotizing granulomas may be seen. The pertinent negative findings are lack of tracking along lymphatic routes (bronchovascular bundles, pleura and interlobular septa) which are characteristic of lymphomas, inconspicuous or absent organizing pneumonia, lack of Dutcher bodies, lack of monoclonality on immunohistochemistry for light chains, lack of extensive pleural involvement or lymph node involvement and lack of necrotizing granuloma.[1,10]

The differential diagnosis for LIP includes diffuse lymphoid hyperplasia (hyperplasia of bronchial mucosa-associated lymphoid tissue), nodular lymphoid hyperplasia, lymphoma [of Mucosa-Associated Lymphoid Tissue (MALT) or small lymphocytic types], and the patterns of OP, NSIP, hypersensitivity pneumonitis, and UIP.[1] The hypersensitivity pneumonitis tends to have lesser inflammation, a peribronchiolar distribution, poorly formed granulomas and intraluminal organizing fibrosis. There are no precise criteria to distinguish LIP and cellular NSIP, but it has been observed that the extent of interstitial lymphocytic and/or plasma cell infiltrate is generally less severe in NSIP. The Bronchus-Associated Lymphoid Tissue (BALT) differs from LIP in that it lacks extensive alveolar septal infiltration. Malignant lymphomas show a monomorphous population of lymphoid cells with the destruction of alveolar architecture, pleural infiltration and tracking along lymphatic routes.

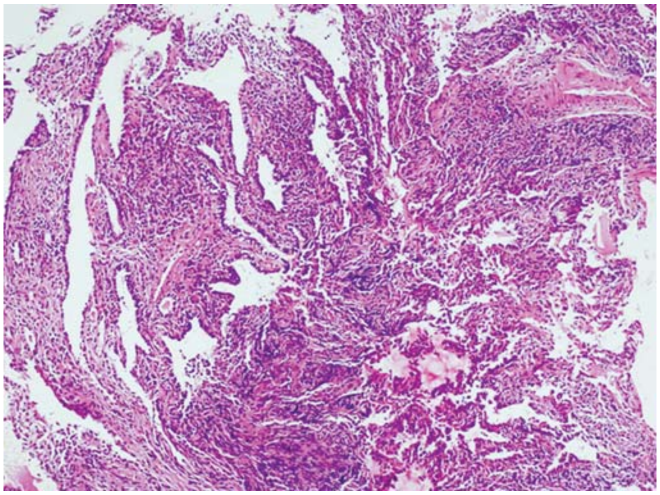


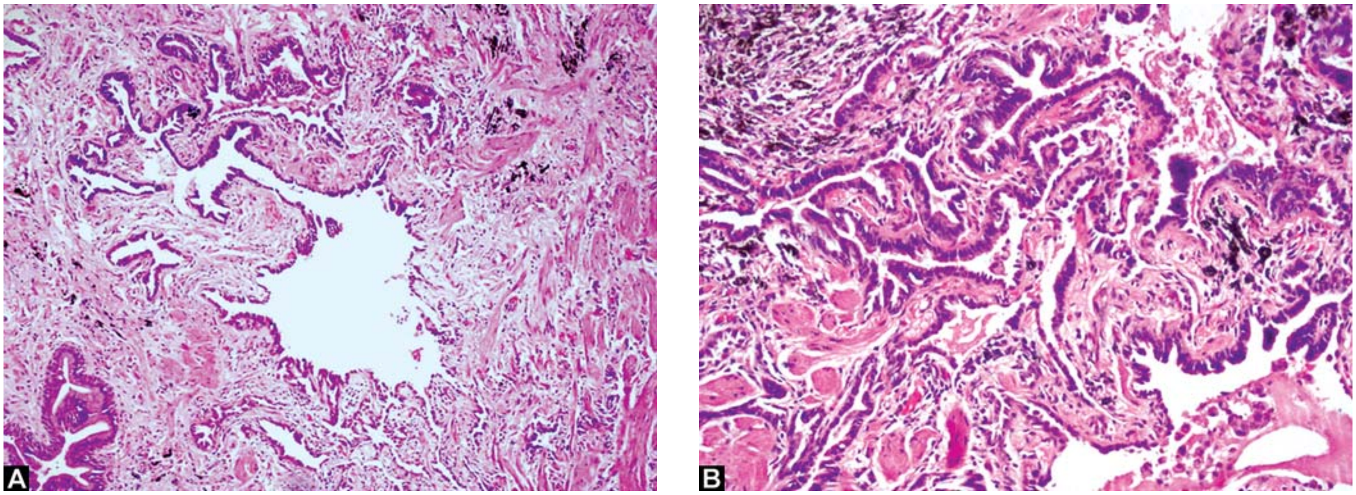
Fig. 94.7: Lymphocytic interstitial pneumonia showing diffuse dense lymphomononuclear cell infiltrate in the interstitium

IDIOPATHIC BRONCHIOLOCENTRIC INTERSTITIAL PNEUMONIA (BrIP)/AIRWAY CENTERED INTERSTITIAL FIBROSIS

Idiopathic bronchiolocentric interstitial pneumonia is a new entity described after 2002 ATS/ERS consensus classification. It is a bronchiolocentric process associated with centrilobular peribronchiolar fibrosis and distal lymphocytic alveolitis.[11] Patients present with symptoms, such as progressive dyspnea and dry cough. Studies have reported female predominance and history of inhalational exposure to smoke, birds, cotton and agrochemicals. Chest radiographs and HRCT shows bilateral dominant lower lobe reticular and reticulo-nodular infiltrates. Like other interstitial pneumonias, BrIP is associated with functional restrictive lung disease.

Histopathological Features

The most striking finding is centrilobular and bronchiolocentric nature of inflammatory infiltrate.[12,13] The inflammation extends into the peribronchiolar alveolar septa and distal interstitium of the acinus. There is relative sparing of the subpleural and peripheral lung parenchyma. The inflammation is accompanied by peribronchiolar fibrosis and bronchiolar metaplasia (Fig. 94.8A and B). There is ingrowth of bronchiolar epithelium along the alveolar ducts to alveoli through canal of Lambert. This process of bronchiolar metaplasia of alveolar lining is termed as “Lambertosis’ or “microscopic honeycomb change”. Bronchiolocentric interstitial pneumonia has histologic similarity to hypersensitivity



Figs 94.8A and B: (A) Bronchiolocentric interstitial pneumonia showing interstitial fibrosis and bronchiolar metaplasia of the adjoining alveolar spaces termed as lambertosis. (B) Higher power showing metaplastic bronchiolar epithelium in bronchiolocentric interstitial pneumonia

pneumonia with a higher degree of centrilobular fibrosis and absent granulomas. It can be hypothesised that BrIP represents chronic hypersensitivity pneumonia.

DRUG INDUCED INTERSTITIAL LUNG DISEASE (DIILD)

An increasing number of drugs are recognized to induce distinctive patterns of ILD, ranging from benign infiltrates to life-threatening adult respiratory distress syndromes. In addition to drugs, biomolecules such as proteins and cytokines, and medicinal plants are also capable of inducing respiratory disease. A list of drugs having the potential to cause pulmonary disease continues to grow and now at least 350 agents are recognized[14] (Table 94.2).

TABLE 94.2: Drugs known to cause interstitial lung disease

Anticonvulsant, anti-psychotic, antidepressant	Carbamazepine, Chlordiazepoxide, Fluoxetine Phenothiazines, Phenytoin
Anti-inflammatory	Aspirin, Gold, Methotrexate, Penicillamine
Antimetabolic	Azathioprine, Cytarabine, Fludarabine Gemcitabine, 6-Mercaptopurine
Antimicrobial	Amphotericin B, Ethambutol, Isoniazid Minocycline, Nitrofurantoin
Biologic response modifiers	Granulocyte-macrophage colony-stimulating factor, Interferon, Interleukin-2, Tumor necrosis factor
Cardiovascular	Amiodarone, Angiotensin-converting enzyme inhibitors, Anticoagulants
Chemotherapeutic and immunosuppressive	Bleomycin, Busulfan, Chlorambucil Cyclophosphamide, Cyclosporin A
Illicit drugs	Cocaine, Heroin, Methadone, Methylphenidate Narcotic and sedative drugs

A carefully obtained history that includes medications is essential in suspecting a drug-induced reaction. A major, but largely unresolved question is why, out of the treated population of patients, only some individuals will develop DI-ILD. Explanations for the unequal risks among patients include the following:

- Prior respiratory reactions to the drug, or to unrelated compounds
- Type of underlying disease for which the drug is being given. Diseases such as rheumatoid arthritis or ulcerative colitis may increase the relative risk of developing respiratory disease from disease modifying drugs
- Occupational factors, such as exposure to asbestos, may potentiate the noxious respiratory effects of ergot drugs
- Activation and detoxification pathways of drugs and chemicals, which differ quantitatively and qualitatively among individuals

Drug-induced pulmonary diseases can present in a variety of syndromes, clinical presentations and radiographic patterns. The most common presentations of drug-induced pulmonary disease are an abnormality on a chest radiograph or a symptom complex.

Clinicoradiological Patterns

The clinicoradiographical correlates of DI-ILD range from subclinical opacities to a picture of white lungs with the criteria of ARDS. In the patient with migratory opacities with or without chest pain that could be suggestive of organizing pneumonia, a careful drug history should be taken, as this clinical pattern may relate to exposure to drugs or radiation. Transient infiltrates have been described in mild form of DI-ILD.

Pathology

Reports of DI-ILD in which histological data were obtained indicate that drugs can induce many distinctive histopathological patterns of ILD.[15] Drugs can trigger the development of such conventional patterns of ILD as:

- Hypersensitivity pneumonia
- Mild eosinophilic pneumonia
- Nonspecific interstitial pneumonia (cellular or fibrotic)
- Usual interstitial pneumonia
- Organizing pneumonia (OP or BOOP)
- Desquamative Interstitial Pneumonia (DIP)

While some drugs (e.g. minocycline, nitrofurantoin) induce quite stereotyped reactions in the lung (eosinophilic pneumonia and the cellular type of nonspecific interstitial pneumonia, respectively) other drugs (e.g. amiodarone, bleomycin), can induce a palette of variegated histopathological patterns in different patients. Patterns described under the term "amiodarone pneumonitis" may include nonspecific interstitial pneumonia (cellular or fibrotic type), alveolar filling by foamy macrophages, organizing pneumonia, diffuse alveolar damage, interstitial lung fibrosis, a pattern of "usual interstitial pneumonia," or any combination thereof depending on the patient and, possibly, the site of the lung biopsy. A notable clue that suggests the drug as a cause is the fact that the ILD will demonstrate a relative refractoriness to steroids, or will recur while the patient is still receiving relatively high dosages of steroids. Early diagnosis is important, because stopping the drug usually reverses toxicity, whereas unrecognized toxicity can be progressive and even fatal. Diagnosis requires being alert and vigilant for adverse pulmonary reactions in the appropriate clinical settings.

CONNECTIVE TISSUE DISORDER ASSOCIATED INTERSTITIAL LUNG DISEASE

The Connective Tissue Disorders (CTDs) comprise a heterogeneous group of diseases including rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis (PM/DM), Systemic Lupus Erythematosus (SLE), Sjögren's syndrome and mixed connective tissue disorders. Pulmonary complications are commonly associated with connective tissue disorders and can affect various anatomical compartments of the lung (airways, vasculature, interstitium, pleura, etc.) either individually or in combination. The reported prevalence of clinically overt pulmonary parenchymal disease ranges from 30% in patients with PM/DM to 10% in patients with Sjögren's syndrome and 5% in those with rheumatoid arthritis and SLE.[16] In some occasions, the lung disease precedes the more typical systemic manifestations and the evolution of the pulmonary disease is independent from the systemic disease and is associated with greater mortality and morbidity.

Rheumatoid Arthritis Associated Interstitial Lung Disease (RA-ILD)

Rheumatoid Arthritis (RA) is a destructive, systemic, inflammatory disorder that is defined by its characteristic attack on diarthrodial joints. A major portion of RA's disease burden, including the excess mortality, appears to be due to its extra-articular manifestations and pulmonary complications are directly responsible for 10 to 20% of all mortality. The prevalence of ILD in rheumatoid varies depending on the criteria used to establish the diagnosis. Clinically, significant ILD has been described in approximately 7% of subjects, whereas autopsy studies have described a prevalence of up to 35%.[17] Histopathological patterns of ILD associated with RA include:

- Usual Interstitial Pneumonia (UIP)
- Nonspecific Interstitial Pneumonia (NSIP)
- Organizing Pneumonia (OP)
- Lymphocytic Interstitial Pneumonia (LIP)
- Diffuse alveolar damage
- Rheumatoid nodules

In RA, UIP pattern is more commonly seen on surgical lung biopsy than NSIP.[18] In RA-ILD, cellular inflammatory, fibrosing, and mixed changes are seen, and these pathologic patterns fully overlap with those seen in the idiopathic interstitial pneumonias. The information provided by these pathologic patterns is important predictor of early mortality, with patterns characterized by fibrosis (e.g. UIP, fibrosing NSIP) having a worse prognosis than those characterized by cellular disease (e.g. cellular NSIP). Park and colleagues supports the hypothesis that the prognosis of subjects with Collagen Vascular Disease (CVD)-ILD, and particularly those with

CVD-UIP, is better than that of patients with idiopathic UIP.

Hypothesis for the development of lung fibrosis in RA is that a cellular inflammatory process is required for initiation of secondary fibroproliferative process, and the fibroproliferative process may then become progressive and independent of its initiating cause. However, once the fibroproliferative process begins, the clinical course and gene expression profile become similar to those of IPF, the prototypical fibrosing lung disease, and the disease becomes unresponsive to immunosuppression. The presence and number of fibrotic foci have been shown to correlate with mortality. The presence of areas of lymphoplasmacytic infiltrate is associated with physiologic improvement in response to cyclophosphamide and corticosteroid therapy, whereas fibroblast foci and areas of airspace organization are associated with a decline in function.

Systemic Lupus Erythematosus (SLE)

Parenchymal lung lesions especially NSIP and LIP are more common in SLE as compared to extensive fibrotic lesions seen in other collagen vascular diseases. Less commonly, the pathological changes include alveolar hemorrhages with associated expansion and destruction of alveolar septa by capillaritis. In addition, variety of pulmonary vascular changes like intimal thickening, medial hypertrophy and periadventitial fibrosis have been reported.

Polymyositis/Dermatomyositis

Nonspecific interstitial pneumonia and organizing pneumonia are the most common pattern of ILD associated with PM/DM.

Sjögren’s Syndrome

Lymphocytic interstitial pneumonia and amyloidosis are the most common pattern of ILD associated with Sjögren’s syndrome.

HYPERSENSITIVITY PNEUMONITIS (HP)

Hypersensitivity pneumonitis also known as extrinsic allergic alveolitis is an interstitial lung disease caused by immunological response to inhalation of organic substances and certain inorganic chemicals. It is thought to result from combination of type III (immune complex) and type IV (cell mediated) immune reactions.[19] The main etiological agents include thermophilic bacteria, fungi and animal proteins. The most common occupation related HP is farmer’s lung followed by air conditioner lung, humidifier lung and pigeon breeder’s lung. Hypersensitivity pneumonitis may present in three forms: Acute, subacute and chronic depending upon the intensity and frequency of exposure. High resolution computed tomography findings include centrilobular nodular opacities and areas of ground glass attenuation.

Histopathological Features

The diagnostic features of HP include triad of patchy, nonspecific interstitial pneumonia with peribronchiolar attenuation, non-necrotizing granulomas and foci of bronchiolitis obliterans. The inflammatory infiltrate is composed of lymphocytes and plasma cells present around bronchioles and extending into alveolar septa. The granulomas are interstitial, poorly formed and composed of epithelioid histiocytes and Langhans’ giant cells. In absence of granulomas the morphological changes can resemble cellular NSIP, thus requiring careful identification of specific antigen.

Treatment and Prognosis

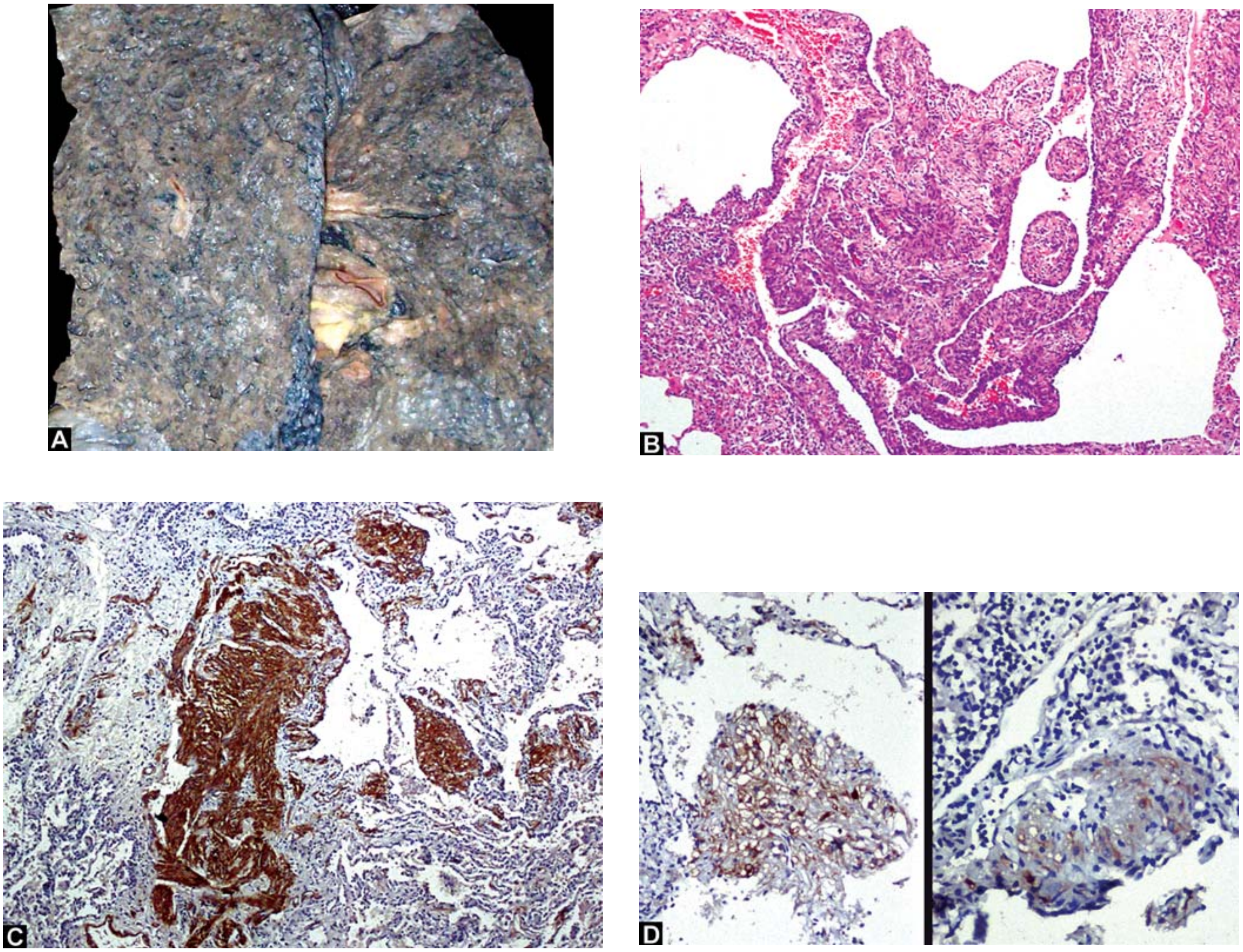
The therapeutic strategy for HP is avoidance of offending agent. The prognosis depends upon the amount and reversibility of damage.

LYMPHANGIOLEIOMYOMATOSIS (LAM)

Pulmonary lymphangioleiomyomatosis is a rare disease characterized by the haphazard proliferation of immature myoid cells throughout the interstitium of the lung. Lymphangioleiomyomatosis is currently classified by the World Health Organization under the broad group of tumors known as PEComas, derived from Perivascular Epithelioid Cells (PECs).[20] The PEC cells are perivascular cells with myoid features characterized by positivity for smooth muscle actin, HMB-45 and Melan A immunostains. It occurs exclusively in women during reproductive years of life, either sporadically or in association with tuberous sclerosis. Patients present with progressive dyspnea, chylous pleural effusions and recurrent pneumothoraces. Radiological examination shows diffuse reticular or reticulonodular shadows. Thin walled cystic spaces seen on HRCT are highly suggestive of LAM.

Histopathological Features

Gross appearance of lungs in LAM is characteristic and shows multiple air filled cysts (Fig. 94.9A).



Figs 94.9A to D: (A) Lymphangioleiomyomatosis; Gross showing innumerable cysts throughout the lung. (B) Varying proliferation of immature smooth muscle cells in the walls of cystic spaces. (C) Smooth muscle cells positive for smooth muscle actin. (D) Smooth muscle cells positive for Melan A and HMB45 immunostains

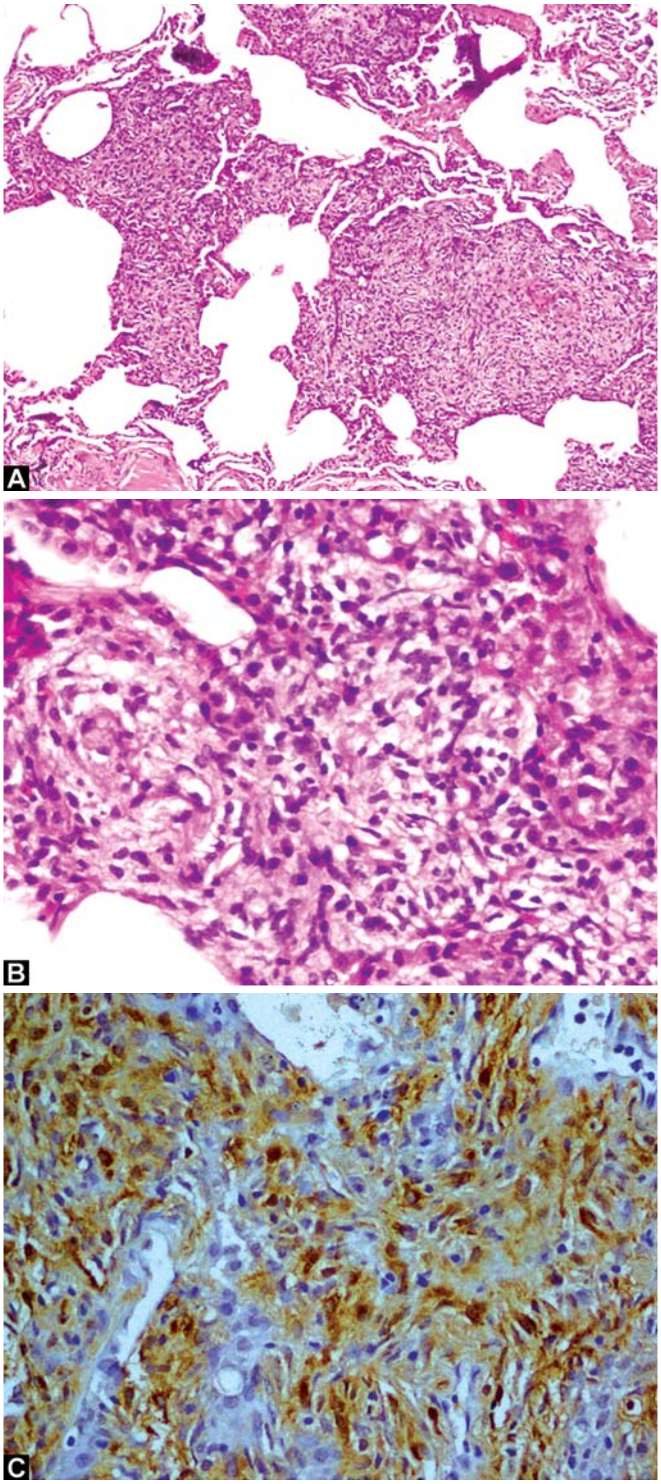
Microscopically, cystic change is the striking feature. There is randomly distributed proliferation of immature smooth muscle cells in the interstitium (Fig. 94.9B), around bronchioles, blood vessels, lymphatics, alveolar septa and walls of cystic spaces. These myoid cells are positive for smooth muscle actin (Fig. 94.9C), HMB-45 and Melan A (Fig. 94.9D).

PULMONARY LANGERHANS CELL HISTIOCYTOSIS (LCH)

Pulmonary langerhans cell histiocytosis, also known as pulmonary eosinophilic granuloma and pulmonary histiocytosis X is characterized by abnormal proliferation of Langerhans cells. Langerhans cells are dendritic or antigen presenting cells of the body that express CD1a, langerin and S-100 protein.[21] Pulmonary LCH has been linked to cigarette smoking. Experimental studies have shown increased number of dendritic cells in lungs chronically exposed to cigarette smoke.[22,23] The most common presenting symptoms include dyspnea, cough, chest pain, fever and hemoptysis.

Histopathological Features

Grossly lung parenchyma shows well demarcated grayish white nodules of 1 to 2 cm in maximum dimension. In chronic phases, there is pulmonary fibrosis, cystic change and honeycombing. The characteristic microscopic feature is nodular aggregates of Langerhans cells (Fig. 94.10A). These cells have pale convoluted nuclei with small nucleoli, pale eosinophilic cytoplasm and ill defined cell borders (Fig. 94.10B). These cells are associated with other inflammatory cells like lymphocytes, plasma cells and eosinophils. These Langerhans cells are positive for S-100 (Fig. 94.10C) and CD1a immunostains. The adjacent lung parenchyma shows interstitial fibrosis and alveolar cell hyperplasia. With the evolution of disease, fibrosis evolves and cellular nodules are replaced by stellate fibrous nodules.



Figs 94.10A to C: (A) Nodules of Langerhans cell histiocytosis admixed with other inflammatory cells. (B) High power showing Langerhans cells with pale nuclear chromatin and convoluted nuclear membranes admixed with lymphocytes and plasma cells. (C) S-100 immunostain highlighting Langerhans histiocytes

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Idiopathic Interstitial Pneumonias

H Shigemitsu, Ngozi Orjioke

INTRODUCTION

The pulmonary interstitium is defined as the loose connective tissue surrounding the lungs. It consists of alveolar epithelium, pulmonary capillary endothelium, basement membrane, and perivascular and perilymphatic tissues. Idiopathic Interstitial Pneumonias (IIPs) is a condition in which the interstitium is replaced with the extracellular matrix and inflammatory cells resulting in impaired gas exchange. As the name suggests, the IIPs is a heterogeneous group of diseases of unknown etiology that share some common clinical features and are distinguished primarily by radiography and histopathology. This distinction is important as it impacts therapeutic options and prognosis.

EPIDEMIOLOGY

Among the IIPs, Idiopathic Pulmonary Fibrosis (IPF) is the most commonly described with annual incidence in the US estimated at 6.8 to 16.3 per 1,00,000 and a prevalence of 14.0 to 42.7 per 1,00,000.[1] Nearly two-third of the patients are predominantly men above 60 years of age. Reports from India suggests that there is a trend towards higher incidence of IPF with advancing age; however age at presentation is almost a decade earlier.[2]

CLASSIFICATION

Based on the ATS/ERS consensus statement,[3] IIPs are classified under the umbrella of Diffuse Parenchymal Lung Diseases (DPLDs). Idiopathic interstitial pneumonias are further subclassified into: Idiopathic Pulmonary Fibrosis (IPF)/Cryptogenic Fibrosing Alveolitis (CFA) and IIPs other than IPF.

The latter includes the following six histologic subtypes:

1. Nonspecific Interstitial Pneumonia (NSIP)
2. Cryptogenic Organizing Pneumonia (COP)
3. Respiratory Bronchiolitis-associated Interstitial Lung Disease (RB-ILD)
4. Desquamative Interstitial Pneumonia (DIP)
5. Acute Interstitial Pneumonia (AIP)
6. Lymphoid Interstitial Pneumonia (LIP)

Although this classification is mainly based on the histologic patterns, the clinical and radiological features correlate well with the associated pathology.

CLINICAL FEATURES

It has increasingly been recognized that the diagnosis of IIPs require an interdisciplinary approach between the clinicians, radiologists and the pathologists. The signs and symptoms are usually nonspecific, but referable to the pulmonary system (Table 95.1).[1-4] Nonproductive cough and progressive dyspnea with exertion usually prompts the patient to seek medical attention. The onset and progression can be variable, thus a detailed history of the onset of symptoms, symptom duration and associated features must be obtained. Furthermore, particular attention should be paid to obtain detailed history of tobacco use; family history of lung disease especially with pulmonary fibrosis and to the current and prior drug use to rule out medication induced lung fibrosis. Occupational exposure history with attention to duration, degree and latency of exposure must also be carefully elucidated. In the developing countries where expensive diagnostic

TABLE 95.1: Summary of clinical features of IIPs

Diagnosis	*Features*	*PFTS*	*BAL*	*Histological pattern*	*Treatment*	*Prognosis*
IPF	Gradual onset, mostly men >50 year. Constitutional symptoms are unusual.	Restrictive pattern, decrease DLCO, low resting PaO_2	Neutrophilic predominant with mild or moderate increase in eosinophils usually <20%	UIP	Ineffective, Lung transplantation	Mortality 50–70% in 5 years
NSIP	Mean age 40-50 year, no sexual predominance, no association with smoking. Gradual onset. Constitutional symptoms may be present.	Restrictive, mild airflow limitation in minority, reduced DLCO, hypoxemia on exercise	Lymphocytic predominant	**NSIP** Cellular pattern, fibrosing pattern	Corticosteroids	Mortality <10% in 5 years
COP	Mean age 55 year Equal sex distribution. Cough may be productive. Nonsmokers outnumber smokers. Constitutional symptoms Laboratory findings include neutrophilia with elevated ESR/CRP	Restrictive, mild airflow limitation reduced DLCO, mild resting hypoxemia	Lymphocyte predominant with ratio of $CD4^+$ to $CD8^+$ is decreased.	OP	Corticosteroids	Complete recovery >65%, Relapses in many mortality rare
RB-ILD	Rarely symptomatic Nonspecific respiratory symptoms 40–50 years Current smokers	Obstructive/restrictive patterns Mild to moderate decrease in DLCO Isolated increase in RV	Modest increase in neutrophils Alveolar macrophages with black pigmented inclusions	RB	Smoking cessation	Mortality rare
AIP	Acute Rapidly progressive Prior illness suggestive of viral URI Mean age 50 year No gender predilection Not associated with smoking	Restrictive pattern Decreased DLCO Hypoxemia	Increased total cells, hemorrhage, atypical pneumocytes, fragments of hyaline membrane	DAD	No proven treatment	Mortality >50% within 1–2 months
DIP	Insidious 40–50 year Smokers Digital clubbing in 50% M:F 2:1	Normal or Restrictive pattern Decreased DLCO	Modest increase in neutrophils/eosinophils and lymphocytes. Alveolar macrophages with black pigmented inclusions	DIP	Smoking cessation	Mortality rate 5% in 5 years
LIP	F>M 50 years Insidious Constitutional symptoms +/– adenopathy Mild anemia Monoclonal increase in IgG or IgM in 75%		Lymphocytes without clonality on immunophenotyping	LIP	Corticosteroids	Not well characterized

AIP: Acute interstitial pneumonia; BAL: Bronchoalveolar lavage; COP: Cryptogenic fibrosing alveolitis; DAD: Diffuse alveolar damage; DIP: Desquamative interstitial pneumonia; IPF: Idiopathic pulmonary fibrosis; LIP: Lymphoid interstitial pneumonia; NSIP: Nonspecific interstitial pneumonia; OP: Organizing pneumonia; PFTS: Pulmonary function tests; RB-ILD: Respiratory bronchiolitis-associated interstitial lung disease; UIP: Usual interstitial pneumonia

TABLE 95.2: Radiographic features of IIPs

Clinical diagnosis	*Radiographic features*	*CT distribution*	*CT findings*
IPF/CFA	Reticular Basilar Low lung volumes	Peripheral Subpleural/basal	Architectural distortion Honeycombing Traction bronchiectasis Focal ground glass
NSIP	Reticular	Peripheral Subpleural/basal Symmetric	Ground glass Consolidation Irregular lines
COP	Patchy bilateral consolidations	Subpleural/peribronchial Lower zone predominant	Patchy consolidation Nodules
AIP	Progressive diffuse consolidation	Diffuse	Consolidation Ground-glass with lobular sparing Traction bronchiectasis (late)
DIP	Ground glass opacity	Peripheral Lower zone	Reticular lines Nodular texture to ground glass opacification Honeycombing <1/3 of cases
RB-ILD	Ground-glass Bronchial wall thickening	Diffuse	Patchy ground glass Bronchial wall thickening Centrilobular nodules
LIP	Reticulonodular	Diffuse	Ground glass Septal/bronchovascular thickening Centrilobular nodules Thin-walled cysts

AIP = Acute interstitial pneumonia; CFP= Cryptogenic fibrosing alveolitis; COP = Cryptogenic organizing pneumonia; DAD = Diffuse alveolar damage; DIP = Desquamative interstitial pneumonia; IPF= Idiopathic pulmonary fibrosis; LIP= Lymphoid interstitial pneumonia; NSIP= Non-specific interstitial pneumonia; RBILD= Respiratory bronchiolitis-associated interstitial lung disease; UIP = Usual interstitial pneumonia.

equipment and surgical personnel may not be readily available, such detailed history in combination with the clinical features and radiographic features (Table 95.2), may help direct the diagnostic approach and rule out other diseases in the differential diagnosis.[4]

When the clinicoradiological features are atypical of IPF, a diagnosis of idiopathic interstitial pneumonia, that is not IPF, is made.[3] At this time lung tissue, obtained by surgical biopsy or Bronchoalveolar Lavage (BAL) with Transbronchial Biopsy (TBBx) based on available modalities to evaluate the histopathology, is essential in the diagnostic algorithm (Fig. 95.1). Laboratory tests for autoimmune disease, vasculitides and immunological response to organic inhalational exposure may assist in directing the clinician to various etiologies that are known to cause IIPs. However, routine laboratory investigations usually play no significant role in the diagnostic process.

HISTOLOGICAL FEATURES

Histopathological examination of the lung is the gold standard in confirming the diagnosis. The patterns observed have been shown to correlate with the clinical course and response to treatment. In IPF, the characteristic injury pattern is Usual Interstitial Pneumonia (UIP). The hallmark of UIP is fibroblastic foci which consist of dense eosinophilic fibrosis with scattered foci of young myxoid fibrosis and fibroblasts. These foci represent the advancing or progressive edge of the disease and are required to be a major component of the histological pattern for a confident diagnosis. The injury

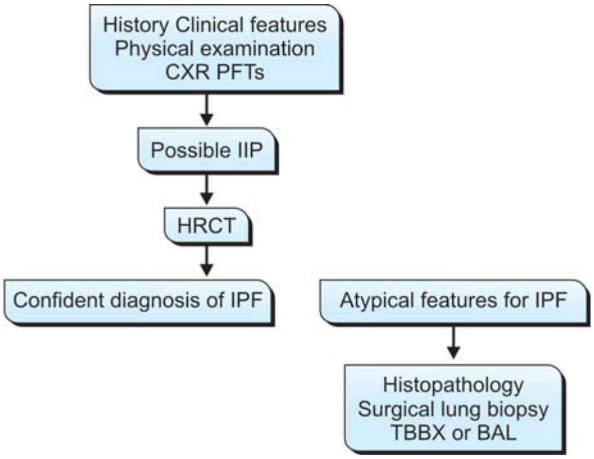


Fig. 95.1: Simplified algorithm for diagnosis of idiopathic interstitial pneumonias

is predominantly seen in the subpleural region and consists of a pattern of temporal heterogeneity.[2,3] In other words, the areas of injury with fibroblastic foci and honeycomb changes are seen adjacent to relatively unaffected tissue. Other histological patterns of IIPs are summarized in Table 95.3.

TREATMENT

Management usually involves supportive therapy with oxygen supplementation, immunizations and treatment of any intercurrent infections and management of complications that may arise from treatment.[5] For the majority of IIPs, the mainstay of treatment is corticosteroids. Other treatments options, including immunosuppressive therapies and antifibrotic agents, are discussed individually.

IDIOPATHIC PULMONARY FIBROSIS (IPF)

Epidemiology

Idiopathic pulmonary fibrosis, also known as cryptogenic fibrosing alveolitis, is a distinctive type of chronic fibrosing interstitial pneumonitis of unknown etiology accounting for over 50% of all IIPs. It is associated with

TABLE 95.3: Histological patterns in the IIPs

Diagnosis	*Histological pattern*	*Description*
IPF	Usual interstitial pneumonia	Patchy/focal involvement of the lung: dense fibrosis and honeycombing with areas of “normal lung” adjacent to heavily involved areas.Subpleural distribution, paraseptal and peribronchiolar. Fibrosis, temporal heterogeneity. Alveolar component reduced or completely lost in affected areas. Bronchiolar component damage and abnormal regeneration
NSIP	Non-specific interstitial pneumonitis	**Cellular pattern:** Homogenous interstitial chronic inflammatory infiltrate focal alveolar collections of macrophages. Focal alveolar damage with pneumocyte type II hyperplasia and organizing pneumonia **Fibrosing pattern:** Dense or loose interstitial fibrosis with homogeneous involvement of the lung. Mild inflammatory infiltrate. No evidence of fibroblast foci or honeycombing.
COP	Organizing pneumonia	Organizing tissue (polyps) within alveolar ducts and alveoli. Mild interstitial inflammatory infiltrate/intra-alveolar foamy macrophages. Focal alveolar damage with pneumocyte type II hyperplasia. Preservation of lung structure, the process appears mainly centered on small airways.
RB-ILD	Respiratory bronchiolitis	Bronchiolocentric alveolar macrophage accumulation. Mild bronchiolar fibrosis and chronic inflammation. Macrophages have dusty brown cytoplasm (may be positive for iron stains)
AIP	Diffuse alveolar damage	Diffuse involvement of the lung parenchyma. Fibrosis of uniform temporal appearance with myofibroblast accumulation within alveolar interstitial spaces. Diffuse features of acute alveolar damage with pneumocyte type II hyperplasia, atypia and hyaline membranes.
DIP	Diffuse interstitial pneumonitis	Chronic interstitial inflammation and numerous intra-alveolar mononuclear cells, macrophages. Diffuse alveolar mononuclear cell (macrophage) accumulation. Cuboidal epithelial cells (type 2 cells) line alveoli. Mild diffuse interstitial fibrosis and chronic inflammation. Occasional lymphoid follicles. No dense scarring or revamping of architecture
LIP	Lymphoid interstitial pneumonia	Intense and diffuse chronic accumulation of lymphocytes occurs in alveolar interstitial spaces. Follicular reaction may occur along lymphatic routes.

a surgical lung biopsy showing a UIP pattern. It is predominantly seen in middle-aged men with a median age of 66 years at time of diagnosis.[6] In a series from India, the age of presentation was a decade earlier.[4] The incidence is higher with the increasing age.[6]

Etiology

The cause of IPF is unclear, but it is increasingly becoming clear that it represents in part a response to injurious agent(s), which results in dysregulated inflammation and repair of the interstitium and alveolar epithelium. Eventually chronic inflammation and an imbalance in the production of various cytokines, growth factors and profibrotic agents result in inexorable fibrotic response with collagen deposition.[7] Thus, agents targeted at the cytokine release and processes implicated in the perpetuation of the pulmonary fibrosis and vascular remodeling are currently being investigated.

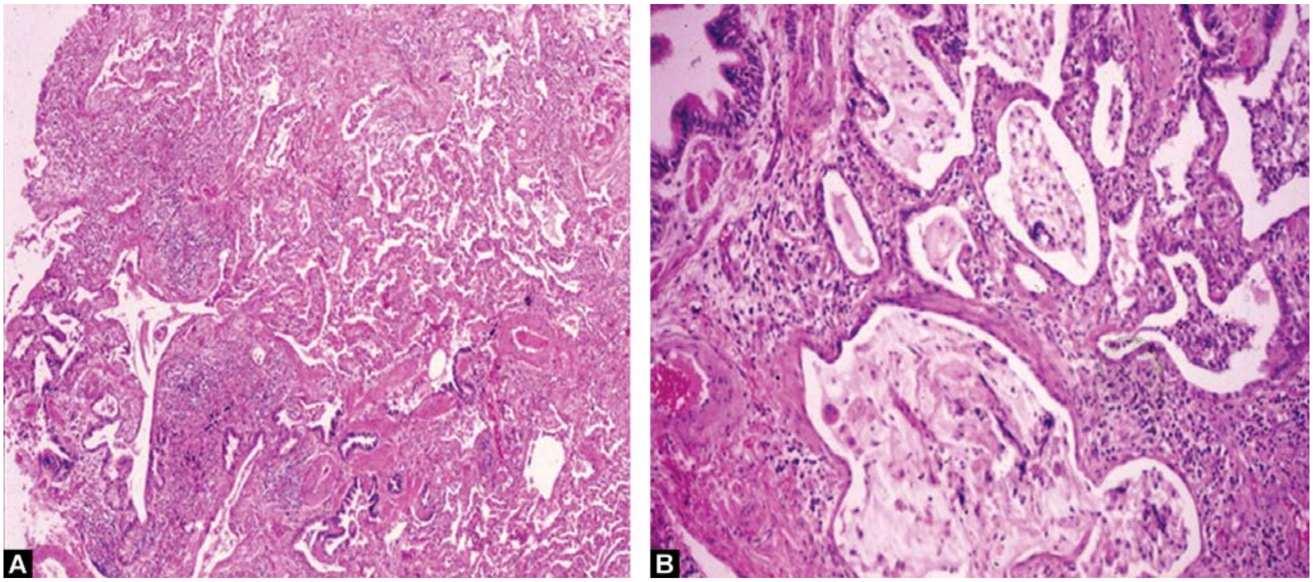
Signs and Symptoms

Paroxysmal nonproductive cough associated with the progressively worsening of shortness of breath are the most common symptoms. These symptoms have an insidious onset and are often present for months prior to the diagnosis.[6] End inspiratory crackles are present on lung examination, with finger clubbing in 25 to 50% of patients. In late stages of the disease, signs attributable to pulmonary hypertension or right heart failure may be present.

Diagnosis

The exclusion of any other interstitial lung disease based on history, physical examination and ancillary studies is the first step to making a diagnosis of IPF in the absence of an open-lung biopsy.[6] Idiopathic pulmonary fibrosis is characterized morphologically with a UIP pattern on pathology (Figs 95.2A and B). The findings on chest radiography, CT and gross pathological examination of lung with IPF/UIP is demonstrated in Figs 95.3A to C. The pulmonary function test usually reveals a restrictive physiology with abnormal gas exchange.[3] The typical chest radiographic features include diffuse peripheral reticular opacities with basilar predilection.[3,6] High Resolution Computed Tomograhy (HRCT) scan shows predominantly peripheral, subpleural, bibasilar reticular abnormalities; traction bronchiectasis and subpleural honeycombing. If ground-glass opacities appear to be the predominant radiographic finding, an alternate diagnosis other than IPF must be strongly considered.[2,8]

Clinical and radiographic findings well described that the American Thoracic Society (ATS) and European Respiratory Society (ERS) endorsed clinical criteria for a definitive diagnosis of IPF in the absence of a surgical lung biopsy (Table 95.4).[3] Specifically, radiological features with HRCT can be especially helpful in the diagnostic accuracy of IPF. This is useful in some developing countries where the option of rendering the diagnosis to a surgically obtained biopsy may not be readily available. However, if these typical features are



Figs 95.2A and B: UIP pattern on histopathology. Temporal heterogeneity and geographic heterogeneity. Patchy involvement of the lung with variation in the age of the fibrosis. Interstitial and alveolar inflammation, cellular proliferation and honeycombing cysts

TABLE 95.4: Diagnostic criteria of IPF/UIP in ATS/ERS criteria

DIAGNOSIS OF IPF IN THE ABSENCE OF SLB
Major criteria (All four must be present)

- Exclusion of other known causes of ILD such as drug toxicities, environmental exposuresand connective tissue diseases
- Abnormal pulmonary function studies that include evidence of restriction [reduced VC, often with an increased. Forced Expiratory Volume in One Second/Forced Vital Capacity (FEV_1/FVC) ratio] and impaired gas exchange [Increased P (A-a) O_2, decreased PaO_2] with rest or exercise or decreased. Diffusion lung capacity for carbon monoxide (DLCO)
- Bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans
- Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis

Minor criteria (Three or four must be present)

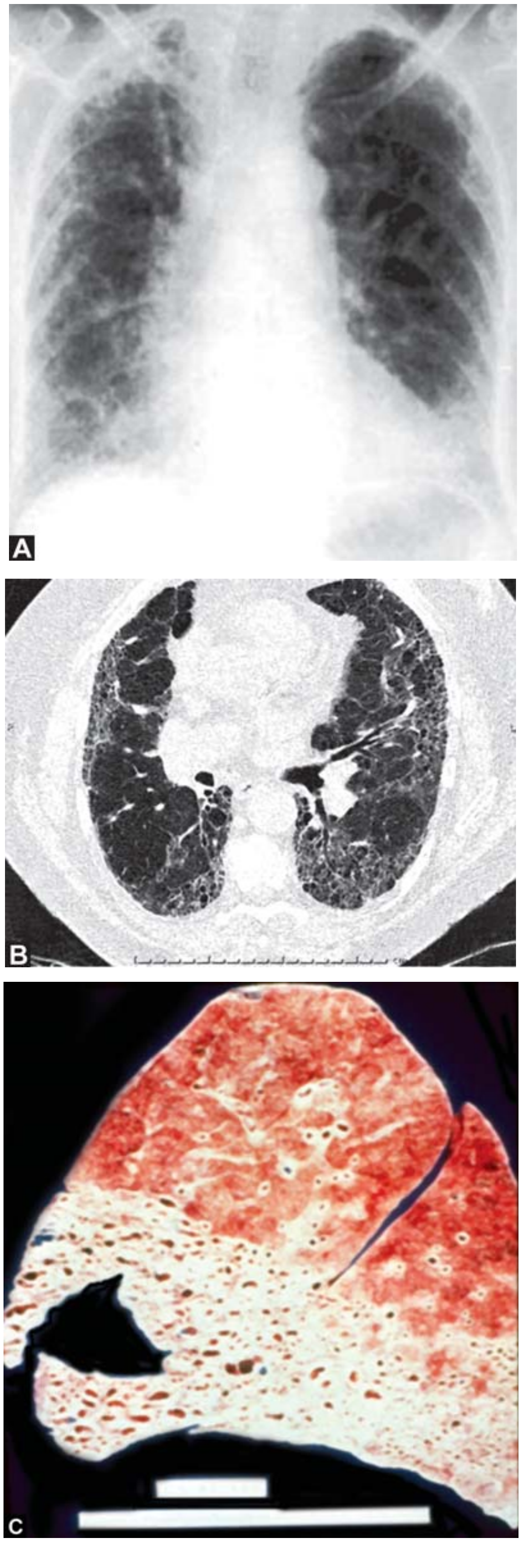
- Age >50 years
- Insidious onset of otherwise unexplained dyspnea on exertion
- Duration of illness >3 months
- Bibasilar, inspiratory crackles (dry or “Velcro” type in quality)

not present, a diagnosis of atypical IPF or other IIPs must be taken into consideration and a surgical lung biopsy may be necessary to confirm the diagnosis.

Treatment

Treatment is targeted at resolution and slowing down the progression of disease.[5,6,8] Corticosteroids[6,8] and immunosuppressive/cytotoxic agents such as azathioprine and cyclophosphamide,[6] have been the mainstay of treatment to date as recommended by the ATS/ERS consensus statement. However, there is a little evidence to support the use of these immunosuppressive therapies in IPF and thus the author believes this recommendation may change in the near future. As for the dosing, according to the ATS/ERS consensus statement, prednisone should be started at a dose of 0.5 mg/kg and tapered to a maintenance dose of 0.125 mg/kg. This should be combined with azathioprine or cyclophosphamide at a target dose of 2–3 mg/kg in carefully selected patients to spare the toxic effects of corticosteroids.

There is also evidence that the antioxidant N-acetylcysteine (NAC), at a dose of 600 mg three times a day, in combination with azathioprine and corticosteroids improves physiological parameters and may slow down progression of disease.[9] The rationale for NAC is based on the fact that NAC will replete the



Figs 95.3A to C: Chest radiograph, CT chest, and gross pathology of the explanted lung with IPF/UIP. Note that the distribution is predominantly in the bases and subpleural region

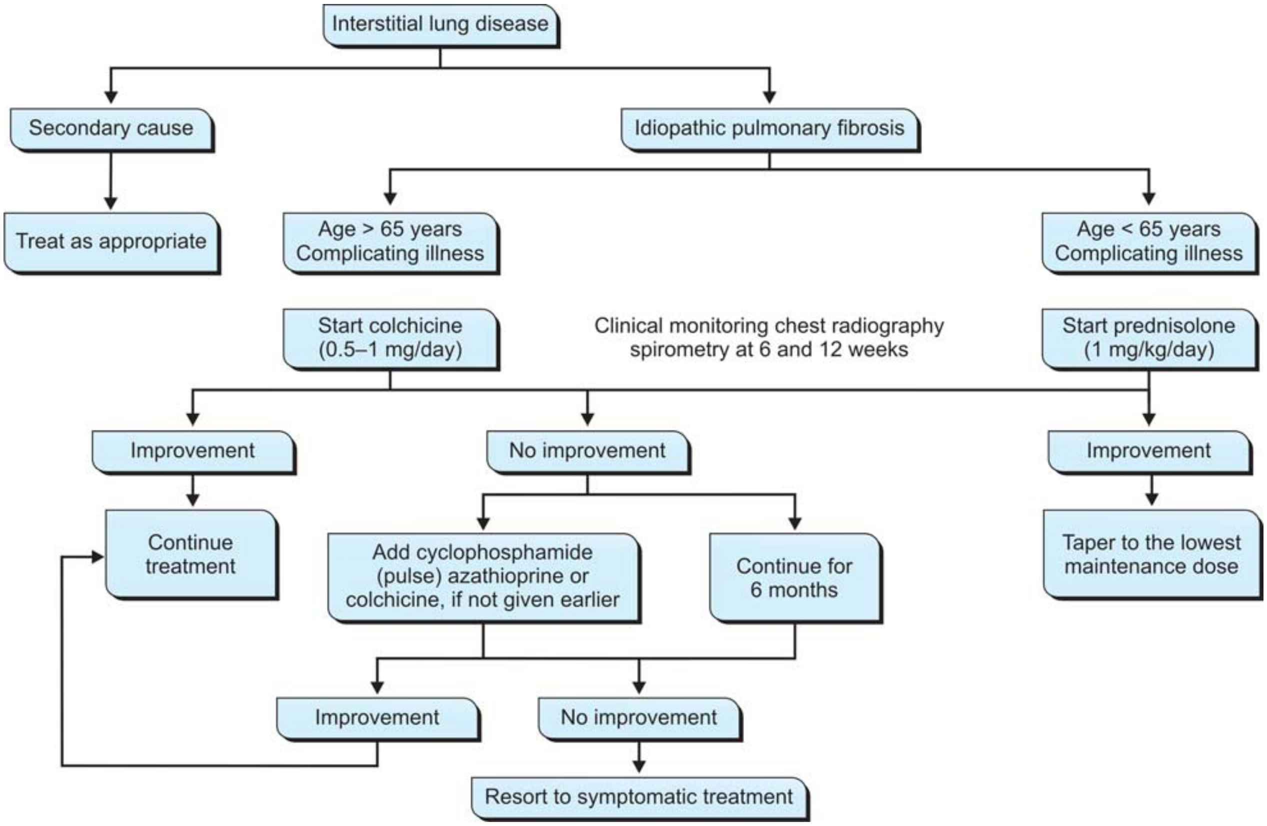

Interstitial lung disease
Secondary cause
Idiopathic pulmonary fibrosis
Treat as appropriate
Age > 65 years
Complicating illness
Age < 65 years
Complicating illness
Start colchicine
(0.5–1 mg/day)
Clinical monitoring chest radiography
spirometry at 6 and 12 weeks
Start prednisolone
(1 mg/kg/day)
Improvement
No improvement
Improvement
Continue
treatment
Add cyclophosphamide
(pulse) azathioprine or
colchicine, if not given earlier
Continue for
6 months
Taper to the lowest
maintenance dose
Improvement
No improvement
Resort to symptomatic treatment

Fig. 95.4: Algorithm for treatment of pulmonary fibrosis in developing countries[5]

glutathione levels and prevent oxidative injury that leads to fibroproliferation in IPF. Other antifibrotic agents, such as D-penicillamine and colchicine and pirfenidone, have been used alone or in combination.[5,8] A trial with pirfenidone was carried out in Japanese patients and found to be effective in stabilizing lung function and reducing the frequency of acute exacerbations.[10]

Clinical and physiological responses to therapy should be evaluated periodically at three to six months after the initiation of therapy to justify continuing the treatment. Supportive care with supplemental oxygen, immunizations, prompt treatment of infections and pulmonary rehabilitation helps to improve the quality of life.[5,8] In spite of theses therapies IPF portends a poor prognosis with a median five-year survival of less than 50%.[2,5] Lung transplantation becomes the only option for treatment for eligible patients, although this is not readily available in many developing countries.

Given the constraints and challenges in the developing world, Jindal et al. proposed a treatment protocol for IPF in developing countries (Fig. 95.4).[5]

Prognosis

The general clinical course is one of the progressive impairment of lung function resulting in respiratory failure. Patients often die from progression of the disease or as a result of complications of therapy, usually opportunistic infection.

Indicators for longer survival include younger age, female sex and early presentation with preserved lung function. Increased portion of lymphocytosis (20% to 25%) on BAL and a beneficial response or stable disease three to six months after the initiation of corticosteroid therapy[6,9] also appear to correlate with survival. As for younger patients with earlier onset, this appears to confer a more favorable response to therapy.[5]

NONSPECIFIC INTERSTITIAL PNEUMONIAS (NSIP)

Epidemiology

The mean age of onset is 40–50 years of age, which is about a decade earlier than in IPF, has been also reported in the pediatric population.[11] It occurs equally in both men and women, has no known association with cigarette smoking.[12]

Etiology

Unlike IPF, the etiology of NSIP may be more evident with autoimmune diseases, hypersensitivity pneumonitis and certain inhalational exposure. Therefore a diagnosis of NSIP should prompt clinical evaluation for an underlying etiology. However, the etiology in a significant number of patients with NSIP remains elusive and coined as idiopathic NSIP which has unique features from other forms of NSIP.

Signs and Symptoms

Onset is gradual and some patients have associated constitutional symptoms such as fever and weight loss in addition to respiratory symptoms such as chronic cough and dyspnea.[3] Finger clubbing is less common than in IPF, can occur in 10 to 35% of patients.[12] Inspiratory crackles are usually present on lung examination.

Diagnosis

Clinical features in the presence of a restrictive pattern and a reduction in DLCO suggest the diagnosis of an interstitial pulmonary disease. Histologically, NSIP can be further separated into cellular and fibrotic NSIP. In cellular NSIP, mild-to-moderate homogenous interstitial chronic inflammation is the predominant feature, unlike fibrosing NSIP where uniformly dense fibrosis is a prominent feature.[11] Temporal uniformity, the paucity of fibroblastic foci and honeycomb lesions are the features that histologically differentiate NSIP from UIP.[3] Radiographically, cellular NSIP in contrary to IPF show diffuse symmetric interstitial infiltrates and ground-glass opacities. In fibrotic NSIP, the radiographic signs of fibrotic disease are seen in some cases similarly to IPF.

Treatment/Prognosis

Katzenstein classified NSIP into three subgroups based on the degree of inflammation and fibrosis on histopathology: Group 1 primarily has interstitial fibrosis; group 2 inflammation and fibrosis; and group 3 primarily fibrosis.[11] Patients with cellular NSIP usually respond well to corticosteroids unlike fibrotic NSIP.[3] Thus the prognosis is good in cellular NSIP, as opposed to fibrotic NSIP, which has been shown to mirror that of IPF, given the similarities in histology and clinical features.

DESQUAMATIVE INTERSTITIAL PNEUMONIA (DIP)

Epidemiology

Desquamative interstitial pneumonia is a rare IIP primarily seen in smokers in the fourth to fifth decade of life.[13,14] The term DIP was coined by Myers et al. based on findings in six patients who had interstitial pattern on chest radiograph with restrictive pulmonary function test and respiratory bronchiolitis on histopathology.[15]

Etiology

In at-risk patients, tobacco induces injury to the bronchiolar and alveolar epithelium. The pathobiology is not completely understood as to why and how this occurs.[16] As in patients with pulmonary Langerhans cell histiocytosis, abnormal T-cell proliferation and increased secretion of peptides has been described.[16] It is likely that this disorder, like other cigarette smoking related lung diseases, occurs in susceptible individuals following initial injury to the pulmonary epithelium.

Signs and Symptoms

Dyspnea at rest or on exertion is the most common presenting symptom.[13] Onset is insidious. Cough may be dry or productive of nonpurulent sputum.[13] Systemic symptoms are usually absent with digital clubbing in some patients.[3] Physical examination shows crackles in less than 50% of patients.[3,13]

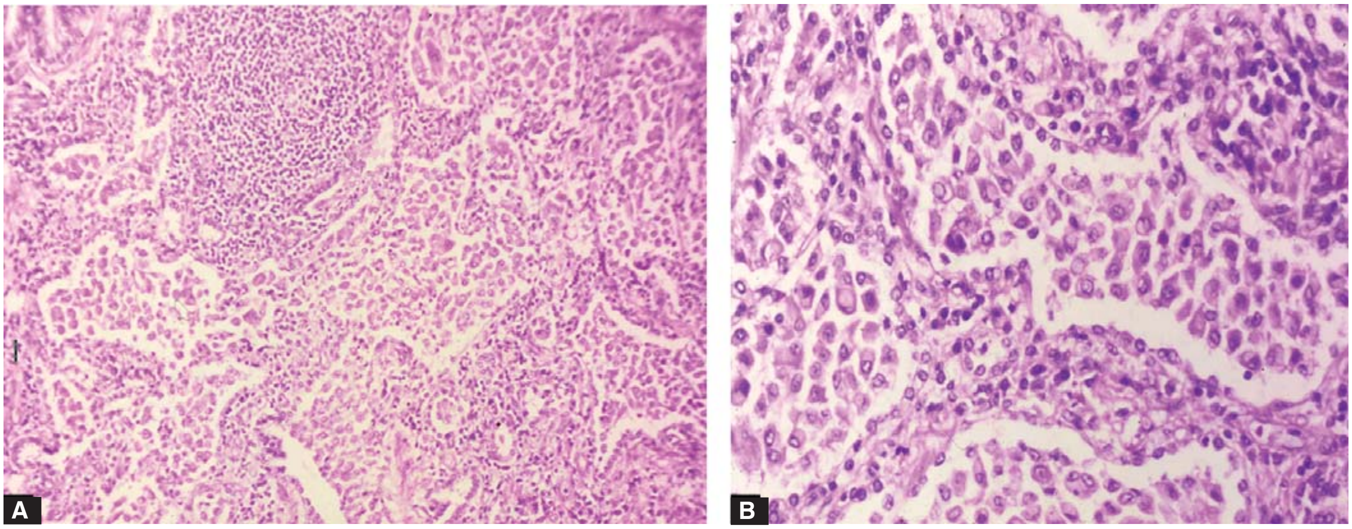
Diagnosis

The diagnosis should be suspected when these clinical and epidemiological features are seen in combination with radiographic findings.[3] Typical radiographic findings include patchy ground glass opacification with a predilection for the lower zones, though in rare cases it can even be normal.[16] The PFTs can show a combined obstructive and restrictive defect, often with a decrease in DLCO.[3,15]

The histological pattern is characterized by chronic interstitial inflammation and numerous intra-alveolar mononuclear cells, thought to be desquamated epithelial cells (hence the name) but subsequently proved to be macrophages (Figs 95.5A and B).[17]

Treatment

There is reported clinical response to smoking cessation alone or in combination with corticosteroid therapy.[3,14] In some cases, in spite of clinical stability, abnormal radiographic features may persist.[14]



Figs 95.5A and B: DIP pattern on histopathology. Diffuse macrophage accumulation with type 2 cells lining alveoli. Mild interstitial fibrosis, chronic inflammation and no dense scarring or architectural distortion is seen

Prognosis

Treatment outcomes are generally good. Some patients however have persistent disease despite smoking cessation; corticosteroid therapy may be useful in these cases.[14]

RESPIRATORY BRONCHIOLITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE (RB-ILD)

Epidemiology

Recent studies have linked idiopathic DIP to Respiratory Bronchiolitis (RB) and RB-ILD in a spectrum of smoking related lung injury.[17]

It is considered a variant of DIP and has a patchy distribution rather than a diffuse process. Smokers in the third to fourth decade of life are usually affected.[18]

Signs and Symptoms

Most patients are asymptomatic or have mild symptoms of dyspnea and cough of insidious onset.[3,13,14] Inspiratory crackles are present on lung examination with digital clubbing in up to 25% in one series.[14]

Diagnosis

On spirometry, a combined defect with abnormalities of gas exchange is often seen.[3,17] Ground glass opacities and attenuation may be seen on chest imaging, associated with thickening of walls of central and peripheral airways. These findings are ultimately associated with the pathological lesion of respiratory bronchiolitis (Figs 95.6A and B).

Treatment

The only proven therapy for RB-ILD is smoking cessation. Only those who continue to be symptomatic in spite of smoking cessation should be considered for corticosteroid therapy.[3,16]

Prognosis

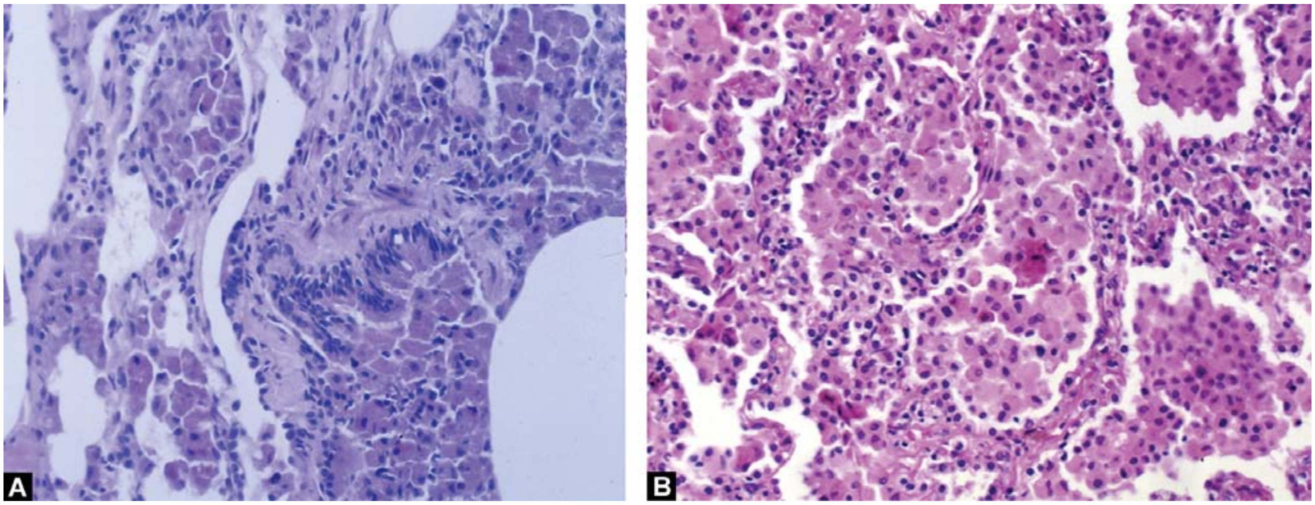
Prognosis is good and patients usually improve with smoking cessation. To date there are no documented cases of respiratory failure or death directly attributable to RB-ILD.[3,16]

CRYPTOGENIC ORGANIZING PNEUMONIA (COP)

Epidemiology

Cryptogenic organizing pneumonia, previously known as Bronchiolitis Obliterans with Organizing Pneumonia (BOOP), often presents clinically as a flu-like illness of subacute onset (weeks to a few months). The disease process was initially described by Grinblat and colleagues in two patients.[19] Organizing pneumonia is often a non-specific response to lung injury and is classified as cryptogenic when an underlying disease cannot be identified.

Cryptogenic organizing pneumonia is commonly diagnosed during the fifth decade of life; there have been case reports in adolescence.[20] In most series from



Figs 95.6A and B: RB-ILD pattern on histopathology. Clusters of dusty brown macrophages in respiratory bronchioles, alveolar ducts and peribronchiolar alveolar spaces are seen in RB-ILD

developing countries including data from the Middle East[21,22] and Southeast Asia,[23] there is no correlation between smoking status and the disease. Men and women are affected equally.

Etiology

Organizing pneumonia is a non-specific response of the lung to injury. It is termed cryptogenic when an inciting agent or disease process is absent. Increased expression of interleukin-8 and fibronectin genes by alveolar macrophages has been described in COP.[24] This suggests that the lung injury and inflammation may be initiated and perpetuated by inflammatory cytokines produced in situ by alveolar macrophages.[24] In mice models, there is a suggestion that genetic host factors play an important role in the development of lung fibrosis in COP.[24]

Signs and Symptoms

Cryptogenic organizing pneumonia often presents clinically as a flu-like illness of subacute onset (weeks to a few months).[3] Fever, dry cough with malaise, anorexia and weight loss are often present with mild dyspnea, especially on exertion.[3] Physical findings are sparse, with inspiratory crackles being present on lung examination.[3]

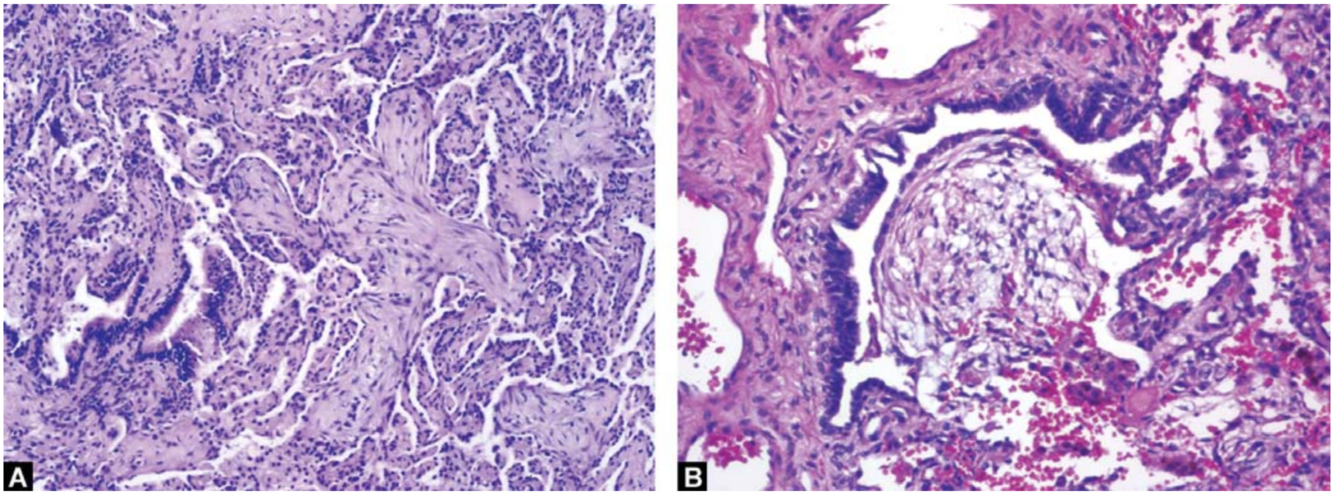
Diagnosis

The diagnosis should be considered in patients with features of a nonresolving pneumonia. Chest X-ray shows patchy migratory unilateral or bilateral airspace disease with predominantly peripheral distribution.[3] On CT scan, the opacities range from ground glass to dense consolidation. Though these radiographic findings are typical, they can be seen in other conditions.[24] Less commonly, radiographic features of diffuse interstitial opacities and solitary focal lesions may be seen.[24] Spirometry may be normal; however it typically reveals a restrictive pattern with some gas exchange abnormalities. In smokers, there may be an obstructive component to pulmonary function tests. Buds of granulation tissue are found within the lumen of the distal airways on histology (Masson bodies). This pattern is nonspecific and reflects an inflammatory response to lung injury. There is a preservation of lung architecture with the absence of scarring or honeycombing on histopathology (Figs 95.7A and B).[3]

Treatment/Prognosis

Most patients respond well to corticosteroids, but relapses can occur requiring chronic steroid therapy.[3] Cytotoxic drugs and steroid sparing agents are used in addition to corticosteroid where there is slow response to steroids alone.[24] A small group (10 to 15%) may progress to pulmonary fibrosis.[3] Factors that may predict poor outcomes include the lack of lymphocytosis on BAL, predominantly interstitial pattern on imaging and histological features of scarring and remodeling of lung parenchyma.[24]

Polypoid plugs of fibrous tissue (Masson bodies) within bronchiolar lumens, alveolar ducts and alveoli. Clusters of alveolar foamy macrophages are also present.



Figs 95.7A and B: Cryptogenic organizing pneumonia pattern on histopathology

ACUTE INTERSTITIAL PNEUMONIA (AIP)

Epidemiology

Hamman-Rich described a series of four patients who died from rapidly progressive lung disease, associated with respiratory failure and death within a few months of onset. Autopsy was characterized by a diffuse interstitial pneumonia and fibrosis.[25] Acute interstitial pneumonia is a rare and often fatal disease encountered in apparently healthy individuals after an acute respiratory illness and characterized by diffuse alveolar damage.[25] The syndrome mimics Acute Respiratory Distress Syndrome (ARDS).

Etiology

The exact mechanism responsible for AIP are poorly understood;[26] however there is diffuse acute lung injury resulting in acute respiratory failure. Several mediators have been described and implicated in this process. Proinflammatory, anti-inflammatory, metalloproteinases and proteins regulating apoptosis have all been implicated.[27-29]

Signs and Symptoms

The presentation is similar to that of ARDS. The onset is acute and often preceded by the symptoms suggestive of a viral upper respiratory tract infection followed by widespread pneumonia. Hypoxemia develops early followed by respiratory failure requiring mechanical ventilatory support. There is no association with smoking.[3]

Diagnosis

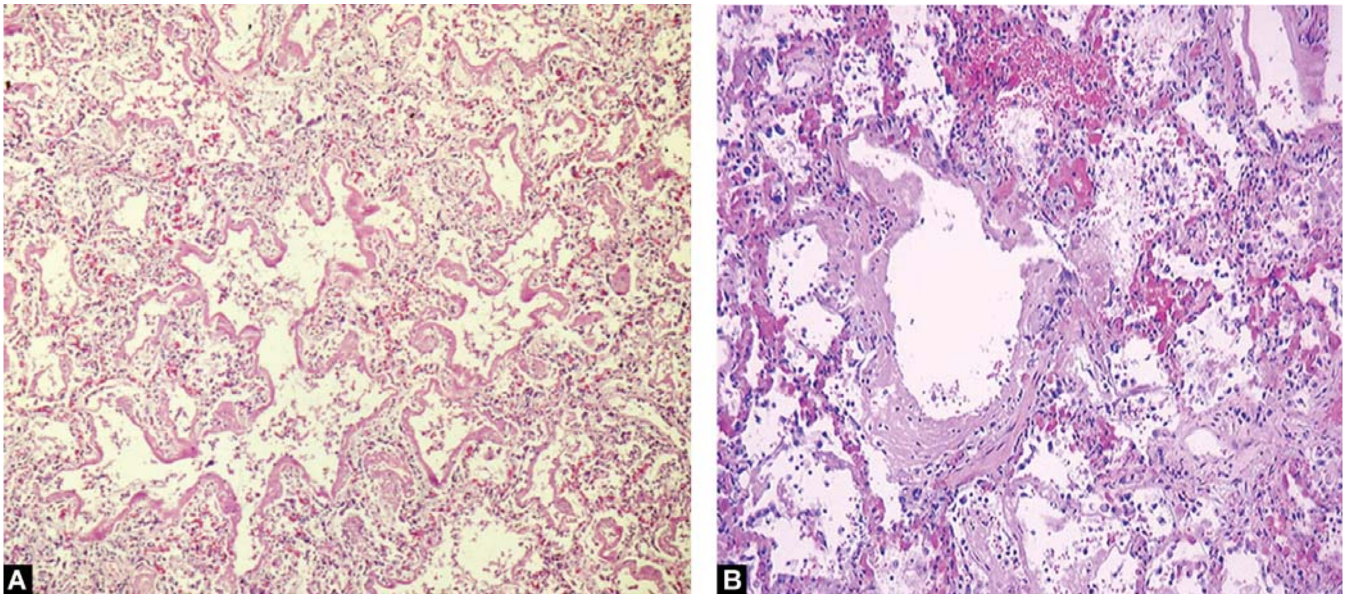
Based on the American Thoracic Society/European Respiratory Society guidelines[3] the criteria include rapidly progressive clinical course (less than 2 months) leading to respiratory failure; exclusion of infectious, toxic, autoimmune or any other cause of ARDS; Diffuse Alveolar Damage (DAD) on biopsy specimens; radiological findings consistent with ILD; and absence of chronic lung disease.[2] Bilateral airspace disease seen radiographically correlates with DAD seen on histology (Figs 95.8A and B).

Treatment

Since there is no proven treatment, supportive care with oxygen supplementation and mechanical ventilation is indicated. Early corticosteroid therapy and combination therapy with intravenous cyclophosphamide and vincristine have been reported.[30] Newer agents, such as inhaled nitric oxide, anticytokine antibodies and surfactant, may be useful.[31,32] There is a report of single lung transplantation as therapy for AIP.[33]

Prognosis

Mortality is greater than 60%.[3,26] Based on the morphology of lung parenchyma on CT, some authors report that this may help differentiate fulminant forms of AIP.[34,35] Those who survive may have no residual lung damage or residual pulmonary fibrosis.



Figs 95.8A and B: Acute interstitial pneumonia pattern on histopathology. Hyaline membranes with eosinophilic material lining alveolar spaces consistent with DAD are present with areas of progressive fibrosis

LYMPHOID INTERSTITIAL PNEUMONIA (LIP)

Epidemiology

One of the rarest of the IIPs, LIP mostly affects women in the fifth decade of life but can occur at any age.[3,26] Although part of IIPs, there is a thought that LIP possibly represents a lymphoproliferative disorder confined to the lungs that was initially described by Liebow and Carrington.[36] Lymphoid interstitial pneumonia has also been described in developing countries such as Africa and the Caribbean, but all in association with systemic diseases, most notably Human Immunodeficiency Virus (HIV) infection [or Acquired Immunodeficiency Syndrome (AIDS)] although some cases remain idiopathic. It has also been described in post bone marrow transplantation.[37]

Etiology

There is some evidence that this is a lymphoproliferative disorder rather than a primary interstitial pulmonary process.[38] It may result from a lymphoproliferative response to chronically presented viral antigens or cytokines with or without recruitment of circulating lymphocytes. Mutations of the B-cell CLL/lymphoma 6 gene have been associated with LIP.[38]

Signs and Symptoms

It is slow in onset with increasing cough and breathlessness. Constitutional symptoms, such as fever, weight loss, arthralgias, may be prominent features.[3] Chest examination often reveals bibasilar crackles with digital clubbing being rare.[39] Dysproteinemia with an isolated increase in IgG or IgM may be present in 75% of cases.[3]

Diagnosis

Chest X-ray may show an alveolar pattern predominantly at the bases or a diffuse disease with honeycombing. The predominant cell type on BAL is lymphocyte with a restrictive pattern on lung function tests. Histology reveals dense interstitial lymphoid infiltrate. This pathological finding has been described in other connective tissue disorders, such that the diagnosis can only be made once underlying connective tissue or systemic diseases have been excluded.[3]

Treatment

Some patients improve spontaneously without any treatment. Clinical improvement to corticosteroid therapy has been reported. In some cases, cytotoxic agents including cyclophosphamide, azathioprine and cyclosporine have been used.[38] Supplemental oxygen therapy and treatment of pulmonary infections may be necessary.

Prognosis

Survival is impaired; however mortality data are sparse because of the rarity of the condition.[3,39]

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Sarcoidosis

Dheeraj Gupta, Om P Sharma

INTRODUCTION

Sarcoidosis, a multisystem disorder, is characterized by depression of cutaneous delayed-type hypersensitivity and a heightened helper T cell type 1 (Th1) immune response in the affected organs. The disease occurs worldwide and affects young and middle-aged adults of both sexes. However, in the past sarcoidosis was considered rare in India and other developing countries. However, in the first decade of the 21st century, sarcoidosis is being recognized frequently because of the increasing awareness and the availability of better diagnostic modalities. In the tropics differential diagnosis from tuberculosis, which is far more prevalent and a close clinical mimic of sarcoidosis, remains a challenge. The lungs are the most frequently involved organs, but its chameleon-like presentation can involve any organ including the eyes, skin, bones, heart, liver and the brain. The diagnosis of sarcoidosis rests on the triad of clinical, radiologic and histologic criteria. Despite extensive research carried out over a century the cause of sarcoidosis remains unknown. The most accepted hypothesis favors an environmental or infectious agent in a genetically susceptible host. The mainstay of treatment is corticosteroids. In general, sarcoidosis has good prognosis.

HISTORY AND EPIDEMIOLOGY

The early descriptions of sarcoidosis were only limited to its skin manifestations. In 1877, Jonathan Hutchinson, a London general practitioner, described a patient with chronic multiple, raised, purplish cutaneous patches over hands and feet. This most likely was the first reported case of sarcoidosis.[1] The term ‘Sarcoidosis’ is credited to Caesar Boeck, who described histological findings of epithelioid cells and giant cells in skin biopsy and termed it “multiple benign sarkoid of the skin,” implying that the histology resembled “sarcoma” but was benign.[2] The major landmarks in the description and understanding of the disease are summarized in Table 96.1. Detailed accounts of history of sarcoidosis have appeared elsewhere.[3,4]

Epidemiology

Sarcoidosis has evolved from a dermatological curiosity in the nineteenth century to a common multisystem disorder in the 21st century. Epidemiology of sarcoidosis has been a confusing field because of the varied clinical presentation of the disease in different parts of the world, despite the fact that there is a vast body of evidence worldwide on the prevalence, racial predilection, familial, geographic, climatic and occupational clustering of sarcoidosis.[16-20] However there are significant differences in disease prevalence between countries, e.g. compared to a high prevalence rate of 28.2/100,000 in Finland; in Japan this is as low as 3.7/100,000 population.[16] The definite prevalence figures are not available from India, but the disease has moved from position of a disease of relative obscurity to an increasing recognition.[17-23] At our hospital, which is a tertiary care referral center for the Northern India, North of Delhi; we have been diagnosing over 100 new cases every year since 2001 (Fig. 96.1).

A Case Control Etiologic Study of Sarcoidosis (ACCESS) conducted across 10 centers in the United

TABLE 96.1: Some important historical landmarks in sarcoidosis

Year(s)	*Landmark*
1869	Hutchinson describes skin lesions
1889	Besnier described “Lupus pernio”[5]
1904	Kreibich described Sarcoid bone cysts[6]
1909	Heerfordt described uveoparotid fever[7]
1916-17	Schaumann recognized multiple-organ involvement and separates sarcoidosis from lymphoma[8]
1939	Association of hypercalcemia or hypercalciuria with sarcoidosis was described[9]
1941	Kveim described a test to help diagnose sarcoidosis[10] Siltzbach later refined and popularized the test[11] James christened the test as Kveim-Siltzbach test.
1946	Löfgren linked erythema nodosum, bilateral hilar lymphadenopathy, fever and polyarthritis[12]
1951	Corticosteroids were first used to treat sarcoidosis[13]
1958	Wurm and colleagues proposed radiographic staging[14] First International Conference held in London, UK
1975	Serum Angiotensin-Converting Enzyme (ACE) was first recognized as a possible biochemical marker by Lieberman[15]
1984	Rizzato started journal Sarcoidosis (now called Sarcoidosis, Vasculitis and Diffuse Lung Diseases)
1987	Rizzato and James formed the World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG)

States, has clarified and confirmed some epidemiological and etiologic aspects of the disease.[24,25] In addition to investigating the possible etiology of the disease, this study examined the psychosocial characteristics[26] and clinical course of 736 patients enrolled in the first six months after histological diagnosis of sarcoidosis and compared them with control subjects paired by age, sex and race. A follow-up study of the first 215 cases was undertaken two years after enrollment.[27] Women were somewhat more likely to be affected, and there were gender differences in clinical manifestations; women tended more to ocular and neurological involvement, whereas men had a higher risk of hypercalcemia. African-Americans were more likely to have uveitis, skin and liver disease. In the United States the lifetime risk of sarcoidosis for those of Afro-Caribbean origin is nearly three times that for Caucasians (2.4 vs 0.85%, respectively).[28]

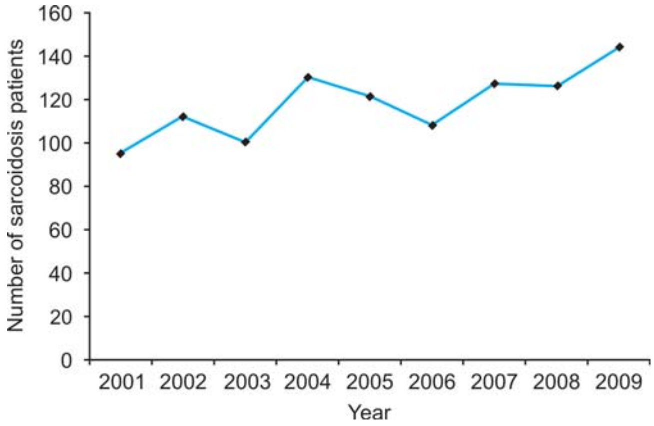


Fig. 96.1: Number of newly diagnosed patients of sarcoidosis from 2001 to 2009 at Department of Pulmonary Medicine, PGI Chandigarh, India

RISK FACTORS

Genetic Predisposition

Clustering of sarcoidosis in families occurs. Nearly 6% of patients in the United Kingdom have an affected relative[29] and the relative risk of sarcoidosis for family members in the United States is 4.7%, siblings have the highest (5.8%) risk.[30] The familial clustering is higher for white than black families. The majority of familial “clusters” involve only parent-child pairs or sibling pairs, more complex pedigrees are rare. This suggests a summation of more than one minor genetic influences rather than a single causative gene mutation.

Blau syndrome, an autosomal dominant chronic granulomatous disease clinically identical to sporadic infantile-onset sarcoidosis, had its gene locus mapped to 16p12-q21 and subsequently both diseases were found to be associated with mutations in the CARD15 gene.[31] However, no association is found with adult sarcoidosis.[32]

In recent years, many of class II MHC alleles have been implicated in the certain aspects of the disease. HLADR5, HLA-DR6, HLA-DR8 and HLA-DR9 seem to confer risk of having disease in Japanese patients, although HLA-DR9 is protective in the Scandinavian population. In German patients, HLA-DR5 is associated with chronic disease and HLA-DR3 with acute forms. Likewise, in Scandinavians, HLA-DR14 and HLA-DR15 are associated with chronic forms and HLA-DR17 with self-limiting ones.[33] The ACCESS study identified a significant association between HLA-DRB1 alleles (specifically HLA-DRB1*1101) and the development of the disease, both in blacks and Caucasians.[24] The only class II allele that was distributed differently among different races with respect to the disease was HLA-DRB1*1501, which was associated with controls in blacks and with cases in whites. This would indicate that, in general, alleles similar to class II HLA may be associated with sarcoidosis in both populations. Similarly, other studies have identified specific alleles of HLA-DQB1 as determining susceptibility to sarcoidosis in the African-American population.[25,34,35] In a study from India presence of DRB1*11 and DRB1*14, and absence of DRB1*07 and DQB1*0201 alleles, were found to be independent predictors of sarcoidosis.[36]

Environmental and Occupational Risk Factors

Barnard et al.[37] based on data from the ACCESS study, observed a greater risk among workers with industrial exposure to organic powders, particularly in those who worked for the suppliers of hardware, building and gardening materials. The jobs associated with childcare and occupational exposure to metal vapors or dusts were not associated with sarcoidosis. These associations were seen particularly among Caucasians.

Occupational exposures identified in the case control studies among Afro-American patients of sarcoidosis were of wood-burning stoves, fireplaces, consumption of water from wells (not from the public mains supply), living or working on a farm,[38] exposed to metals at work, and working in humid places with musty smells.[39]

Tobacco smoking is considered protective for sarcoidosis. In 1961, Comstock et al. in their study of possible risk factors for sarcoidosis observed that patients with sarcoidosis smoked less than matched controls. This inverse association was however noted only among white subjects.[40] Similar findings were subsequently reported in several studies with a reduction in the prevalence of smokers among sarcoidosis patients varying between 21% to 79%.[41-48] The large multicentric ACCESS study demonstrated lesser odds for ever smoking among patients (OR 0.65, CI 0.51-0.82) [49] Fewer alveolar macrophages are recovered by lavage from smokers with sarcoidosis than from normal subjects with a similar smoking history. This supports the possibility that smokers, particularly those with a lower accumulation of alveolar macrophages in the lower respiratory tract, may be less prone to develop sarcoidosis.[41,47] This was further supported by Blanchet and coworkers, who demonstrated in animal models and cell lines that concomitant exposure to nicotine with agents known to induce granulomatous inflammation, had a protective effect.[50] However, simultaneously studies have reported insignificant association or even increased prevalence of smoking among sarcoidosis patients.[51,52] A recent study has reported the impact of active smoking and Environmental Tobacco Smoke (ETS) exposure on disease severity in newly diagnosed cases of sarcoidosis from India. In this study smoking or ETS exposure did not have any significant negative association with sarcoidosis. Also, tobacco smoke did not have any effect on the clinical behavior or disease severity in sarcoidosis.[53]

Infectious Agents as Risk Factors

The granulomatous diseases are the result of continued presentation of a poorly degradable antigen.[54] In the case of sarcoidosis, numerous etiologic agents have been incriminated, both infective and noninfective.[55] Non-infective agents have been implicated because of their epidemiologic association,[56] but have not stood the test of time.[57] Examination of the sarcoid granuloma with an electron microscope and immunohistochemical techniques has identified structures similar to organisms such as *Leptospira species, Mycoplasma species* and *Propionibacterium species*.[55] Other microbiological agents that have been implicated from time to time include herpes virus, retrovirus, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, *Rickettsia helvetica*, and finally *Pneumocystis jiroveci*.[55,58] The two strongest contenders are *Propionibacterium* and *Mycobacterium*.[59-61]

From the time sarcoidosis has been described, there has always been a belief that the disease is in some way related to tuberculosis.[62] However, the inability to identify mycobacteria by histologic staining or culture from pathologic tissues continues to be one of the strongest arguments against a potential role for mycobacteria. A recent meta-analysis suggested a 30% prevalence rate of mycobacterial DNA in sarcoid samples but the individual studies reported detection rates from 0% to 50%.[63] Moreover, most of these studies were published from countries with low prevalence for tuberculosis. If indeed mycobacteria are etiologically linked to sarcoidosis then the detection rates for mycobacterial Deoxyribonucleic Acid (DNA) in sarcoid samples would be higher in countries with high prevalence of Tuberculosis (TB). A recent prospective case-control study aimed at the detection of mycobacterial DNA in patients with sarcoidosis from India, has reinforced the hypothesis by showing mycobacterial DNA with PCR for 65 kDa protein gene in 48% of samples [Bronchoalveolar Lavage (BAL) or biopsy] from freshly diagnosed patients of sarcoidosis.[64]

The factors that favor mycobacteria being a trigger for sarcoidosis include histopathological appearances of the granulomas,[54] reports of mycobacterial disease either existing before, during or after sarcoidosis[65,66] and the finding of mycobacteria in occasional granulomas of sarcoidosis.[67-69] Passage experiments have also suggested that mycobacteria with the characteristics of *Mycobacterium tuberculosis* may be the incriminating agent.[70-73] Recent studies on humoral immunity to mycobacterial antigens from sarcoidosis patients have renewed interest in a potential of mycobacteria in sarcoidosis.[74] It has been shown that mycobacterial ESAT-6 and katG are recognized by sarcoidosis CD4+ T cells when presented by known sarcoidosis susceptibility allele, DRB1*1101.[75] It is possible that the presence of mycobacterial infection or BCG vaccination in genetically predisposed host may be involved in the development of autoimmunity.[76] It has also been suggested that the organism might exist in a cell wall deficient L-form and may be difficult to isolate.[77] Evidence even if tantalizing, is not conclusive to support the contention that tubercle bacillus causes sarcoidosis.

PATHOGENESIS AND IMMUNOLOGY

Non-caseating granuloma is the hallmark of sarcoidosis. The granulomatous reaction is a protective response to an inciting agent. It limits inflammation and protects the tissue. Though exact antigen inciting this response is yet unclear and it may in fact be different in different patients and different demographic areas (Fig. 96.2). Essentially there are four stages involved. First is the presence of the inciting antigen and its contact with Antigen Processing Cells (APC), which are mostly the alveolar macrophages. Second stage is the interaction APCs and CD4+ T lymphocytes to initiate the formation of a simple granuloma, Third stage includes further recruitment of CD4+ T-lymphocytes and elicitation of Type 1 and Type 2 helper responses, which lead to the final or fourth stage of formation and maintenance of complex granulomas. Macrophages differentiate to form epithelioid cells under the influence of cytokine production. These epithelioid cells fuse to form Multinucleated Giant Cells (MNGC) and gain secretary properties. Granulomas secrete many chemicals, including calcitriol and angiotensin converting enzyme. These events, however, are dependent on a susceptible genetic background described by a variety of functional polymorphisms.[78,79]

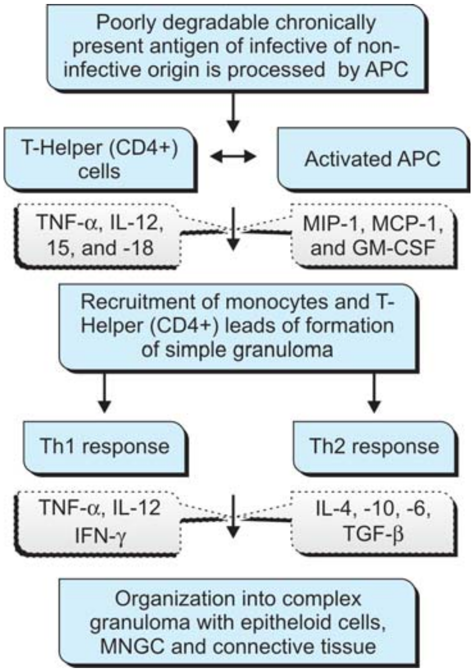

Poorly degradable chronically present antigen of infective of non-infective origin is processed by APC
T-Helper (CD4+) cells
Activated APC
TNF-α, IL-12, 15, and -18
MIP-1, MCP-1, and GM-CSF
Recruitment of monocytes and T-Helper (CD4+) leads of formation of simple granuloma
Th1 response
Th2 response
TNF-α, IL-12 IFN-γ
IL-4, -10, -6, TGF-β
Organization into complex granuloma with epitheloid cells, MNGC and connective tissue

Fig. 96.2: Hypothesis of the development of granulomatous inflammation in sarcoidosis

What Controls the Course of Granulomas?

Extensive research over past two decades has helped to delineate the sequence of events in the immunopathogenesis of sarcoidosis. The earliest event is accumulation CD4+ helper T cells and release of Interleukin-2 (IL-2) in the alveoli and interstitium.[80-82] This is followed by a progressive and selective oligoclonal expansion of αβ T cell.[83] There is increased in situ production of Th1 cell-derived cytokines (IL-2 and IFN-γ) during granuloma formation.[84,85] The alveolar macrophages in sarcoidosis have immense secretary properties and there is an increased release of macrophage-derived cytokines (IL-1, IL-6, IL-8, IL-15, TNF-α, IFN-γ, GM-CSF) and chemokines (RANTES, MIP-1α, IL-16). Most of these cytokines favor granuloma formation and lung damage.[86-89] The progression and maintenance of granulomatous reaction is also helped by the accumulation of these monocyte-macrophages with antigen-presenting cell capacity and expressing the increased levels of activation markers (HLA-DR, HLA-DQ, CD71) and adhesion molecules (CD49a, CD54, CD102). The chemoattractant cytokines like IL-8, IL-15, IL-16 and RANTES recruit the CD4+ T cells from the peripheral blood to the site of inflammation,[85-87] while IL-2 induces an *in situ* proliferation of these cells.[90,91] The mechanism(s) that result in spontaneous resolution or progression to chronic disease and fibrosis are unclear but may be linked to host susceptibility and genetic factors. The sarcoid granulomatous inflammation is characterized by an altered balance of Th1/Th2 responses with a dominant expression of Th1 cytokines [IFN-γ and interleukin (IL)-2] with the low levels of expression of T helper 2 (Th2) cytokines (IL-4 and IL-5).[82,92] IL-12 contributes to proliferation of activated T cells in early disease. Elevated levels of IL-6 and IL-8 are reported in the BAL fluid of active sarcoidosis, and these may modify the disease process. IL-15 may aid in the proliferation of T and B cells.[93] IL-12 and IL-18 are also increased in the lungs of sarcoidosis, and they stimulate IFN-γ production.[82,94] Transforming Growth Factor-Beta (TGF-β) is an inhibitor of IL-12 and IFN-production. Its production is increased in those patients undergoing the remission of sarcoidosis, suggesting a key role for TGF-β in the down regulation of granulomatous inflammation of sarcoidosis.[95]

Another clinically important phenomenon that occurs in sarcoidosis is the depression of delayed type hypersensitivity. Commonly utilized as a diagnostic tool, this is often impaired in active sarcoidosis and not seen when sarcoidosis resolves. A subgroup of CD4+ T cells may account for this anergy by abolishing IL-2 production and inhibiting T cell proliferation.[96,97] It is also suggested that anergy state may be related to diminished dendritic cell function.[98]

PATHOLOGY

The most common organs of involvement are lymph nodes, lungs, liver, spleen and skin. In lungs the common site of involvement is along the bronchovascular spaces (lymphangitic pattern), that makes the transbronchial biopsy a preferred choice for obtaining histological diagnosis. However, any organ can be involved and the histological features are similar in all organs.[13,99,100] Many a times, the pathological involvement of organs may remain clinically silent, making sarcoidosis an iceberg syndrome (Fig. 96.3). Pulmonary vascular involvement has also been reported quite frequently.[101]

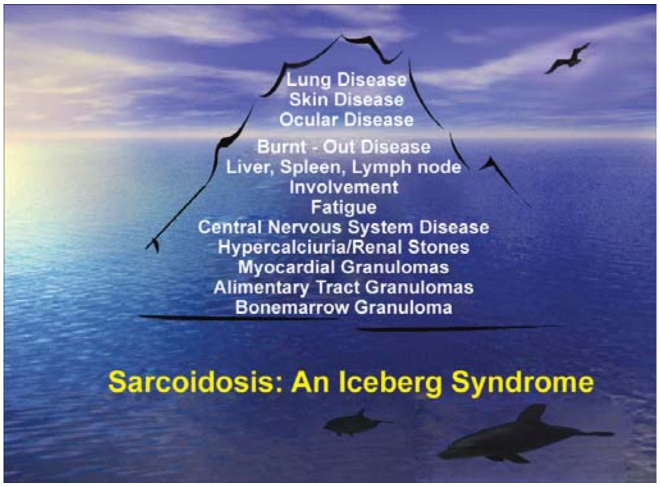

Lung Disease
Skin Disease
Ocular Disease
Burnt - Out Disease
Liver, Spleen, Lymph node Involvement
Fatigue
Central Nervous System Disease
Hypercalciuria/Renal Stones
Myocardial Granulomas
Alimentary Tract Granulomas
Bonemarrow Granuloma
Sarcoidosis: An Iceberg Syndrome

Fig. 96.3: Sarcoidosis: An Iceberg syndrome. Pathological involvement of various organs may not be clinically apparent

The hallmark of sarcoidosis is the noncaseating, compact, "naked" granulomas. On histology, a sarcoid granuloma is comprised of lymphocytes, macrophages, well differentiated epithelioid cells, multinucleated giant cells, fibroblasts and mast cells. The sarcoid granulomas have CD4+ T cells in the center and CD8+ T cells and B lymphocytes in the periphery.[13,102-104] Histologic findings differ based on the stage of the disease. In early stages of disease, the sarcoid granuloma is a compact structure that consists of radially arranged pale, pink epithelioid cells seen most often in the center of the granulomas. Lymphocytes and fibroblasts form a surrounding rim. Multinucleated Langerhans' type giant cells, usually only a few, are often seen in the granuloma. Caseation is absent. However, focal coagulative necrosis may be seen.[103] In rare cases, fibrinoid necrosis is seen in nodular and necrotizing sarcoid granulomatosis.[105,106] Nonspecific cytoplasmic inclusions can be seen in sarcoidosis, such as asteroid bodies, Schaumann's bodies, Hamazaki-Wesenberg bodies and calcium oxalate crystals. Granuloma may resolve totally with or without therapy. It may also persist and show hyalinization. In chronic sarcoidosis, fibrosis and scarring occur.[103,105]

CLINICAL FEATURES

In spite of the common observations that sarcoidosis often presents with significant clinical and radiological features, and that clinical medicine is relied upon rather heavily in most developing countries, the physicians in India are generally reluctant to make the diagnosis of sarcoidosis. The physician's reluctance is partly attributed to the belief that it is rarer in India and more importantly to the overwhelming prevalence of tuberculosis, which presents with very similar clinical, radiological and histological findings.

Besides thoracic manifestations, both sarcoidosis and tuberculosis involve multiple organs. Although the involvement of extrapulmonary sites was considered less frequent, a systematic review and cumulative analysis of all the major studies from India that have reported on clinical features (Table 96.2) show almost similar figures as reported from other countries, while extrapulmonary lymphadenopathy is distinctly more frequent.[107] Lung is the most common organ affected with sarcoidosis, the

TABLE 96.2: Summary of clinical findings as computed from major studies published from India

	Center (reference)					*Total n/N*	*%*
	AIIMS, Delhi		*Eastern India*[110]	*South India*[19]	*PGI, Chandigarh*[19,53,111-117]		
	Sharma[108]	*Tahir*[109]					
Total patients	106	72	200	22	492	892	-
Gender (Females)	38	36	89	13	203	379/892	42.48%
Constitutional symptoms							
Arthralgia	47	27	122	6	124	326/892	36.54%
Malaise	NA	NA	26	NA	73	99/692	13.29%
Fever	60	NA	140	9	224	433/820	52.8%
Pulmonary symptoms							
Cough/dyspnea	88	NA	186	17	338	629/820	76.7%
Extrapulmonary symptoms							
Eye	19	17	NA	2	54	92/692	13.29%
Lymph nodes	48	NA	44	NA	21	113/698	16.18%
Liver	48	9	87	NA	41	185/870	21.26%
Spleen	NA	6	65	NA	17	88/764	11.5%
Skin	45	22	NA	7	43	117/692	16.9%
Parotidomegaly	13	6	NA	NA	12	31/670	4.62%
Neurological	9	3	NA	1	7	20/692	2.89%
Chest radiograph							
Stage I	25	1	NA	8	216	250/692	36.12%
Stage II	67	35	NA	10	244	356/692	51.44%
Stage III	14	35	NA	3	24	76/692	10.98%
Stage IV	NA	1	NA	1	8	10/692	1.44%

disease may involve any part of the body.[27] Prominent manifestations of sarcoidosis are described below, and the similarities and differences from tuberculosis have been discussed subsequently.

Pulmonary Involvement

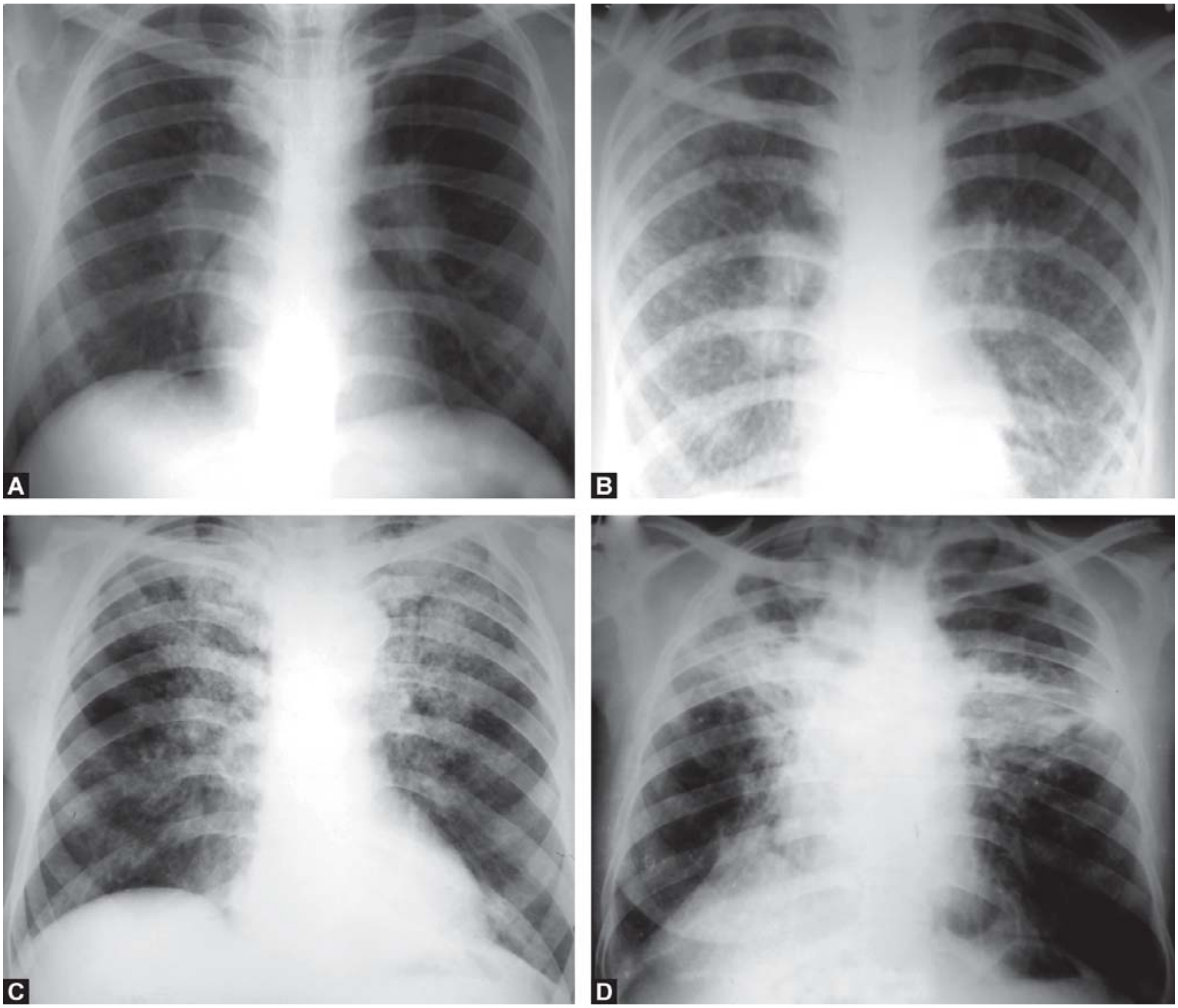
Clinical

The symptoms of sarcoidosis are often nonspecific and 20% to 50% of patients with sarcoidosis are asymptomatic. The diagnosis is pursued after an abnormality is detected on a chest X-ray film obtained for an unrelated reason.[118] Dry cough and dyspnea are the most common clinical symptoms attributable to the intrathoracic manifestations of sarcoidosis. Chest pain may be present and is often vague and nonspecific; however, it may be severe and suggestive of cardiac pain.[119,120] Chest pain may also indicate an unusual complication such as pleuritis or pneumothorax, or possibly pulmonary embolism, as antiphospholipid antibody syndrome has been associated with sarcoidosis on rare occasions.[118] Wheezing suggests airway obstruction secondary to endobronchial granulomatous disease, extrinsic compression by mediastinal adenopathy, or bronchial distortion secondary to fibrotic lung disease. Wheezing may also be contributed by bronchial hyper-reactivity.[121,122] A productive cough may indicate traction bronchiectasis due to parenchymal fibrosis, hemoptysis suggests bronchiectasis or the presence of an aspergilloma.

Radiographic Findings

The chest radiograph is abnormal in more than 90% of sarcoidosis patients and diagnosis of sarcoidosis is first suspected on routine chest roentgenography in most patients. Bilateral hilar lymphadenopathy is noted in 50% to 85% of cases. The presence of symmetrical bihilar and mediastinal lymphadenopathy is almost characteristic in sarcoidosis. Lymph nodes are generally big and sharply defined, with a clear line of translucency between the mediastinal shadow and the nodes—classically described as “potato nodes.” Unilateral hilar adenopathy is rare and pulmonary parenchymal infiltrates are seen in 25% to 60% of patients. Typically the infiltrates are bilateral and symmetrical and are most common in the upper and mid lung fields.[123,124]

A chest radiographic staging system[125] for sarcoidosis is shown in Table 96.3 and Figs 96.4A to D.

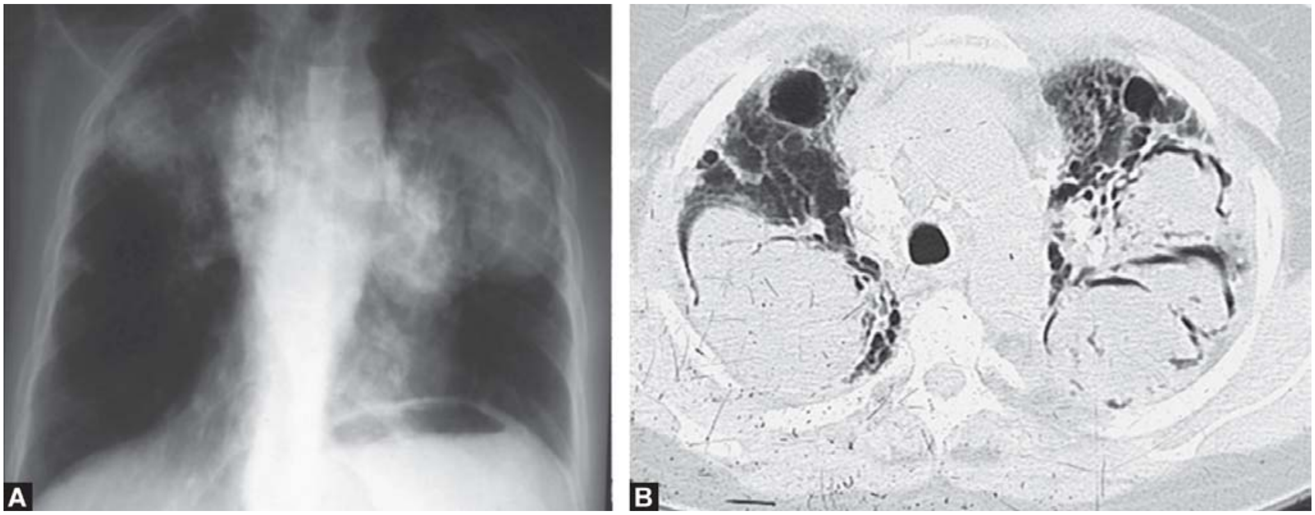


Figs 96.4A to D: Typical chest radiographs in sarcoidosis. Panel A: Stage 1, showing bilateral hilar and paratracheal lymphadenopathy; Panel B: Stage 2, Hilar and paratracheal lymphadenopathy with pulmonary infiltrates; Panel C: Stage 3, Pulmonary infiltrates with no lymphadenopathy; Panel D: Stage 4, Pulmonary fibrosis with architectural distortion

Higher radiographic stages have been associated with poorer prognosis.[126,127] However, there is significant overlap between the groups and prognosticating individual patients based on radiographic stage alone are unreliable. Nevertheless, the patients with stage IV chest radiographs rarely undergo spontaneous remission. In Stage IV pulmonary sarcoidosis the lung parenchyma is destroyed with upward traction of the hila, lung distortion, upper lobe volume loss, fibrocystic disease, honeycombed cysts and reduced lung volumes. Large bullae may house one or more fungus balls or an

TABLE 96.3: Chest radiographic staging of sarcoidosis

Stages	*Features*
Stage 0	No involvement
Stage 1	Bilateral hilar adenopathy, often with right paratracheal adenopathy
Stage 2	Stage 1 + Pulmonary infiltrates
Stage 3	Pulmonary infiltrates without adenopathy as described in stage 1
Stage 4	Advanced parenchymal lung disease, including fibrosis, honeycomb lung, traction bronchiectasis, cysts, bullae, and emphysema, with or without adenopathy



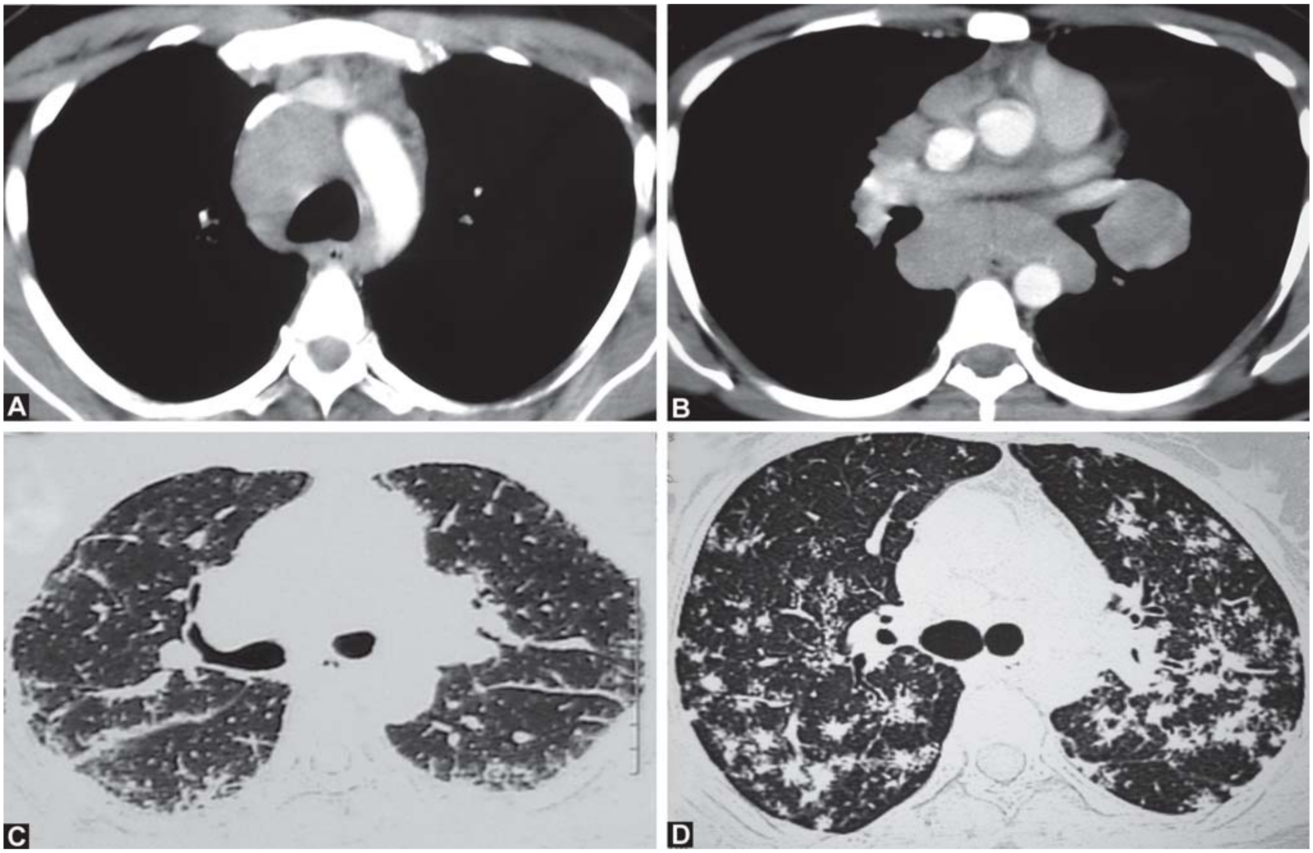
Figs 96.5A and B: Bilateral upper lobe aspergillomas in sarcoidosis

aspergilloma (Figs 96.5A and B).[128] Cystic or traction bronchiectasis may develop.

Chest computed tomography (CT) though reveals more disease than the chest radiograph, there is no evidence that CT has a superior prognostic or therapeutic value compared with the chest radiograph in the management of pulmonary sarcoidosis. Currently chest CT is not a recommended standard test for sarcoidosis.[3] Computed tomography scans can have several typical and atypical findings.[123,129] Typically the high-resolution CT reveals nodules along the bronchovascular bundle and subpleural regions.[129,130] Coalescence of these granulomata may result in mass-like lesions with or without air bronchograms. Occasionally these conglomerate nodules are surrounded by small nodules giving an appearance that is known as “sarcoid galaxy sign” (Figs 96.6A to D).[131] More extensive lymphadenopathy is also more commonly seen on CT than the typical hilar and paratracheal nodes seen on chest radiograph. Ground glass attenuation, often thought to represent acute alveolitis, has been shown to represent granulomatous inflammation.[132] “Reverse halo” sign typically described with invasive fungal infections has also been reported in sarcoidosis recently.[133] Typical findings, if found may be useful in suggesting sarcoidosis in the evaluation of an undiagnosed interstitial lung disease.

Functional Abnormalities

Pulmonary function abnormalities can be seen in 20% to 40% sarcoidosis patients with a normal lung parenchyma on a chest radiograph and 50% to 70% of cases when the lung parenchyma is visibly abnormal.[134] These include abnormalities in the vital capacity, diffusing capacity, PaO_2 at rest, PaO_2 with exercise and lung compliance.[134] Lung function testing with the help of spirometry is a simple procedure to grade the disease extent. Lung function changes have been shown to bear a clinical correlation with overall histopathological scoring assessed from the granuloma load and interstitial inflammation.[113,135] Lung functions have also been correlated with the radiological extent of the parenchymal disease; patients with stage IV fibrocystic disease have the most severe pulmonary function impairment.[136] Being an interstitial lung disease, a restrictive ventilatory defect is to be expected. However, as mentioned previously, endobronchial involvement may result in airflow obstruction being the major abnormality on pulmonary function testing. In addition, airflow obstruction is common in chronic sarcoidosis, possibly the result of airway distortion from lung fibrosis. Granulomatous involvement of skeletal muscle occurs in 50% to 80% of patients with sarcoidosis and this may affect respiratory muscle function in sarcoidosis.[137] Measurements of respiratory pressures has been used as an index of functional work capacity and reflection of activities of daily living.[138] Pulmonary hypertension is a serious complication of pulmonary sarcoidosis and is a risk factor for death.[139] Pulmonary hypertension may occur via a number of mechanisms, including parenchymal fibrosis distorting the pulmonary vasculature (pulmonary arterial or venous system), granulomatous inflammation of the pulmonary vasculature, hypoxic pulmonary arterial vasoconstriction from parenchymal



Figs 96.6A to D: Some representative CT pictures in sarcoidosis. Panel A: Paratracheal lymphadenopathy, Panel B: Hilar and subcarinal lymphadenopathy. Lymph nodes are typically homogenous with no central necrosis; Panel C: Pulmonary nodular infiltrates with typical lymphangitic distribution; Panel D: "Sarcoid Galaxy" sign: large conglomerate nodules surrounded by small nodules

pulmonary disease, and from elevated left ventricular end diastolic pressure because of cardiac involvement with sarcoidosis.[139,140]

Other Intrathoracic Manifestations

Pleural involvement (including effusions and thickening) may be detected in 5% to 10% of patients with sarcoidosis (Fig. 96.7). Pleural effusions are estimated to occur in 1 to 3% of patients with sarcoidosis and are more likely to be seen in patients with stage 2 and 3 disease.[141,142] These effusions are more often right-sided (45% vs 33% left- sided and 22% bilateral), have relatively few cells (mostly lymphocytes), and are often discordant with respect to Light's criteria in that the effusions are characteristically exudative by protein criteria and transudative by Lactate Dehydrogenase (LDH) criteria.[141] Chylothorax, hemothorax and pneumothorax have also been reported rarely.[143-145] Contrary to the infrequency with which the above pleural diseases affect patients with sarcoidosis, pleural thickening on CT scan may be seen in up to the one-third of patients, the clinical significance of which remains unclear.[146]

Hemoptysis, at times serious, can occur due to a variety of reasons such as formation of a fungal ball (Aspergilloma) in a pre-existing cyst or cavity, bronchiectasis (most often due to traction in association with parenchymal fibrosis) and necrotizing sarcoid angiitis.[147,148] Rare consequences of mediastinal lymphadenopathy include superior vena cava syndrome,[149] mediastinal lymph node calcification and mediastinal fibrosis.[150] Rarely giant bullae resulting from sarcoidosis may lead to the "vanishing lung syndrome."[151] Several of these rare manifestations have also been documented from India.[152]

Extrapulmonary Involvement

Involvement of extrapulmonary sites is fairly common and often of major clinical importance. When carefully looked for, one or more of the extrapulmonary organs were involved in about two-thirds of patients from

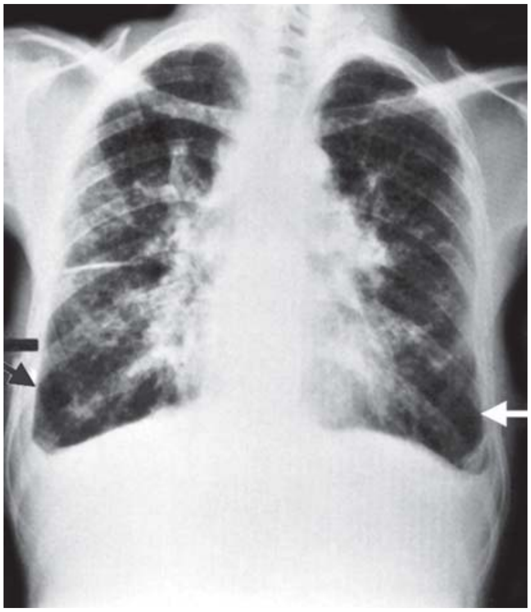
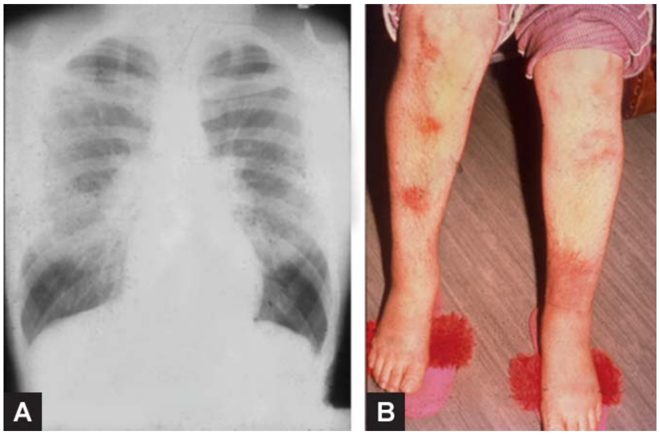


Fig. 96.7: Bilateral pleural thickening in sarcoidosis

Chandigarh, India.[21] Constitutional symptoms of fever, night sweats, weight loss, fatigue, myalgia and arthralgia occur very frequently with extrathoracic sarcoidosis. Fatigue, in particular, is an important symptom.[153] Although any organ can be involved, skin and eyes are most common, whereas cardiac and neurological involvements are most serious. Major extrapulmonary manifestations of sarcoidosis are outlined below, detailed descriptions can be found elsewhere.[154,155]

Skin

Erythema nodosum (EN), subcutaneous nodules and plaques, lupus pernio and maculopapular eruptions are the important manifestations of sarcoidosis.[156] Skin lesions are divided into two categories: Specific and nonspecific. Specific lesions demonstrate granulomatous inflammation on biopsy. Nonspecific skin lesions are inflammatory skin reactions with no evidence of granulomatous inflammation. Erythema nodosum is the most common nonspecific skin lesion of sarcoidosis. It presents as tender nodules on the extremities. Erythema nodosum with hilar lymphadenopathy (Löfgren's syndrome, also often with polyarthropathy and nongranulomatous uveitis) is a typical subset of sarcoidosis with particular characteristics (Figs 96.8A and B). Known to carry a very favorable prognosis for resolution, it has been described with a spring seasonal peak in both the Northern and Southern Hemispheres.[141,142] Specific skin lesions are usually asymptomatic. Disfigurement is the most common complaint. The most common lesions are firm, 2 to 5 mm papules that often have a translucent red-brown or yellow-brown appearance. Lupus pernio is the most severe form of dermatological manifestation that usually affects the nose, cheeks, lips and ears in the form of indolent, red-purple or violaceous skin lesions. These lesions can erode into cartilage and bone, especially around the nose.[157-159] Lupus pernio is associated with the poor prognosis of sarcoidosis and is associated with more severe pulmonary disease.[160,161]



Figs 96.8A and B: Löfgren syndrome: bilateral hilar adenopathy + erythema nodosum

Eye

Eyes are involved in sarcoidosis in up to 25% patients and it can affect any part of the eye and may be the major manifestation of the disease.[162,163] Japanese patients have ocular involvement in more than 70% patients.[164] A careful eye check-up should be a part of routine clinical workup of sarcoidosis. Uveitis is the most common ocular manifestation of sarcoidosis.[165] Depending upon the site of involvement the symptoms vary from blurred vision, red eye, painful eye or photophobia in anterior uveitis to vision loss in posterior uveitis. Retinal perivasculitis, retinal scarring and glaucoma can also occur. One-third of the patients with anterior uveitis have no symptoms (a "quiet eye").[163,166] Besides uveitis, involvement of lachrymal glands is also common, which may occasionally cause dry eyes. Optic neuropathy is rare, but can result in rapid, permanent vision loss.[163,166,167] Funduscopic exam shows papillitis, papilledema and neovascularization with optic atrophy ultimately. This condition is an ophthalmologic emergency and mandates immediate systemic therapy.

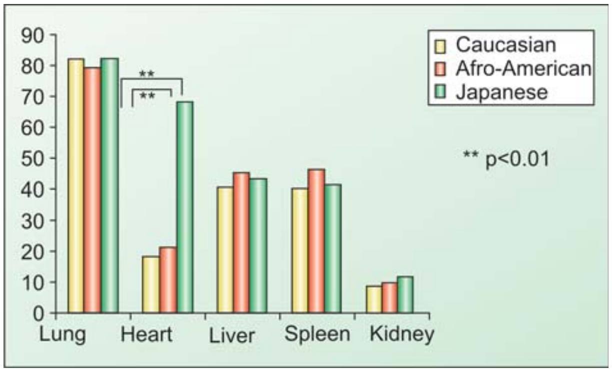
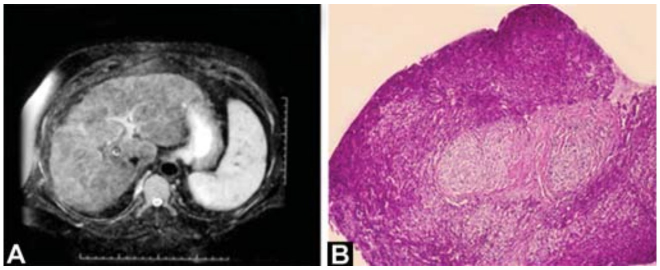


Fig. 96.9: Frequency of organ involvement in sarcoidosis. Cardiac involvement is much higher in Japanese patients than other groups

Cardiac and Neurologic

Rare cardiac or neurologic sarcoidosis are important to recognize as they may be life-threatening. Though clinically detectable in only 5% of sarcoidosis patients, cardiac involvement may be picked up in 25% patients at autopsy.[168,169] Japanese show a markedly higher rate of cardiac involvement compared to the Caucasians and Afro-Americans (Fig. 96.9). Cardiac sarcoidosis may cause left ventricular dysfunction and cardiac arrhythmias that can result in sudden death.[170-173] Endomyocardial biopsy is the gold standard diagnostic test, which is very specific, however it has a poor sensitivity of less than 25% because of sampling error.[174] For the noninvasive diagnosis of cardiac involvement in sarcoidosis various investigations such as echocardiography, thallium scanning, gallium scanning, Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) scanning can be used coupled with a typical clinical presentation.[173, 175-181]

Sarcoidosis can mimic diverse neurological conditions. Diagnosis of neurosarcoidosis is based on a confirmation of systemic sarcoidosis since pathologic confirmation is rarely available from the Central Nervous System (CNS). Central nervous system infection and malignancy should be reasonably excluded before making a diagnosis of CNS sarcoidosis.[182] Overall CNS involvement may be seen in about 10% patients of sarcoidosis.[183] The most common manifestation of neurosarcoidosis is seventh cranial nerve palsy, and it may precede the diagnosis of the disease. Sarcoidosis may affect any part of the nervous system causing a cranial nerve palsy, mononeuropathy or polyneuropathy, aseptic meningitis, seizures, mass lesions in the brain or spinal cord, and encephalopathy.[184,185] Rarely it may also mimic multiple sclerosis.[186]

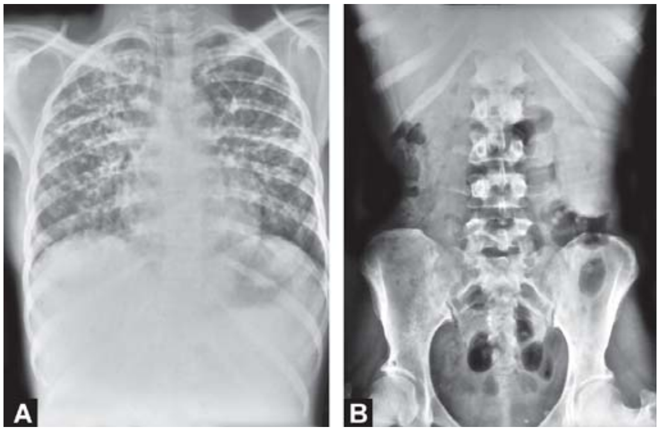


Figs 96.10A and B: Hepatic sarcoidosis

Other Extrapulmonary Organ Involvement

Sarcoidosis may affect gastrointestinal, Ear, Nose and Throat (ENT), hematological, endocrinal, genitourinary and musculoskeletal systems.[187] Almost all types of organs involvement have been described from India and the other developing countries as well. Asymptomatic histological involvement of liver may be seen in 50% to 65% patients. Abnormalities in liver function tests are seen in less than 35%, the most common abnormality being an elevation in the serum alkaline phosphatase (Figs 96.10A and B).[188-192] Similarly spleen may also be involved with minimal or no symptoms. Large splenomegaly with hypersplenism is seen more commonly in Afro-American patients (Figs 96.11A and B).[193-196] Sarcoidosis causes clinically apparent peripheral lymphadenopathy in more than 10% of patients.[197] Sarcoidosis of the upper respiratory tract is underappreciated. It may occur in the nasopharynx, hypopharynx, larynx, sinuses or rarely vocal cord palsy.[198,199]

Typical bone lesions of sarcoidosis are small cysts or cortical defects in the small bones of the hands or feet, which occur occasionally (about 4% in one series) and



Figs 96.11A and B: A patient with sarcoidosis and massive splenomegaly. Enlarged spleen and hypersplenism is common in African-American patients

are possibly more frequent in females and in patients with lupus pernio.[200] Joints if involved acutely, as is often seen in patients with Löfgren's syndrome carry a good prognosis.[201] Chronic sarcoid arthritis is rare but can progress to cause joint deformities.[202,203]

Abnormalities of Calcium Metabolism

On any general medical ward, there are three common causes of hypercalcemia: hyperparathyroidism, lymphoma or malignancy, and sarcoidosis. In sarcoidosis hypercalcemia has been reported to occur in 2% to 63% of patients; hypercalciuria is three times more common than hypercalcemia.[204] Therefore serum and urine calcium levels should be measured regularly over the whole course of the illness. The mechanism of hypercalcemia in sarcoidosis is due to excess extrarenal calcitriol production.[205] The alveolar macrophages present within the granulomas contain the enzyme 1-α hydroxylase, which converts precursor vitamin D to active calcitriol.[206] Normally high levels of calcitriol cause feedback inhibition of 1-α hydroxylase; calcitriol also causes up regulation of 25 (OH)D3 24 hydroxylase, the enzyme which converts 25 (OH)D3 to 24, 25 (OH)2D3, the metabolically inactive form of vitamin D. Both the feedback mechanisms are lost in alveolar macrophages which lead to the continuous production of calcitriol.[207] Another recently described mechanism is the excess production of parathyroid hormone related peptide (PTHrP), which like parathyroid hormone causes upregulation of 1-α hydroxylase.[208] Unlike parathyroid hormone, PTHrp is not regulated by calcium but by interleukin-2 and tumor necrosis factor α both of which are increased in sarcoidosis.[209] It is possible that these cytokines released by the alveolar macrophages act in a paracrine fashion to up regulate PTHrP production by the macrophages.[207] Hypercalciuria or hypercalcemia can lead to nephrolithiasis and renal failure. Rarely hypercalcemia may cause acute pancreatitis.[210]

DIAGNOSIS

The diagnosis of sarcoidosis rests on a triad of clinical, radiologic and histological criteria. If the clinical and radiologic picture is typical and tuberculosis is definitely excluded then sarcoidosis can be presumptuously diagnosed. However, in the absence of positive biopsy diagnosis of sarcoidosis will remain in doubt. Most often, the chest radiograph showing hilar and mediastinal lymphadenopathy raises the suspicion of sarcoidosis. But, there are many causes of hilar and mediastinal lymphadenopathy (Table 96.4). Diagnosis in the presence of atypical radiological findings or Interstitial Lung Disease (ILD) is more difficult. While the presence of hilar adenopathy in a patient with ILD is a clue to the diagnosis of sarcoidosis (stage II), it is difficult in the presence of only the interstitial infiltrates (stage III) or pulmonary fibrosis (stage IV). High Resolution CT (HRCT) scan is helpful to delineate interstitial involvement, but the etiological diagnosis often needs histological investigations. The algorithm meant for diagnosis of ILD in the developing countries can be followed in all such patients.[211]

TABLE 96.4: Common pathological differential diagnosis of sarcoidosis

*Mycobacterial**
- Tuberculosis
- Atypical Mycobacteria

*Fungal Infections**
- Cryptococcocosis
- Aspergillosis
- Histoplasmosis
- Coccidioidomycosis
- Blastomycosis
- Pneumocystis

Bacterial
- Mycoplasma
- Brucella

Hypersenstivity Pneumonias

*Drug Reactions**

Pneumoconiosis
- Beryllium (chronic beryllium disease)*
- Titanium
- Aluminum

Malignancy
- Lymphoma*

Others
- Wegener's granulomatosis (sarcoid-type granulomas are rare)
- Chronic interstitial pneumonia (UIP, LIP)
- Necrotizing sarcoid granulomatosis (NSG)
- Granulomatous lesions of unknown significance (GLUS syndrome)

Adapted from reference 3; Conditions marked with (*) can also present with hilar and mediastinal lymphadenopathy.

Histological Diagnosis

Biopsy is indicated for all patients presumed to have sarcoidosis, except those with Löfgren's syndrome.

Because of the varied clinical presentations of sarcoidosis, one should select the least invasive biopsy site.[212] Although the biopsy of peripheral lymph nodes or other organs had been practiced since long, the outcome had never been universally useful. This was because the other organs are not involved as frequently as the lungs. Moreover some of the internal organs are difficult to approach and take biopsy from. A lung biopsy obtained with the help of fiberoptic bronchoscopy has made a major difference in the diagnosis of sarcoidosis in India.[213] Transbronchial lung biopsy is positive in over 80% of patients of sarcoidosis.[17, 214, 215] Similar diagnostic yield is obtained in almost all stages of sarcoidosis.

Combining endobronchial with transbronchial biopsy improves the diagnostic yield by about 10%.[216,217] Endobronchial abnormalities are more commonly seen in patients with respiratory symptoms.[217] Labial biopsy has also been shown to have a high discriminatory value in the differentiation of sarcoidosis from tuberculosis.[218] Mediastinal lymph node biopsy is often confirmatory.[219] Transbronchial Needle Aspiration (TBNA), a widely used procedure, has a diagnostic sensitivity of almost 100%.[220-222] Combiming TBNA with Endobronchial Ultrasound (EBUS) increases the sensitivity with or without onsite cytologists.[223-229]

The characteristic findings on biopsy is the presence of compact noncaseating epithelioid cell granulomas, however, an alternative diagnosis has to be excluded. A general differential diagnosis of granulomatous inflammation is given in Table 96.4.

Tuberculin Skin Test (TST)

The tuberculin sensitivity is depressed in sarcoidosis even in the background of high prevalence of tuberculosis and a cut-off of 10 mm reaction to 5TU tuberculin test has virtually 100% sensitivity for sarcoidosis, however, it is not specific.[112] The problem is further confounded by the coexistence of two diseases.[230] A negative tuberculin test is heavily relied upon for diagnosis of sarcoidosis. It is cheap and simple to perform. A positive TST in a patient suspected to suffer from sarcoidosis should alert the treating physician for a thorough work-up for tuberculosis.

Miscellaneous Investigations

Bronchoalveolar lavage: Bronchoalveolar lavage has also been frequently used. Studies have shown a very high positive predictive value for the diagnosis of sarcoidosis with an elevated ratio of CD4/CD8 in BAL fluid. However, the samples require >15% lymphocytes on cell count to be useful.[231] A CD4:CD8 ratio greater than 3.5 shows a high specificity of 93% to 96% for sarcoidosis, but the sensitivity is low (53% to 59%).[232]

Kveim test: The Kveim–Siltzbach test is performed using intradermal injections of human sarcoid tissue. Four weeks later the papule that forms at the site of the injection is biopsied. Kveim's test had been reported as a reliable test for the diagnosis of sarcoidosis with positivity of even up to 98%.[11,233] But a validated good quality antigen is not available.[234] Moreover, it requires four to six weeks following intradermal injection of the antigen before a positive reaction is obtained. This generally is a long period to wait, especially in symptomatic or hospitalized patients. Further, the frequency of positivity depends upon the disease-duration. There is also a risk of transmission of the etiological agent by the Kveim test. Mechanism of the Kveim test vis a vis sarcoidosis is still not clearly understood.[235] Its clinical application is limited.

Serum angiotensin converting enzyme (SACE): SACE estimation was introduced as a promising test of diagnosis in the mid-seventies.[15] A rise in SACE activity in active sarcoidosis has been shown in a few reports from this country as well.[236,237] Angiotensin converting enzyme is produced by the epithelioid cells of sarcoid granulomas. As other disorders such as diabetes mellitus, cirrhosis, acute hepatitis, chronic renal disease, silicosis, Gaucher's disease, leprosy, asbestosis and berylliosis may demonstrate elevated SACE levels, the test is neither sensitive nor specific enough to be used as a diagnostic tool.[223,224] Overall clinical sensitivity for elevated SACE levels is about 55% with a specificity of 90%.[225] There is also no apparent association between serum ACE level and radiographic staging.[223] In spite of the lack of specificity as a test for sarcoidosis, SACE provides a good monitor of disease activity. The presence of inhibitors may interfere with SACE levels unless sensitive radioimmunoassay techniques are used for assessment.[226] Some studies have suggested that SACE levels may vary with genetic factors and the use of genotype corrected ACE levels may make it a more useful diagnostic tool.[227,228]

Other tests: Gallium scanning demonstrates inflammation throughout the body. Its use has largely fallen out of favor due to the advances in bronchoscopic techniques. Uptake in the hilar lymph nodes and right paratracheal nodes results in the "lambda sign," whereas lacrimal and salivary gland uptake results in the "panda sign."[229] Fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning is emerging as a potentially useful study in the diagnosis of sarcoidosis.[238] Fluorodeoxyglucose uptake is found in up to two-thirds of patients with stage 2 and 3 disease, whereas negative uptake is associated with stage 0, 1 and 4 disease. In addition, FDG-PET has been demonstrated to assist in detecting clinically silent sites, which may be biopsied for definitive diagnosis. F-methyltyrosine-PET (FMT-PET) uses an amino acid that is preferentially taken up and expressed on the surface of tumor cells, and is negative in patients with sarcoidosis.[239]

Assessment of Activity

Assessing activity and/or severity of disease is sarcoidosis is a tough task as no single variable in isolation is accurate.[240] Several laboratory and cell biological markers in serum [e.g. ACE, lysozyme, neopterin, soluble IL-2-receptor, Soluble Intracellular Adhesion Molecule (ICAM)-1, IFN-γ] or in BAL fluid (e.g. high lymphocytes, activation marker expression on T-cells, CD4/C8 ratio, macrophage Tumor Necrosis Factor-Alpha (TNF-α) release, collagenase, procollagen-III-peptide, vitronectin, fibronectin, hyaluronan) have been studied as potential indices of active disease. [241-243] However, nothing can be recommended for routine assessment, perhaps with the exception of serum ACE.[244] The magnitude of the initial ACE levels has no prognostic significance and the initial levels are no different between patients who deteriorate and those who improve. After the initiation of treatment, serum ACE levels can be helpful in monitoring the treatment effect, since increased serum ACE activity will usually be reduced within a few weeks of the start of corticosteroid treatment. At present, still the best way to assess the activity of sarcoidosis is through clinical activity. This is based on the mode of onset, the worsening or persistence of symptoms, and the presence of skin lesions, in combination with changes in chest radiography and lung function tests, with or without treatment. Pulmonary function studies have shown rough correlation with histological severity and may be used as a surrogate.[115]

THE TUBERCULOSIS ENIGMA

Relationship between sarcoidosis and tuberculosis remains a riddle. Caesar Boeck, a Norwegian dermatologist, who probably first time described the histological appearance of sarcoidosis as "multiple benign sarcoid of the skin," believed that the histological features resembled sarcoma. Nevertheless, the remarkable similarity of sarcoidosis to tuberculosis in both the clinical and histological features was soon noticed. A possible link between the two conditions has been debated ever since.[62] The possible relationship has implications in three areas: i. pathogenesis, ii. diagnosis and iii. treatment.

Almost a quarter of a century ago, in a cooperative study of sarcoidosis in several countries of Asia, the authors commented that the chronological increase in sarcoidosis was related to the decrease in infectious diseases represented by tuberculosis.[245] This evidence on tuberculosis relationship of sarcoidosis is weak and needs to be reanalyzed. Sarcoidosis has increased in India; this has happened in spite of the continued high prevalence of tuberculosis.

Sarcoidosis and tuberculosis mimic each other not only in clinicoradiological presentations, but also in the results of several investigations, including histopathology. In such situations the differential diagnosis may become impossible, particularly when the two diseases can rarely coexist.[230] Hilar lymphadenopathy, the commonest clinical presentation of sarcoidosis is also a manifestation of tuberculosis.[246] However, the nodes in sarcoidosis only rarely show a central hypodensity on CT scan, which is frequently observed finding in tuberculosis.[129] Fibrosis, especially in the apical regions, can occur in both conditions although cavitation is rarer in sarcoidosis.[247] Similarly, miliary distribution of lesions, characteristically described in tuberculosis, can also occur in sarcoidosis.[248, 249] Miliary disease in particular poses a great difficulty in differential diagnosis particularly in India where it is considered a sine qua non for tuberculosis.[250] In fact, most patients of miliary sarcoidosis, described from India, had received antitubercular therapy before the diagnosis of sarcoidosis was established.[248,249] A report from Greece describes a patient of miliary sarcoidosis one year after successful treatment for miliary tuberculosis.[251]

The tuberculin sensitivity is depressed in sarcoidosis even in the background of high prevalence of tuberculosis and a cut-off of 10 mm reaction to 5TU tuberculin test has virtually 100% sensitivity for sarcoidosis.[110] A negative tuberculin test excludes tuberculosis except in seriously sick or otherwise immunosuppressed individuals. Diagnosis of tuberculosis in tuberculin negative individuals is required to be supported by strong bacteriological evidence.[252] A positive tuberculin test in sarcoidosis should also be looked with high suspicion as discussed above. In India, tuberculin test is positive in about 30% to 50% of general population and in 64% to 85% in the age group of 25–45 years.[253,254] A higher cut-off point of tuberculin test is therefore suggested to diagnose tuberculosis.[255]

Interferon-Gamma Release Assays (IGRAs) have a higher sensitivity and specificity for detecting Mycobacterium Tuberculosis (MTB) infection than the conventional TST, as they utilize antigens specific for MTB complex.[256] Clinicians in high prevalence countries erroneously make a diagnosis of tuberculosis based on a positive IGRA test. In clinical practice we have observed that patients with sarcoidosis have been misdiagnosed as TB based on a positive IGRA. There are few conflicting reports of IGRAs in sarcoidosis.[257] We have recently shown that IGRA (Quantiferon in tube^{r}) being more sensitive test than TST continues to remain positive in many patients with sarcoidosis and in high prevalence countries it should not be a deterrent for making a diagnosis of sarcoidosis, since it merely represents an underlying tubercular infection.[258]

Both tuberculosis and sarcoidosis can present with similar constitutional symptoms of fever, malaise, generalized aches, myalgias, easy fatigability and tiredness. Anorexia and weight loss may also occur. Respiratory symptoms of cough and breathlessness are common in both conditions. Chest tightness and wheezing may also occur. Expectoration and/or hemoptysis are distinctly more frequent in fibrocavitary tuberculosis, but can be occasionally present in fibrocystic sarcoidosis. In general, patients with untreated tuberculosis have more signs and symptoms compared to sarcoidosis. But the severity and magnitude may not always help in the differential diagnosis.

Although non-necrotizing granulomas are the usual findings in sarcoidosis, necrosis can occur. Prior to the widespread use of transbronchial biopsy necrosis was reported in up to 30% of large biopsy specimens (open lung, lymph node). The incidence of necrosis is far lower in small specimens such as transbronchial biopsies because of the small number of granulomas usually sampled. Compared with the "caseous" necrosis seen in TB granulomas, the necrosis in the granulomas of sarcoidosis is most often focal, very small in size and involves very few of the granulomas unrecognizable to the naked eye. The foci of necrosis are acidophilic with a fibrinoid, granular appearance and usually located within the centers of granulomas. Rarely, biopsy material from patients with well documented sarcoidosis will exhibit extensive necrosis.[103, 259]

The site and type of organ involvement may help in making a distinction. For example, lacrimal and parotid glands and myocardium are rarely involved in tuberculosis. Subtle differences which may help in differential diagnosis from tuberculosis are summarized in Table 96.5.

Finally, there are treatment issues to be considered in the relationship of sarcoidosis and tuberculosis. Reactivation of tuberculosis after corticosteroid treatment is instituted for sarcoidosis is a genuine concern, given the high prevalence of latent infection in our country.[261] If indeed tuberculosis is a causal factor in sarcoidosis, then the hypothesis can be further reinforced, if Antitubercular Therapy (ATT) is useful in the treatment of sarcoidosis. Very few trials have been conducted in the past, but the results of these trials have been discouraging. These trials were generally small studies and limited by time bias and used older regimens based on isoniazid, aminosalicylic acid and streptomycin.[262,263] In our experience, nearly one-third of patients who are finally diagnosed to have sarcoidosis, have received ATT for the variable length of time, but its impact of final outcome of sarcoidosis has not been studied. Role of antimicrobial therapy in sarcoidosis has recently been reviewed and it gives us a definite thought for the future research.[264]

TREATMENT

There are even more challenges in treating sarcoidosis than in diagnosing it. It is especially so in the developing countries, where the availability of medical expertise is limited, the referral system is insufficient and facilities to monitor efficacy and complications of treatment are inadequate. This is very true with reference to corticosteroid-treated patients who could be harboring mycobacteria in quiescent lesions.

When to Treat?[265-267]

Pulmonary Sarcoidosis

- Asymptomatic patient with bilateral hilar lymphadenopathy (Stage I) with or without erythema nodosum but without extrapulmonary involvement should be left untreated.[268,269]
- Patients with fever and joint pains respond to nonsteroidal anti-inflammatory agents. Occasionally, a short-term course of prednisone 15–20 mg/day may be needed to control symptoms that do not respond to anti-inflammatory drugs. Symptoms of cough and dyspnea may be associated with airway obstruction—even in this early stage—and should be treated with inhaled corticosteroids.
- Patients with bilateral hilar adenopathy and infiltration (Stage II) and symptoms (cough, dyspnea, chest pain and effort intolerance) should be treated. Spirometry, diffusing capacity, a chest radiograph

TABLE 96.5: Differentiating sarcoidosis form tuberculosis in high TB prevalence countries, some useful "INDICATORS"*

Indicator	*Sarcoidosis*	*Tuberculosis*
History of close contact with patient having tuberculosis infection	Not present	May be present
Constitutional symptoms	Asymptomatic or with mild fever, anorexia and loss of weight: Particularly with advanced radiological abnormalities "Patients walk-in"	More symptomatic and ill: "Patients are brought–-in"
Cough	Mainly dry, hemoptysis is rare	Usually productive, hemoptysis is common
Intrathoracic lymph node involvement	Typically symmetrical bi-hilar and paratcheal, smooth, discrete, and solid looking nodes	Asymmetrical, large, may be conglomerate, usually with central areas of hypodensity
Extrathoracic lymph node involvement	Seen in about 10% patients only	Cervical and axillary lymph node involvement is common
Lacrimal, parotid glands and myocardial involvement	May be seen	Rarely, if ever
Pleural, peritoneal, meningeal and adrenal involvement	Rarely, if ever (Fig. 96.12)	May be seen
Radiology: Necrotizing pneumonia, cavitation and pleural involvement with effusion	Rare	Common
HRCT scan of lungs (In case of diffuse involvement): Fig. 96.13	Micro and macro nodules which have characteristic distribution in peribronchovascular region, subpleural interstitium and interlobular septa	Micronodules, randomly distributed with tree-in-bud appearance
Clinico-radiological dissociation, i.e. patient relatively asymptomatic despite extensive pulmonary involvement	Often seen	Rare
Tuberculin test	*Nearly always negative*	*Nearly always positive*
Increased SACE level.	More common	Less common
Increased serum calcium or hypercalciuria	May be seen	Not seen
Sputum - Positive for *M. tuberculosis* on smear or culture	False-positive acid fast bacilli or rarely coexisting TB with sarcoidosis. Patient should never receive glucocorticoids alone	Confirmatory for TB
PCR of biopsy tissues is positive for *M. tuberculosis* DNA	Quantitative tests can be positive in up to half of the patients in high TB prevalence countries. Qualitative test show low copy numbers.[260]	Should be positive with high copy numbers if quantitative tests are done
Biopsy of involved site shows showing caseation necrosis (Figs 96.13A to D)	Noncaseating, compact granulomas, sparse lymphocytic cuffing around granuloma ('naked') with inclusion bodies at times	Caseating necrosis, ill formed granuloma with intense inflammatory reaction and may be positive for acid fast bacilli
No expected response to anti-tubercular therapy	Very common, however spontaneous resolution in sarcoidosis is known	Very rare, only in case of primary multidrug resistance
Dramatic clinical-radiological response to steroids	Usual	No response or may worsen

*These indicators are only based on common clinical observations with unknown sensitivity and specificity for most of them.

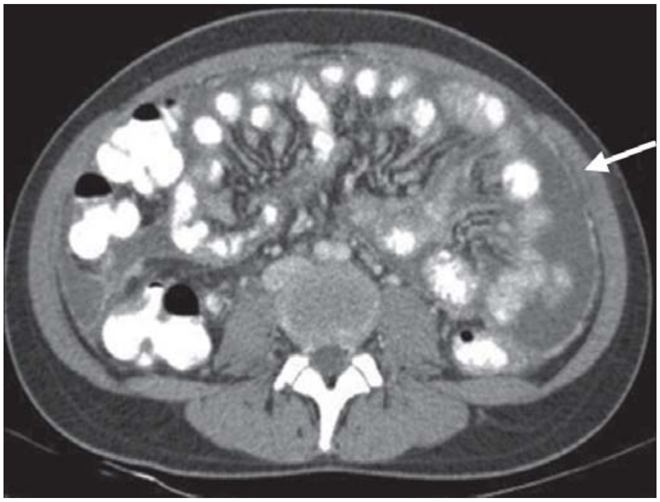
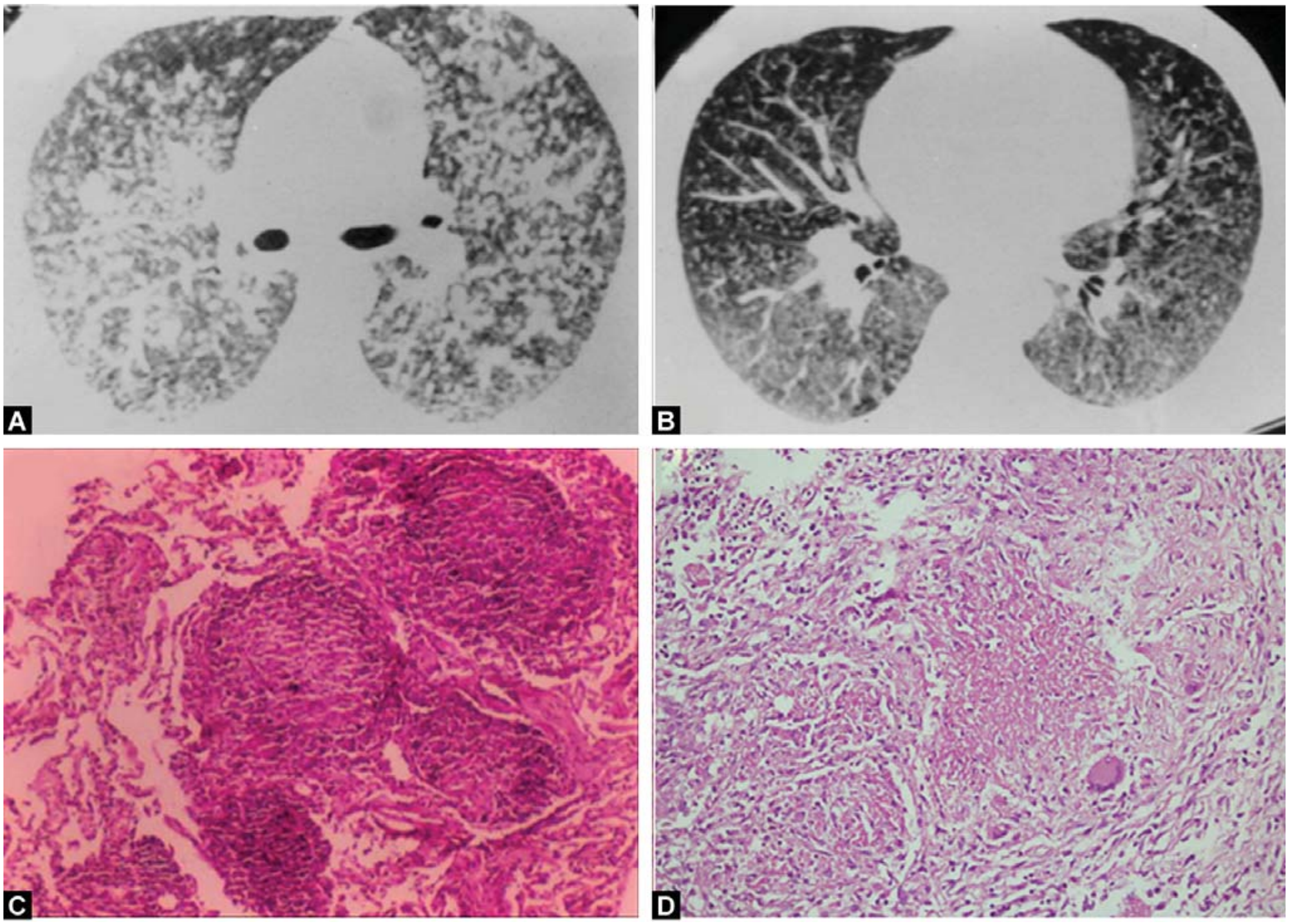


Fig. 96.12: Peritoneal sarcoidosis is rare and it resembles tuberculous peritonitis

and serum ACE should be used to monitor the course of the disease.

- Patients with Stage II who are asymptomatic and have only mild lung function impairment can be followed without any specific treatment. However, if the deterioration of lung function should occur over a period of three to six months, the treatment should be instituted.
- Patients with Stage II who are asymptomatic with severe lung function impairment should be treated. Serial lung function measurement should be performed to establish the maximum response prior to tapering the drug to the maintenance dose.
- Patients with Stage III disease with diffuse pulmonary infiltration usually have symptoms along with lung function abnormalities and almost always need treatment. Asymptomatic stage III patients with



Figs 96.13A to D: Miliary sarcoidosis (panel A, C) versus miliary tuberculosis (panel B, D). On CT, the nodules in sarcoidosis are larger than tuberculosis with typical lymphangitic distribution. On histopathology, the granulomas in sarcoidosis are typically compact, with no necrosis and minimal lymphocytic cuffing (panel C) compared to the large areas of necrosis and intense lymphomononuclear cell infiltrates in tuberculosis (panel D)

progressive pulmonary function impairment may respond to corticosteroids because of the presence of reversible alveolitis intermingled with diffuse fibrosis.

- Stage IV diseases with extensive fibrosis and bullae formation respond poorly or not at all to corticosteroids and immunosuppressive therapy.[270] It should however be emphasized that some stage III and IV patients with irreversible fibrosis may have coexisting active alveolitis and the treatment should be strongly considered in order to control symptoms and functional impairment.[263] Some of the patients with stage IV disease are ideal candidates for lung transplantation. Bronchiectasis, hemoptysis and aspergilloma are treated conservatively with appropriate antibacterial and antifungal agents. An occasional patient with aspergilloma causing hemoptysis can benefit from intracavitary instillation of antifungal agents or arterial embolization. Resection may be necessary for severe hemoptysis if lung function is not severely impaired.

Extrapulmonary Sarcoidosis

Indications for the treatment of extrapulmonary involvement sarcoidosis are relatively straightforward. Ocular, neurologic, cardiac, upper airway involvement and hypercalcemia (Fig. 96.14) almost always need corticosteroids, often in higher doses (60 to 80 mg), and for a long time. Glandular involvement, splenic enlargement, parotid swelling and cutaneous lesions respond to modest doses of 20 to 30 mg daily. Asymptomatic hepatic involvement usually requires no therapy, but regular follow-up evaluation must be provided to exclude progressive impairment of liver function.

Choice of Drug

Corticosteroids

Corticosteroids have been in use for sarcoidosis since 1950s.[271] The steroids are potent anti-inflammatory agents and act by gene transcription leading to the inactivation of nuclear factor-kappa B, which inhibits the synthesis of most known cytokines. In a Cochrane database systematic review on the efficacy of corticosteroid in pulmonary disease, the authors concluded that oral corticosteroid therapy resulted in improvements in chest radiography, but evidence of a beneficial effect on lung function was limited.[272] Prednisolone, administered at a daily dose of 0.5 to 1 mg/kg body weight is effective in most patients. For pulmonary sarcoidosis, a lower dose of 20–40 mg/day is adequate as an initial dose.[273] Despite the paucity of high-quality data for corticosteroid therapy in sarcoidosis, experts in a recent Delphi paper[274] reached a consensus that corticosteroids are the initial therapy of choice and 40 mg of daily prednisone equivalent was the maximum dose recommended for the treatment of acute pulmonary sarcoidosis. The dose is tapered after a period to three to six months to a maintenance dose of 5–10 mg/day in patients responding to therapy with plans for the continuation of treatment for a minimum of 12 months with close monitoring for relapse.

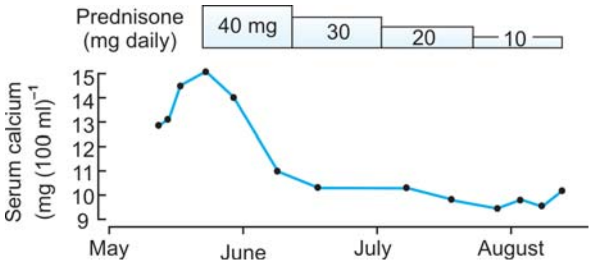


Fig. 96.14: Hypercalcemia in sarcoidosis responds to treatment with corticosteroids

There is insufficient data to recommend routine use of inhaled corticosteroids for the treatment of pulmonary disease.[275] A meta-analysis found inconclusive evidence to support the use of inhaled corticosteroids.[272] Isolated studies have demonstrated a slight improvement in diffusing capacity or improved symptoms.[276,277] Studies have also shown the use of inhaled budesonide after initial oral prednisone and in a placebo-controlled trial, 15 months of inhaled budesonide after three months of prednisone therapy was found to be superior at five-year follow-up for pulmonary function in the treated group.[278]

Corticosteroid therapy is associated with significant toxicity. The usual recommendation by the American Thoracic Society to undertake skin testing for latent tuberculosis before the initiation of corticosteroid therapy[279] is not practical for India for two reasons:

i. There is high prevalence of TB infection in population and a vast majority of our patients with sarcoidosis would be infected
ii. Tuberculin test is likely to be negative in active sarcoidosis (wide supra).

Another major complication of chronic glucocorticoid therapy is osteoporosis. Clinicians should consider calcium and vitamin D supplementation, after ruling out and monitoring of hypercalcemia and hypercalciuria. Use of bisphosphonate has been recommended by the American College of Rheumatology in patients receiving greater than 5 mg of prednisone per day or its equivalent for more than three months.[280] Other common side effects of corticosteroid therapy include increased risk of infection, hypertension, diabetes, mood changes, skin thinning, cataracts, acne and weight gain.

Alternate Drugs to Corticosteroids

Several alternate drugs to corticosteroids have been used by different investigators, often showing only modest benefits. Alternatives are required because of the side effects of corticosteroids and/or concomitant conditions such as diabetes mellitus, hypertension and other diseases which restrict the use of steroids. It is rather rare that sarcoidosis, diagnosed for the first time, does not respond to corticosteroids. Relapses however are refractory more commonly.

Cytotoxic Drugs

Cytotoxic drugs such as chlorambucil, methotrexate, cyclophosphamide and azathioprine constitute the most promising alternative to corticosteroids.[281-284] Methotrexate (MTX) is the preferred second-line drug and can be steroid sparing drug in acute sarcoidosis as well.[274,285,286] The typical dosage of MTX is 10–15 mg once a week often in combination with steroid therapy. The dosage may need to be adjusted for side effects, the most common of which are nausea and leukopenia. Response is relatively slower in onset. Although the clinical symptoms regress within two to four weeks, it takes about six to eight weeks for functional and radiological improvement. Both azathioprine and MTX have been also used as additional drugs to reduce the maintenance dose of prednisolone. A rational use of cytotoxic agents with the low doses of corticosteroids or other immune modifiers may enhance efficacy and reduce toxicity.[287] Careful monitoring is required for the toxicity of cytotoxic drugs with the help of repeated liver and renal function tests and hematological assessment.

Antimalarial Drugs

Antimalarial drugs such as chloroquine and hydroxychloroquine have been used with a fair degree of success, especially for cutaneous sarcoidosis.[288,289] Good response has also been reported in sarcoidosis of the upper respiratory tract,[290] sarcoidosis-related hypercalcemia[291] and neurosarcoid.[265] The typical dosing regimen for hydroxychloroquine is 200–400 mg daily. The risk of irreversible retinopathy and blindness greatly restricts its use for longer periods. This is significantly more likely with chloroquine than hydroxychloroquine, so hydroxychloroquine is the preferred agent. Rare side effects include agranulocytosis and myopathy, so periodic monitoring of the complete blood count and neuromuscular strength are recommended.

Tumor Necrosis Factor-Alpha Antagonists

Tumor necrosis factor-alpha antagonists, such as infliximab, adalimumab, are the latest entrant to this group of drugs. Since TNF-α is believed to play a central role in granuloma formation and inhibitors of this cytokine have been shown to be useful in several studies.[273,266-270,292-295] Besides several case reports and case series reporting clinical improvement in refractory neurosarcoidosis, cardiac sarcoid, cutaneous sarcoid, and sarcoid of the upper airway; two randomized trials have assessed the efficacy of infliximab therapy in pulmonary sarcoidosis and extrapulmonary therapy. In the pulmonary sarcoidosis there was an improvement in forced vital capacity,[293] whereas for extrapulmonary sarcoidosis although there was improvement after 24 weeks of therapy, but this benefit was not sustained after a 24-week washout.[266] Trials demonstrating long-term safety and efficacy of infliximab therapy are lacking. Of all the agents in this class, infliximab is the most studied, etanercept is not very useful and is not recommended for the treatment of sarcoidosis. Case reports of adalimumab are promising and this drug is under further investigation. Infliximab is typically given as an intravenous infusion of 3–5 mg/kg on weeks 0 and 2, with repeat dosing every four to eight weeks thereafter.[273]

One of the major concerns for the use of TNF-α inhibitors is the increased risk of the reactivation of latent tuberculosis and other opportunistic infections. In fact in the United States careful screening for latent tuberculosis and Isoniazid (INH) prophylaxis for all those found positive is recommended for all patients planning to start therapy with a TNF-α inhibitor,[296] a recommendation that is not possible to implement in countries with the high burden of tuberculosis. Therefore, the role of these therapies for the treatment of sarcoidosis in India would remain limited to a few carefully selected patients, where other therapies fail.

Other known side effects include a possible increase in malignancy, such as lymphoma, new onset and worsening of congestive heart failure, and demyelinating diseases. Surprisingly, there are also several reports of development of sarcoidosis during treatment with TNF-α antagonists, which represents a rare and paradoxical adverse event. The occurrence of sarcoidosis has been reported with all three available agents and is probably linked to a cytokine disequilibrium.[297]

Several other drugs which have been employed in sporadic cases or short trials include leflunomide, mycophenolate, colchicine, pentoxifylline and cyclosporin A. None has found an established role as yet.[281,298]

How Long to Continue?

The duration in each patient is individualized on the basis of symptoms, organ involvement and response to therapy. There is frequent relapse of symptoms when the treatment is tapered off.[299-302] Prolonged treatment is recommended for the continued suppression of disease-activity. Most clinicians continue treatment for about one year.[3,269] Significantly better results were observed in patients who had received prolonged treatment for four years or more in the BTS study.[268]

There is a small group of patients with limited but symptomatic disease in whom the treatment is discontinued after a period of three to six months. On the other hand, some of the patients may require low-dose prednisolone treatment for much longer periods of 10 years or more. Alternate day treatment is preferred if required for longer periods. It is considered safer than the daily dose regimen, even when the total dose is similar.[303] Recently, it was shown that treatment of acute exacerbations of pulmonary sarcoidosis with 20 mg prednisone for a median of 21 days improved spirometry back to baseline and improved clinical symptoms.[304]

The status of long-term treatment in developing countries is somewhat depressing.[117] There is a general trend to taper treatment earlier than required, largely for the fear of steroid-induced complications and poor patient compliance. Patients often stop treatment on their own and report back only when symptoms relapse. It is not infrequent to encounter patients who have received multiple courses of steroid treatment for short periods.

Treatment of Complications

Management of complications of disease, different treatments and associated conditions is also important. Steroid-induced complications are frequent and have been discussed above.

Systemic, constitutional symptoms of sarcoidosis are treated with analgesics and nonsteroidal anti-inflammatory drugs. An often overlooked aspect of sarcoidosis is fatigue. Regardless of disease activity, patients often report fatigue, sleep disturbance, and impaired general Quality of Life (QOL),[305] one study had shown good results with use of dexmethylphenidate hydrochloride for the treatment of sarcoidosis-associated fatigue.[306] Sarcoidosis patients should be screened for depression.

Bronchiectasis requires treatment like any other bronchiectasis patient, with anti-inflammatory therapy, postural drainage, and appropriate antibiotic therapy for exacerbations.[307] Extensive fibrosis causing hypoxemia requires supplemental long-term oxygen therapy. Additional treatments for complications due to extrapulmonary organ involvement are needed as appropriate. Decongestive therapy is required for heart failure due to sarcoid cardiomyopathy. Radiation therapy has been successfully used for refractory neurosarcoidosis.[308] Recently, bronchoscopic balloon dilation with adjunctive topical mitomycin-C has been tried in broncostenosis following sarcoidosis.[309] Elderly sarcoidosis patients often present with the unusual clinical features of sarcoidosis. Occasionally, these features resemble malignancy; rarely sarcoidosis and malignancy may coexist.[310]

With severe functional impairment and patient disability, pulmonary hypertension and right heart failure may supervene for which the patient will require oxygen and careful dieresis. Sildenafil and bosentan are effective for pulmonary hypertension .[311] These patients are candidates for Lung Transplantation (LT). Survival rates following LT for sarcoidosis are generally comparable to other indications. Recurrent sarcoidosis in the lung allografts can occur but does not affect survival or risk for complications.

PROGNOSIS AND MORTALITY

Sarcoidosis is a benign process. Many patients remain asymptomatic and spontaneous remission is common. The disease however follows a chronic course in 10% to 30% of the cases, sometimes leading to significant deterioration in lung function. Mortality rates of 1% to 6% have been reported.[312] Fibrosis in the chest radiograph and a forced vital capacity below 1.5 L are predictive of death due to respiratory failure caused by sarcoidosis.[313] When fibrosis and pulmonary hypertension are present at the same time, there is a sharp drop in respiratory functions and such findings should alert the clinician to this serious complication.[314] In the survival analysis, sarcoidosis has a better prognosis at five years (91.6% survival) compared to other diffuse interstitial lung diseases such as nonspecific or desquamative interstitial pneumonia (85.5%), hypersensitivity pneumonitis (84.1%), collagen-related diffuse interstitial lung disease (69.7%), undefined forms of pulmonary fibrosis (69.5%), and idiopathic pulmonary fibrosis (35.4%).[313] Only one case-control study points to a possible increased risk for developing neoplastic processes, such as lymphomas, lung cancer, or cancer of other organs affected by the disease, but these findings have not been confirmed in other studies with long-term follow-up.[315,316] In short, the prognosis of sarcoidosis is linked to the severity of the disease.

FUTURE DIRECTIONS

Despite extensive research, sarcoidosis remains an enigmatic disease. A working group of the National Heart, Lung, and Blood Institute identified several future research directions and opportunities for sarcoidosis. These include developing a tissue bank, using novel methods to identify genetic factors, studying the immunopathogenesis with human tissue and animal models, exploring new approaches to diagnose and manage disease, and, finally, conducting randomized controlled trials to assess new therapies.[317] The remarkable similarity of sarcoidosis to tuberculosis and the continued interrelationship of the two conditions is of special interest to clinicians and researchers from countries with ongoing TB epidemic. The wish list for sarcoidosis research in these countries would therefore include the development of definitive test/s for differentiating the two conditions and also looking for newer therapies or standardizing the existing treatments in a fashion that would reduce the risk of common complications such as the reactivation of latent tuberculosis.

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Pulmonary Eosinophilic Disorders

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INTRODUCTION

Though eosinophils were first described by Paul Ehrlich in 1879,[1] Löeffler described the association between pulmonary infiltrates and eosinophilia in 1932[2] and the term "Pulmonary Infiltrates with Eosinophilia" (PIE) was coined by Reeder and Goodrich in 1952.[3] It has been just over 30 years that the role of these cells in the etiopathogenesis of systemic disease, including that of the lungs, has been better understood and defined.

Eosinophilia and lung disease is currently recognized to be either secondary to known causes or a primary involvement. Eosinophilic lung disease, therefore, includes conditions known to involve the lung that are associated with peripheral and/or pulmonary eosinophilia.

Eosinophils

Eosinophils originate from CD34+ myeloid progenitor cells and share a common immediate precursor with basophils that differentiate towards the eosinophilic lineage under the influence of various cytokines, mainly Interlukin-5 (IL-5), GM-CSF and IL3. Expression of high affinity IL-5 receptor is a prerequisite and an early lineage specific event in this process. Interleukin-5 gene knockout mice produce basal levels of eosinophils; however do not mount expected blood and/or tissue eosinophilia in response to various stimuli. Interlukin-5 is produced by T cells and endothelial cells in the bone marrow, and T cells and parenchymal cells in the lung. Along with the differentiation of eosinophils it also promotes the release of eosinophils into the bloodstream.

Mature eosinophils are characterized by the presence of large membrane limited granules that have an electron dense core and that of small granules. The core of large granules is formed by Major Basic Protein (MBP) while the matrix contains various other enzymes such as Eosinophil-Derived Neurotoxin (EDN), Eosinophil Cationic Protein (ECT) and eosinophil peroxidase. The smaller granules have enzymes like arylsulfatase and acid phosphatase. In addition, dense lipid bodies that are not membrane bound and contain enzymes for metabolizing arachidonic acid, serving as sites of eicosanoid synthesis, are present.

Following its release, the mature eosinophil enters various tissues predominantly those having an epithelial-environment interface such as respiratory, gastrointestinal and genitourinary tracts after a brief intravascular stay. It is eventually phagocytosed by tissue macrophages after a few days. Once in tissues, their survival depends upon the local production of cytokines regulating eosinophil apoptosis. Eosinophils have a diurnal variation in response to the level of endogenous steroids with higher levels in the morning.[4] Pyogenic infections lead to eosinopenia, while parasitic infestations and drugs cause eosinophilia. Eosinopenia can also occur in response to exogenous steroids, estrogens and epinephrine.[5,6]

Circulating eosinophils, like other leukocytes, first move to the margins of the blood stream where, by the process of rolling, they adhere to the vascular endothelium. These then enter the interstitium by passing in between the endothelial cells by diapedesis and then under the influence of various cytokines and chemokines to the site of inflammation. After their arrival, they are

TABLE 97.1: Defining limits of eosinophilia

Normal counts: Differential: $\leq 5\%$
AEC: $\leq 0.5\times10^9$/l

Eosinophilia:

- Mild: AEC $0.5\text{-}1.5\times10^9$/l
- Moderate: AEC $1.5\text{-}5.0\times10^9$/l
- Severe: AEC $>5.0\times10^9$/l

HES: (Chusid et al[7])

- AEC: $>1.5\times10^9$/l lasting for 6 months
- Lack of evidence for known causes of eosinophilia
- Signs and symptoms of organ involvement/dysfunction

primed by cytokines, especially IL-5, platelet activating factor and complement fragment of C5a. This results in the release of various mediators that include MBP, Eosinophil Cationic Protein (ECP), EDN, Erythropoietin (EPO), substance P and also oxygen radicals, lipid mediators and cytokines like IL1, IL3, IL5, IL6, IL8, GMCSF, TGF α and β, eotaxin, the prostaglandins, leukotrienes and platelet-activating factor that finally contribute to the inflammatory actions of the eosinophils.

The role of eosinophils in allergic disorders, parasitic and neoplastic diseases, tissue inflammation or idiopathic eosinophilia as a result of their proinflammatory and cytotoxic effects is now better understood. As discussed, these effects are related to preformed granule constituents and inducible lipid mediators, cytokines and oxidative products. The role of eosinophils in tissue injury has been elucidated by demonstration of both enzymatic and nonenzymatic cationic protein constituents of primary and secondary granules in the tissues involved in eosinophilia related disorders. A large number of conditions are associated with the development of variable levels of eosinophilia (Table 97.1) with manifestations in different organ systems necessitating a careful search for the cause. Though secondary causes of eosinophilia are more likely (allergic disorders in the west and parasitic infections in rest of the world) in many cases, an underlying myeloid malignancy may be detected (clonal eosinophilia); the search may be inconclusive in several instances and lead to a diagnosis of idiopathic Hypereosinophilic Syndrome (HES). As a part of the human leukocyte system, eosinophils have a variety of functions to perform. They are especially important in the defense against helminthic infestations—eosinophilic products are lethal to the larval stages of these parasites.

TABLE 97.2: Pulmonary eosinophilic disorders

- **A. Primary pulmonary eosinophilia**
  1. Predominant involving lung
     - Acute eosinophilic pneumonia
     - Chronic eosinophilic pneumonia
  2. Systemic disease with lung disease
     - Churg-Strauss syndrome
     - Idiopathic hypereosinophilic syndrome
- **B. Secondary pulmonary eosinophilia**
  1. Infections
     - Parasitic infestations
  2. Transient passage (Löffler's syndrome):
     - Ancylostoma, ascaris, strongyloides
     - Tissue resident: paragonimiasis, echinococcosis
     - Heavy hematogenous seeding
       - Trichinella
       - Visceral larva migrans
       - Disseminated strongyloidiasis
       - Schistosomiasis
     - Fungal infections: Coccidiomycosis, Histoplasmosis
     - Other infections: Tuberculosis, Brucellosis
  3. Tropical pulmonary eosinophilia
  4. Allergic bronchopulmonary aspergillosis
  5. Hypersensitivity pneumonia
  6. Drugs, toxins and radiation
- **C. Lung disorders with associated eosinophilia**
  1. Interstitial lung disease
     - Sarcoidosis
     - Idiopathic pulmonary fibrosis
     - Langerhans cell histiocytosis
     - Connective tissue disease
  2. Asthma
  3. Bronchiolitis obliterans-organizing pneumonia
  4. Neoplastic disorders
     - Hematological malignancies
     - Solid organ tumors
  5. Postlung transplant

PULMONARY EOSINOPHILIC DISORDERS

Pulmonary eosinophilic disorders may occur with or without a known cause or as an association of known lung disease (Table 97.2). Since many of these disorders have been dealt with in details elsewhere (Chapter 75—Allergic Bronchopulmonary Aspergillosis, Chapter 62—Parasitic Lung Diseases, and Chapter 64—Bronchial Asthma), we shall restrict the discussion primarily to that of primary pulmonary eosinophilic disorders [Acute Eosinophilic Pneumonia (AEP), Idiopathic Chronic Eosinophilic Pneumonia (ICEP), Churg-Strauss Syndrome (CSS) and HES] and those related to drugs and toxins.

Acute eosinophilic pneumonia and ICEP are only occasionally associated with extrapulmonary involvement and predominant systemic symptoms suggest the possibility of systemic vasculitis, idiopathic HES or other causes. A brief mention of Löffler's syndrome is needed in this review because since its first description by Löffler in 1932,[8] it is recognized that the exact cause of simple pulmonary eosinophilia is not determined in a substantial number of cases. A similar syndrome may be seen secondary to drug reaction. There is no age or sex predilection and the patients typically present with an acute, self limiting disease comprising of low-grade fever, dry cough, dyspnea and rarely, hemoptysis. Blood examination shows moderate to marked eosinophilia; respiratory secretions may also show eosinophilia. The chest X-ray will show transient, migratory, nonsegmental interstitial or alveolar infiltrates. The symptoms typically resolve within one to two weeks.

Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia is an acute onset rapidly progressive disorder that occurs in the previously normal young adult population and causes acute onset, severe respiratory failure.[9,10] The median age at onset is approximately 30 years, has slight male preponderance.[11] The exact cause is not known though it has been associated with unusual activities such as cave exploring and wood working. This has led to a hypothesis that AEP is due to a hypersensitivity reaction to fungal antigens; nothing has been proven as yet. Also, cases have been reported in individuals who have recently taken up smoking.[12]

The clinical presentation is acute with rapid progression to Acute Respiratory Distress Syndrome (ARDS) within two to three days. Patients may present with fever, cough, myalgias, dyspnea, pleuritic chest pain that progresses to frank respiratory failure with ARDS. A somewhat characteristic feature is the absence of any multisystem involvement despite severe respiratory failure.[11]

Investigations typically show leukocytosis with initial absence of peripheral blood eosinophilia, though the IgE levels may be moderately increased. The chest X-ray shows bilateral patchy infiltrates that progress rapidly to ARDS like picture with diffuse alveolar or interstitial infiltrates. The Computed Tomography (CT) scan shows diffuse parenchymal opacities.[13] Bilateral pleural effusions may also be seen, pleural fluid analysis shows marked eosinophilia and high pH. Bronchoalveolar Lavage (BAL) shows marked eosinophilia along with variably elevated levels of beta-D-glucan and many cytokines such as IL-5 and IL-18. Pulmonary function tests during the acute phase show a restrictive defect with reduced DL_{CO}.

Despite its severe clinical presentation, AEP is highly responsive to corticosteroids. The mortality rate is low with prompt treatment that results in a rapid and sustained response and infrequent relapses. The diagnosis requires a high index of suspicion and is made only after exclusion of all other causes.

Idiopathic Chronic Eosinophilic Pneumonia

ICEP was first described by Carrington in 1969.[14] Though it may occur at any age, the peak incidence of the disease is seen between the ages of 30–40 years[15] with a slight female preponderance.

Patients with CEP are generally nonsmokers. A history of antecedent atopy, allergic rhinitis or nasal polyps is present in one-third to half of the patients and that of asthma in about two-third of the patients. The asthma is adult onset and may arise spontaneously or precede ICEP by some time.

The clinical picture is that of an insidious onset and indolent course.[16] Predominant symptoms are low-grade fever, drenching night sweats and weight loss. Associated cough either productive or nonproductive, dyspnea and wheezing are the other presenting features. Dyspnea is generally mild, but at times may progress to a point that mechanical ventilation may be required. Extrapulmonary manifestations other than fever, asthenia and weight loss occur rarely include arthralgias, joint pains and heart failure.

Diagnosis

The peripheral blood examination shows normocytic-normochromic anemia with a mild to moderately elevated Erythrocyte Sedimentaion Rate (ESR). There is usually a moderate leukocytosis with eosinophils constituting less than 30%.[17] However, the absence of peripheral eosinophilia should not preclude the diagnosis. BAL fluid also shows marked eosinophilia ranging from 12 to 95% of the total. Serum IgE levels are moderately elevated in about half of the cases. Pulmonary function testing may either be normal or show an obstructive or restrictive defect. The obstructive defect may occur in patients with asthma though patients without asthma may also develop the same. The restrictive pattern occurs due to eosinophil infiltration into the interstitium. The DL_{CO} will be mildly reduced.

The radiographic features of CEP are quite variable. Characteristically, infiltrates are progressive, bilateral, peripheral and symmetrical that gives an X-ray appearance of the photographic negative of pulmonary edema and disappears with corticosteroid therapy.[18] The infiltrates are usually dense, patchy, irregular opacities which involve the upper and mid zones. They may be subpleural in location. The characteristic "photographic negative of pulmonary edema" that occurs following involvement of extensive areas or whole lung is seen in less than 25% of cases.[19] Pleural effusions are uncommon. HRCT shows more bilateral involvement similar with areas of ill-defined consolidation and ground glass opacification, areas of patchy consolidation with atelectasis and septal thickening. There may be mediastinal lymphadenopathy and nodular infiltrates.

Histopathologic examination reveals infiltration of the interstitium and the alveoli by eosinophils, lymphocytes, macrophages and plasma cells with disruption of the local architecture. Evidence of proliferative bronchiolitis obliterans, microangiitis and microabscesses may also be seen. The diagnosis is suggested by appropriate investigations in the presence of a suitable clinical background. The differential diagnosis includes tuberculosis, fungal infections (like cryptococcosis), sarcoidosis, Löffler's syndrome, Desquamative Interstitial Pneumonia (DIP) and Bronchiolitis Obliterans with Organizing Pneumonia (BOOP), among others.

Management

There is a dramatic response to corticosteroids in CEP with symptoms decreasing within 6 to 48 hours and radiological clearing within two months. Oral steroids in usual doses can be used and treatment in low doses is maintained for at least six to nine months or longer. Relapse occurs in up to half of treated patients after discontinuation of steroids.[16] However, currently no risk factors indicative of relapse are recognized. The relapse can usually be controlled by reinstitution of steroids which may need to be given for prolonged periods of time.[17,19-22]

Churg-Strauss Syndrome (Allergic Granulomatosis and Angiitis)

Churg-Strauss syndrome was first described as a separate entity in the early 1950s.[23,24] It is an uncommon disease and its diagnosis is often missed or delayed. It can affect any age group with peak incidence between 30 and 50 years, without any sex predeliction.[25] The underlying pathology is believed to be an immune hypersensitivity, accounting for the presence of Antinuclear Cytotoxic Antibodies (ANCA) and nearly universal finding of an atopic state in these individuals.

Churg-Strauss syndrome has also been associated with the use of leukotriene inhibitors, montelukast more than zafirlukast.[26] The onset of the disease is variable from 2 days to 12 months after the initiation of therapy and it occurs almost exclusively as corticosteroids are being tapered off. This is considered to be an unmasking of the underlying disease rather than the result of drug use.

Clinical Features

Churg-Strauss syndrome can be divided into three stages, clinically:

1. *Prodromal stage:* This can last for months to years. The patient usually presents with late onset atopic states such as allergic rhinitis, nasal polyposis and asthma in the absence of any family history.
2. *Eosinophilic stage:* This stage is characterized by the infiltration of various tissues by eosinophils, especially the skin, gastrointestinal tract (GIT) and lungs.
3. *Vasculitic stage:* Characterized clinically by the onset of constitutional symptoms and microscopically by eosinophilic infiltration, vasculitis and granulomatous infiltration.

The respiratory manifestations of CSS include upper respiratory tract disease, asthma, pleural effusions and Löffler's like syndrome. The upper respiratory tract is involved in approximately 75 to 85% percent of cases and manifests as allergic rhinitis, sinusitis and nasal polyposis. No necrosis is seen unlike in Wegener's granulomatosis.[27]

Asthma is the predominant feature of CSS. It may be present for many years before the diagnosis of CSS is made.[28] It is usually predominant in the prodromal and eosinophilic stages of the disease and may subside with the onset of the vasculitic phases. A short interval between the onset of asthma and that of vasculitis is considered a sign of increased severity.[29]

Other pulmonary manifestations include a Löffler's like syndrome (40%) and unilateral or bilateral pleural effusions or pleurisy without effusions in up to one-third of patients.

The cardiovascular system is commonly involved and is the leading cause of mortality.[25] Patients may develop coronary vasculitis leading to myocardial infarction[25] and ischemic cardiomyopathy or congestive cardiac failure secondary to eosinophilic myocardial infiltration. Acute and chronic constrictive pericarditis and pericardial tamponade may also occur. The development of coronary vasculitis is associated with high risk of mortality of around 60%.[30]

Systemic manifestations may be prominent, include fever, weight loss, arthralgias and arthritis, lymphadenopathy, splenomegaly, urological and ocular disease.

These generally herald the onset of extrapulmonary disease. Neurological manifestations are seen in up to two-third of patients, include mononeuropathy and polyneuropathy, cranial neuropathy especially optic neuritis, mononeuritis multiplex, seizures, cerebrovascular accidents and subarachnoid hemorrhage.[28]

Gastrointestinal tract manifestations generally consist of eosinophilic gastroenteritis or vasculitis causing abdominal pain, bleeding, diarrhea, intestinal obstruction, bowel perforation, gastric ulcers and liver function test abnormalities.[31] Dermatologic manifestations like palpable purpura, nodules, ulcers, maculopapular rashes and livedo reticularis may occur. Renal involvement consists of interstitial nephritis, focal segmental glomerulosclerosis, hematuria and hypertension following renal infarction. However, chronic renal failure is unusual in CSS as compared to other forms of vasculitis.

Diagnosis

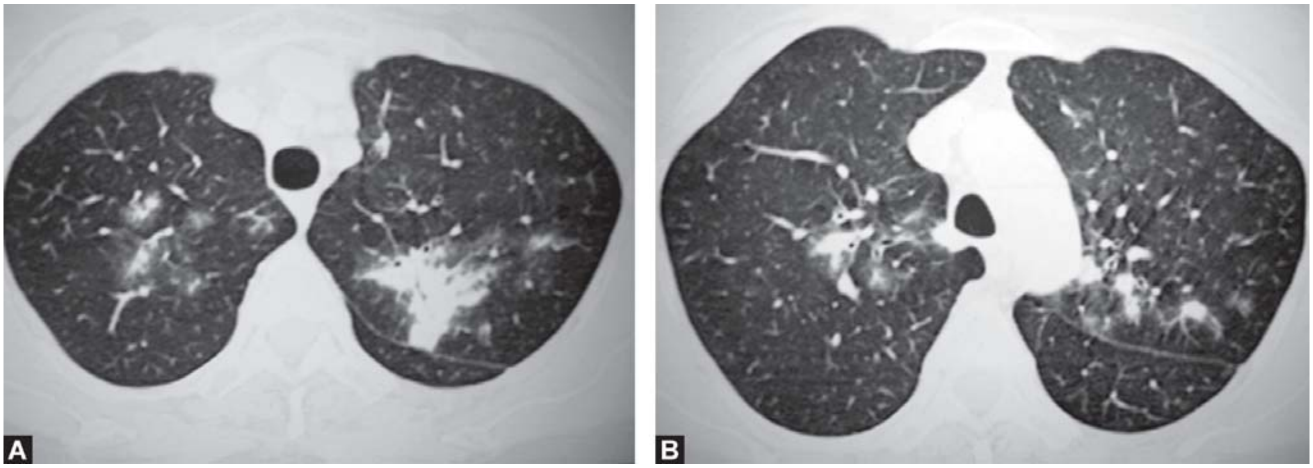
Laboratory examination shows normocytic-normochromic anemia, normal platelet counts and a high ESR. Leukocytosis with variable eosinophilia is commonly noted. Immunoglobulin E (IgE) and IgG levels are elevated and there is hypergammaglobulinemia with rheumatoid factor seropositivity. Immunoglobulin E levels may parallel the disease activity. About two-third of patients have pANCA positivity[31,32] that does not have utility as a marker of disease activity on follow-up examinations.

The chest X-ray may be normal or nonspecific. Löffler's syndrome like infiltrates may be present in up to 40% of individuals (Figs 97.1A and B) and pleural effusions may be seen in one third of cases. Other findings on radiology include noncavitatory nodules, patchy areas of consolidation or ground glass opacification, septal thickening, pulmonary artery enlargement and peribronchial thickening.[25] Pleural fluid is acidic with high eosinophil count and low glucose levels.

Pulmonary function tests show an obstructive physiology while BAL shows variable eosinophilia. Positron Emission Tomography (PET) may show cardiac involvement. Histopathological examination of various tissues, including the lungs, pleura, skin, GIT and nervous tissue reveals both intravascular and extravascular noncaseating granulomas with eosinophilic infiltration accompanied by vasculitis of the small and medium-sized arteries, veins, venules and capillaries.[25] These features give the disorder eponym "Allergic granulomatosis with angiitis." The inflammation may resolve with time and treatment, or lead further to fibrous scarring.

In the absence of universally accepted diagnostic criteria, the diagnosis of CSS is challenging. There are several diagnostic criteria that rely on symptoms of asthma, eosinophilia and evidence of organ involvement secondary to medium and small vessel vasculitis. The American College of Rheumatology criteria published in 1990 require the presence of at least four out of the six given criteria, which give a sensitivity and specificity of 85% and 99.7%, respectively.[33] These include i) asthma, ii) paranasal sinusitis, iii) monoarthropathy or polyarthropathy, iv) migratory or transient pulmonary infiltrates, v) peripheral blood eosinophilia greater than 10%, and vi) extravascular eosinophils in a blood vessel on a biopsy specimen.

The differential diagnosis includes Wegener's granulomatosis, polyarteritis nodosa, tuberculosis, fungal infections, allergic bronchopulmonary aspergillosis,



Figs 97.1A and B: HRCT of a patient with CSS with pulmonary infiltrates

chronic eosinophilic pneumonia, asthma and Hodgkin's disease.

Treatment

The treatment includes corticosteroids and cytotoxic medications.[28,30] Corticosteroid use is indicated in patients with systemic involvement, hypertension and lung involvement. Oral prednisolone may be started at a dose of 60–100 mg per day and continued for 6–12 weeks followed by a gradual taper to a maintenance dose, which might be continued for a year or more. Disease activity may be followed by the disappearance of constitutional symptoms, hypertension, cardiac, renal, neurological and vasculitic disease. Laboratory markers of disease activity include ESR, IgE levels and leukocyte counts; pANCA is not useful for follow-up.

Indications for the use of cytotoxic chemotherapy include nonresponsiveness to steroids and severe systemic disease including cardiac, GIT and renal disease (proteinuria >1g/day or renal insufficiency). Pulse cyclophosphamide is probably the immunosuppressive treatment of choice in an acute phase, whereas azathioprine may be useful for maintenance. Other immunomodulators such as high dose intravenous immunoglobulin and interferon-alpha in standard dose have also been used in severe disease and so has been plasma exchange.[28] Beta blockers use to control hypertension should be avoided since it could precipitate congestive cardiac failure and bronchospasm.

The prognosis of CSS is very poor without treatment. However, the use of corticosteroids has dramatically reduced the mortality rate.[28] Long-term remissions are usually achieved, though relapses may occur.

Hypereosinophilic Syndrome (HES)

It is also known as Löffler's endocarditis and eosinophilic leukemia. Hypereosinophilic syndrome is a disorder characterized by multisystem involvement and a variation in the severity of presentation.[7,34-36] It predominantly affects males and is more common from 20–50 years, though it can occur at any age.[34] The diagnostic criteria, initially proposed by Chushid have been subsequently expanded to include the World Health Organization (WHO) criteria for diagnosis (Tables 97.1 and 97.3).[7,37] There has been a significant confusion in the past over the terminology and at times it was thought that HES constitutes a spectrum of illness with minimal involvement on one hand and eosinophilic leukemia on the other extreme. Recent WHO classification suggests that clonal disorders that show chromosomal or molecular clonality should be classified as neoplastic and HES should include the rest of the disorders without any clear cause for eosinophilia.

TABLE 97.3: WHO criteria for diagnosis of chronic eosinophilic leukemia and hypereosinophilic syndrome[37]

- Persistent eosinophilia $>1.5\times10^9$/l
- Increased number of eosinophils in the bone marrow
- Myeloblasts <20% in both blood and bone marrow

1. Exclude all causes of reactive eosinophilia (secondary to allergy, parasitic diseases, infectious diseases, pulmonary diseases, collagen vascular diseases etc.)
2. Exclude all neoplastic disorders with reactive eosinophilia (T-cell lymphomas, Hodgkin's lymphoma, ALL, B-cell lymphomas, mastocytosis)
3. Exclude other neoplastic disorders in which eosinophils are part of neoplastic clone [Philadelphia (Ph) chromosome &/and/or BCR-ABL positive chronic myelogenous leukemia; acute myeloid leukemia, including those with inv(16), t(16;16)(p13;q22); other myeloproliferative diseases like Polycythemia Vera (PV), Essential Thrombocythemia (ET), Idiopathic Myelofibrosis (IMF)]
4. Exclude T cell populations with aberrant phenotype and abnormal cytokine production
5. Diagnose HES if there is no demonstrable disease that can cause eosinophilia, no evidence of abnormal T cell population and no evidence of clonal myeloid disorder
6. Diagnose CEL if all of the requirements (including conditions 1–4) have been met, and if the myeloid cells demonstrate a clonal cytogenetic abnormality or are shown to be clonal by other means, or if blast cells are present in peripheral blood (<2%) or BM (5%–19%)

The cause of this disorder is unknown and the various hypotheses propose it as a disorder ranging from a primary disturbance of myelopoiesis to a monoclonal expansion of T lymphocytes producing cytokines to an immune hypersensitivity reaction. The organ damage is the result of eosinophilic infiltration and/or thromboembolic phenomena.

Clinical Features

Three major clinical variants of HES are recognized[38] myeloproliferative variant, lymphoproliferative and the familial HES. The myeloproliferative variant has been shown to be associated with FIP1LI-PDGFR α fusion gene. Since these patients have a clonal abnormality, these may also be classified by some as chronic eosinophilic leukemia. The lymphoproliferative variant is associated with monoclonal expansion of T cells that result in increased IL-5 secretion and hypereosinophilia. Familial HES is secondary to genetic defect that results in increased IL-5 and eosinophilia. Currently, even after detailed investigations, a subset of patients may not reveal any cause, termed as true idiopathic HES.

Hypereosinophilic syndrome is a heterogeneous disease. Its clinical manifestations are also highly variable in the terms of duration, severity and organ involvement. The symptoms most often are indolent; include fever, weight loss, fatigue, anorexia, night sweats, skin rash, hepatosplenomegaly, angioedema and other system involvement.

The respiratory system is involved in approximately 40% of cases, manifested predominantly by nocturnal cough, which is usually nonproductive.[7,36,38] Wheezing and dyspnea also occur and occasionally the disease can progress to ARDS. Pleural effusion, pulmonary hypertension and thromboembolism may develop over a period of time.

The cardiovascular system is most commonly involved.[34,39] There is an eosinophilic infiltration of the endocardium and myocardium leading to restrictive cardiomyopathy,[40,41] endocardial fibrosis and mitral regurgitation. Intracardiac thrombus formation occurs, leading to pulmonary thromboembolism. Associated peripheral arterial or venous thrombosis has also been reported.[42]

Neurological manifestations include encephalopathy, neuropsychiatric disturbances, memory loss, visual changes and cerebrovascular accidents secondary to thromboembolism.[43] Other systems are involved less frequently; the symptomatology varies according to the system involved (Table 97.4).

Diagnosis

Blood examination shows anemia, leukocytosis (10,000–50,000/mm^3) with 30 to 70% eosinophils. Erythrocyte sedimentaion rate, serum IgE and gamma globulins are elevated. Also noted are elevated levels of serum B$_{12}$ and leukocyte alkaline phosphatase. Circulating immune complexes are occasionally found. Bone marrow shows an increase in eosinophils and eosinophil precursors (Fig. 97.2). Eosinophilic blast transformation has been noted in 28 to 51% of patients. Eosinophilic infiltration of other organs is also demonstrable on histopathological examination (Fig. 97.3).

TABLE 97.4: End-organ damage in HES and hypereosinophilic disorders

Cardiac	Pericarditis, EMF, cardiomyopathy, myocarditis, intramural thrombi, regurgitation
Neurologic	Thromboemboli, peripheral neuropathy, dementia/psychosis, meningitis, epilepsy
Dermatologic	Angioedema, urticaria, papulonodular lesions, mucosal ulcers, vesiculobullous, microthrombi, Raynaud's phenomenon, digital necrosis
Pulmonary	Infiltrates, fibrosis, effusion, emboli
Ocular	Microthrombi, vasculitis, retinal arteritis
Joints	Arthralgia, effusions, polyarthritis
Gastrointestinal	Ascites, diarrhea, gastritis, colitis, pancreatitis, cholangitis, Budd-Chiari syndrome

Chest X-ray shows focal or diffuse nonspecific infiltrates and pleural effusions. Pulmonary function tests demonstrate an obstructive physiology. Echocardiography may show evidence of intracardiac thrombi, should be done six monthly in follow-up as cardiovascular disease is the major cause of mortality and morbidity in this disease.[42]

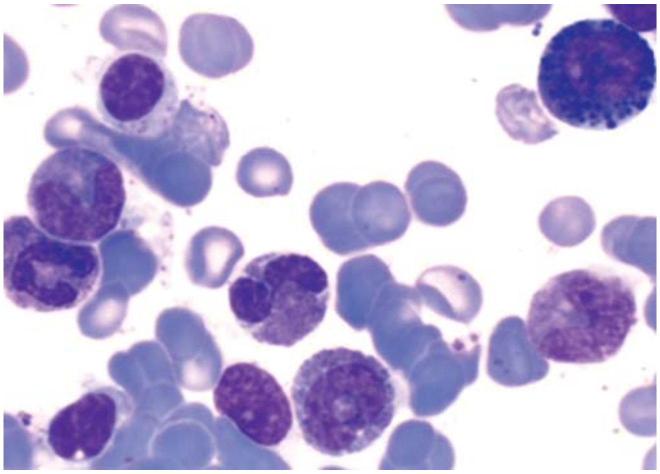


Fig. 97.2: BM smear in HES patient showing two metamyelocytes, one basophil and two eosinophils (one has a ring nucleus)

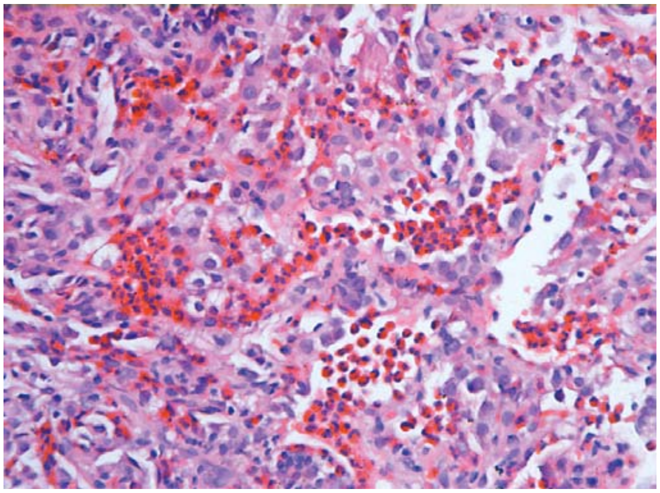


Fig. 97.3: Extensive eosinophilic infiltration of tissues on histopathological examination

TABLE 97.5: Laboratory diagnosis of myeloproliferative and lymphoproliferative variants of HES

Myeloproliferative variant	*Lymphoproliferative variant*
Definitive evidence: • FIP1L1-PDGFRA fusion • Eosinophil clonality	Definitive evidence • Phenotypically aberrent aberrant T Cells • TCR rearrangement • Increased eosinophilopoietic cytokines
Supportive evidence: ≥4 of • Increased serum tryptase • Increased serum B_{12} • Splenomegaly • Anemia, thrombocytopenia • Increased circulating myeloid precursors • Dysplastic eosinophils • Myelofibrosis • Increased spindle shaped mast cells in BM	Supportive evidence • Increased serum TARC • Increased serum IgE • Predominantly cutaneous manifestations • H/O atopy • Steroid responsive

The differential diagnosis includes the different eosinophilic disorders like CEP, CSS, acute eosinophilic pneumonia, tropical pulmonary eosinophilia, fungal infections and parasitic infestations, etc. Different laboratory criteria are used for the differential diagnosis of lymphoproliferative and myeloproliferative variants (Table 97.5).

Treatment

Treatment depends upon the presence of end-organ dysfunction. In clonal and idiopathic hypereosinophilia, the aim of the treatment is to limit/reverse end-organ damage and provide symptomatic improvement. In asymptomatic patients without any evidence of end-organ damage, a careful follow-up and assessment of any end-organ damage may be a prudent policy.

Asymptomatic peripheral eosinophilia can be followed up every three to six months without any treatment. The first line of therapy consists of steroids, which are given orally. Prednisone, in a dose of 1 mg/kg/day for one to two months is followed by a slow taper to a maintenance dose, which can be continued for one year or longer as required. In refractory cases, treatment with hydroxyurea, vincristine, chlorambucil, cyclosporine or interferon-α, can be tried.[34,44] The anti-IL5 antibody, mepolizumab has also been used in patients with high IL5 levels.[45,46]

Even though steroids had been the mainstay of treatment in the past, it is now realized that patients with myeloproliferative variant do not respond well to steroids and in case of FIP1L1-PDGFRA positive patients, use of tyrosine-kinase inhibitors such as imatinib[47] and dasatinib results in a gratifying response. Initial dose for a rapid cytogenetic response should be 400 mg/day with a lower maintenance dose. Whereas this variant is associated with exquisite sensitivity to imatinib even at a dose of 100 mg/day, other variants may require higher dosage and have variable response. Steroids should be added to imatinib in patients with evidence of myocarditis on echocardiography, electrocardiography or biochemical parameters (elevated serum troponin). The anti-CD 52 antibody, alemtuzumab has been tried in refractory cases especially those of lymphoproliferative variant.[48,49] There are several reports of successful treatment using hematopoietic stem cell transplant in refractory cases.[50-56]

The causes of mortality in HES include refractory congestive cardiac failure, renal failure, hepatic failure, venous thromboembolism, gut perforation and infections. However, proper treatment leads to a mean survival of greater than 10 years.

Other Eosinophilic Lung Diseases

Langerhans Cell Granulomatosis

Histiocytosis X consists of three closely related disorders, occurring at different ages: Langerhans cell histiocytosis, Letterer-Siwe disease and Hand-Schüller-Christian disease.[57] Primary pulmonary histiocytosis X, earlier known as eosinophilic granuloma of the lung, is almost exclusively found in smokers. The male to female ratio is 1:1; patients in the third and fourth decades of life are commonly affected.

It presents with cough, dyspnea, hemoptysis, chest pain, fever, wheezing, weight loss and recurrent, often bilateral pneumothorax. Patients also develop diabetes insipidus and bony disease. Chest X-ray shows involvement of the upper and middle zones with sparing of the costophrenic angles, reticulonodular changes, cystic lesions and bullae that may rupture to cause recurrent pneumothorax. Pulmonary function tests (PFTs) may show either a restrictive or an obstructive defect.

Histopathologically, a granulomatous infiltrate of histiocytes, eosinophils and other cells can be seen. The histiocyte is a large cell with an indented nucleus that has Birbeck granules on electron microscopy. S-100 antibody can also be found (Figs 97.3 and 97.4).

Treatment is based on the severity of the disease. Smoking should be stopped and patient treated with corticosteroids. Vincristine, cyclophosphamide and fludarabine have also been used. The mortality rate is less than 5% in adults.

Sarcoidosis

It is a multisystem disorder with pulmonary involvement in the majority of cases (Chapter 96). Patients may present with fever, weight loss, mediastinal lymphadenopathy and lung infiltrates. Histopathological examination reveals noncaseating epithelioid granulomas. Tuberculosis is a close differential diagnosis, especially in the Indian subcontinent. The incidence of eosinophilia in sarcoidosis ranges from 10 to 67%.[58]

Neoplastic Disorders

Eosinophilia may occur in association with several neoplastic conditions, both with hematological malignancies and solid organ tumors. The presence of eosinophilia may or may not be an adverse prognostic sign, depending upon the underlying disorder.

Hematological disorders associated with eosinophilia include systemic mastocytosis (in approximately 20%),[59,60] nodular sclerosing Hodgkin's disease (15%),[61] B-cell non-Hodgkin's disease,[61] T-cell leukemia and Sézary syndrome.[62] Of course, eosinophilic leukemia is a well known variant of acute myelomonocytic leukemia (M4).[63]

Solid organ malignancies include large cell cancer of the lung, squamous cell carcinomas of cervix, skin, nasopharynx, bladder transitional cell carcinoma, etc.[64-68]

Tropical Pulmonary Eosinophilia

It is an important cause of marked eosinophilia, hence an important differential diagnosis (Chapter 62).

Infections

Eosinophilia occurs with a variety of infectious agents, which include bacterial, fungal and parasitic diseases. An undulating pattern of eosinophilia that corresponds to disease activity has been noted in tuberculosis.[69] It has been shown that eosinophilia correlates with a good prognosis while eosinopenia was noted in fulminant or miliary disease.

Chronic brucellosis is also known to be associated with eosinophilia.[70] The fungal infection most commonly associated with eosinophilia is coccidiomycosis in which it occurs as a hypersensitivity phenomenon.[71,72] Other fungal infections include rare case reports of eosinophilia associated with *Histoplasma capsulatum* and cryptococcosis.

Drug- and Toxin-Induced Pulmonary Eosinophilia

A variety of drugs and toxins are associated with eosinophilic lung disease (Table 97.6).[73] The signs and symptoms of disease may manifest anywhere from a few minutes after exposure to weeks afterwards. One of the more common drugs to be implicated is nitrofurantoin, which causes acute, subacute and chronic reactions (Chapter 114).[74]

Symptoms, as already detailed, occur variably after exposure to the drug. These include low-grade fever, cough and dyspnea with or without wheezing. Examination might show wheezing and crackles and the peripheral blood will show eosinophilia. Chest X-ray may reveal diffuse or patchy pulmonary infiltrates; CT scans show bilateral consolidation and ground-glass opacification, both of which may be peripheral. Pulmonary function tests may either be absolutely normal, or show a reduced DLCO or a mild restrictive defect.

The syndrome usually disappears after discontinuation of the responsible drug. Corticosteroids are not universally beneficial, though their use may hasten recovery, especially in sick patients.

APPROACH TO DIAGNOSIS AND CONCLUSION

It is apparent that eosinophilic lung diseases are heterogeneous disorders that require a meticulous history taking, painstaking examination and judicious use of investigations to reach a definite diagnosis. A simplified algorithm that may be useful is given in Fig. 97.4. It is important to reach a diagnosis because these illnesses have different course and complications and thus involve important treatment decisions.

TABLE 97.6: Drugs causing eosinophilic lung disease

1. **Antimicrobials**
    - Para-amino salicylic acid
    - Nitrofurantoin
    - Penicillin
    - Tetracycline
    - Streptomycin
    - Isoniazid
    - Sulfonamides
    - Tetracycline
    - Minocycline
    - Dapsone + pyrimethamine
2. **Antineoplastic and immunosuppressives**
    - Bleomycin
    - Methotrexate
    - Melphalan
    - Gold salts
    - Azathioprine
    - Penicillamine
    - Beclomethasone
3. **Nonsteroidal anti-inflammatory drugs (NSAIDs):**
    - Aspirin
    - Naproxen
    - Piroxicam
    - Nimesulide
    - Phenylbutazone
4. **Cardiovascular and antidiabetics:**
    - Amiodarone
    - Hydralazine
    - Thiazides
    - Clofibrate
    - Sulfonylureas
5. **Miscellaneous**
    - Carbamazepine
    - Phenytoin
    - Dantrolene
    - Methylphenidate
    - Imipramine
    - Cocaine or heroin exposure
    - Iodinated contrast media
    - L-tryptophan.

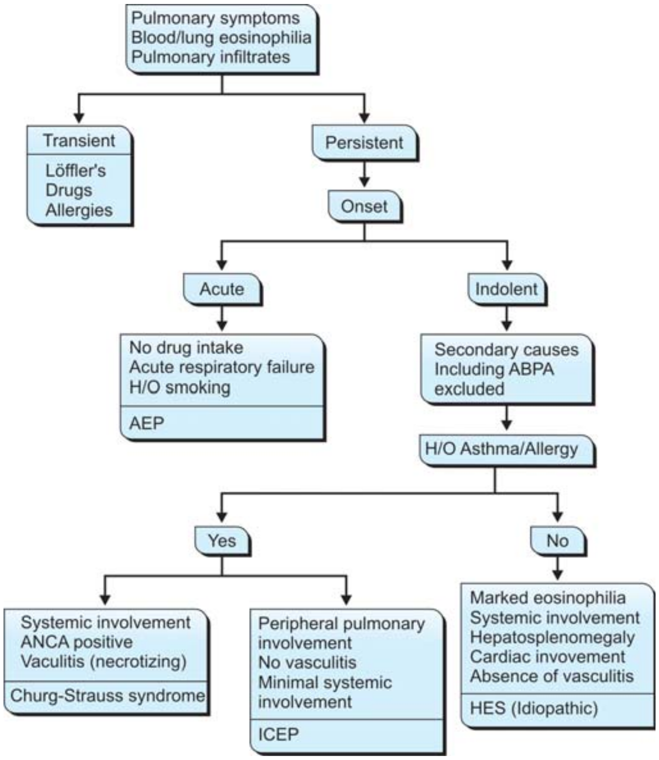

Pulmonary symptoms
Blood/lung eosinophilia
Pulmonary infiltrates
Transient
Löffler's
Drugs
Allergies
Persistent
Onset
Acute
Indolent
No drug intake
Acute respiratory failure
H/O smoking
AEP
Secondary causes
Including ABPA
excluded
H/O Asthma/Allergy
Yes
No
Systemic involvement
ANCA positive
Vaculitis (necrotizing)
Churg-Strauss syndrome
Peripheral pulmonary
involvement
No vasculitis
Minimal systemic
involvement
ICEP
Marked eosinophilia
Systemic involvement
Hepatosplenomegaly
Cardiac invovement
Absence of vasculitis
HES (Idiopathic)

Fig. 97.4: Proposed diagnostic algorithm for pulmonary eosinophilic disorders
AEP: Acute Eosinophilic Pneumonia, HES: Hypereosinophilic Syndrome
ICEP: Idiopathic Chronic Eosinophilic Pneumonia
ABPA: Allergic Bronchopulmonary Aspergillosis

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98

Infiltrative and Deposition Diseases

Pralay Sarkar, Arunabh Talwar

INTRODUCTION

There are several different diseases characterized by the deposition of abnormal materials, either endogenous or exogenous, in the pulmonary parenchyma or in other areas of the respiratory system. Although rare, they frequently pose problems in the differential diagnosis of common clinical conditions, which present with similar respiratory or other clinical manifestations. Not infrequently, they are responsible for long delays in establishing the diagnoses.

PULMONARY AMYLOIDOSIS

Introduction

Amyloidosis is a group of disorders characterized by the extracellular tissue deposition of fibrils as beta-pleated sheets, disrupting organ function. These deposits are composed of low molecular weight subunits (most in the molecular weight range of 5 to 25 kD) of a variety of proteins, which circulate as the constituents of plasma. Current nomenclature of amyloid is based on the precursor proteins.[1] The pattern of organ involvement often depends on the nature of the precursor protein, many of which are associated with specific disease entities[1] (Table 98.1). Most common types of amyloidosis associated with pulmonary involvement are either AL or AA amyloidosis (see below). Amyloidosis has association with a wide range of systemic diseases, most commonly plasma cell dyscrasias, chronic infections or inflammatory conditions (Table 98.2).

Pulmonary Involvement in Amyloidosis

The first case of amyloidosis confined to the lower respiratory tract was described by *Lesser* in 1857, based on an autopsy. Pulmonary involvement with amyloidosis can occur in one of the three circumstances (Table 98.3). The Mayo clinic experience, based on retrospective review of pathological specimens, remains one of the best descriptions of pulmonary involvement with amyloidosis.[2] In their 55 patients recorded over a period of 13 years, 35 (66%) had primary systemic amyloidosis (including 3 of 35 patients with multiple myeloma), while 30% had localized (primary) pulmonary involvement. In systemic amyloidosis, lung is rarely the predominant organ involved clinically.[3] Pathological involvement of lung, however, has been described as a rule in primary systemic amyloidosis with amyloid deposition noted at autopsy in over 90% of patients.[2,4,5] In secondary systemic amyloidosis, pulmonary involvement is reported to be low, is usually mild and takes a different pattern of deposition with prominent perivascular component; most of these patients have no respiratory symptoms attributable to amyloid deposition, and have normal chest radiograph.[4-6]

Amyloid deposition limited only to lungs, called primary (localized) pulmonary amyloidosis is diagnosed on the basis of following criteria:[7] a. positive immunohistochemical staining for k and λ light chains (AL amyloid) in a respiratory tract biopsy *or* negative staining for serum AA protein, hereditary amyloid of transthyretin-type (TTR); b. no evidence of plasma cell dyscrasia on bone marrow biopsy; c. negative urine or

TABLE 98.1: Major types of amyloidosis[1]

Protein class	*Protein name*	*Amyloid type*	*Clinical presentation*	*Pulmonary involvement*
Immunoglobulin gene superfamily	Ig light chain/Ig heavy chains (IgL/IgH)	AL/AH	Primary systemic amyloidosis; Amyloidosis associated with multiple myeloma and other monoclonal gammopathies	Yes, almost universal in autopsy studies
	Beta-2 microglobulin	A β2m	Dialysis amyloidosis	Yes
High-density apolipoproteins	(Apo) serum AA	AA	Amyloid complicating chronic infections or inflammatory diseases; some heredofamilial periodic fever syndromes, such as familial Mediterranean fever (FMF)	Less frequent, usually not significant clinically
Transport protein	Transthyretin (TTR; prealbumin)	ATTR	Hereditary neuropathic and/or cardiopathic amyloids; senile systemic amyloidosis	

TABLE 98.2: Different diseases and other conditions associated with (pulmonary) amyloidosis

Blood dyscrasias/Hematologic malignancies/Lymphoproliferative disorders

Multiple myeloma
Waldenström's macroglobulinemia
Non-Hodgkin's lymphoma (NHL)
MALT lymphoma of the lung

Connective tissue disorders

Rheumatoid arthritis
Systemic lupus erythematosus
Mixed connective tissue disorder
Primary Sjögren's syndrome

Other conditions

End-stage renal disease on hemodialysis
Asbestos inhalation
Liver transplantation
Bone marrow transplant
Sarcoidosis
Familial Mediterranean fever
Dystrophic epidermolysis bullosa

TABLE 98.3: Pulmonary amyloidosis

- Pulmonary involvement in systemic amyloidosis: Lung involvement as a part of multisystem involvement
    - Primary systemic amyloidosis: Pulmonary involvement almost universal
    - Secondary systemic amyloidosis: Pulmonary involvement is infrequent and mild
- Organ specific involvement of lung without any evidence of systemic amyloidosis: Primary (localized) pulmonary amyloidosis
- Organ specific pulmonary amyloidosis in association with other pulmonary disorders
    - Sarcoidosis
    - Sjögren's syndrome with multiple pulmonary cysts
    - Pulmonary neoplasms: Anaplastic tumor or carcinoid
    - Lymphocytic interstitial pneumonia
    - Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma

serum studies for paraproteins; d. characteristic distribution and pattern of localized respiratory tract disease on computed tomography (CT) scan; e. no extrapulmonary involvement on serum amyloid P component (SAP) scan; and f. negative echocardiogram. Amyloid can involve both the upper and the lower respiratory tracts in a variety of pathological patterns (Table 98.4).

Pathogenesis

The pathogenesis of localized pulmonary amyloidosis remains obscure. In case of immunoglobulin light-chain (AL) amyloid, deposition is postulated to occur following a localized monoclonal proliferation of lymphoplasmacytic cells in pulmonary parenchyma; however, monoclonal plasma cell proliferation is not found in

TABLE 98.4: Clinicopathological patterns of respiratory system involvement in amyloidosis

- Tracheobronchial amyloidosis
- Solitary pulmonary nodule
- Nodular amyloidosis
- Alveolar septal amyloidosis
- Pulmonary vascular amyloidosis
- Pleural amyloidosis: Pleural effusion and spontaneous hemothorax
- Other thoracic or respiratory tract amyloidosis
  - Laryngeal
  - Intrathoracic lymphadenopathy
  - Mediastinal mass
  - Mediastinal hemorrhage
  - Pulmonary hypertension
  - Diaphragmatic paralysis

many such cases. Another theory postulates that the circulating amyloid precursor molecule is deposited in the lung as a result of increased regional vascular permeability, possibly due to local inflammation. Polyclonal plasma cell infiltrates, often found in association with the amyloid deposits in the lung, are considered to reflect residual inflammation or a reactive inflammatory reaction to amyloid deposition. It is also possible that lung being in direct contact with environmental antigens, an abnormality of the local secretory immune system may contribute to amyloid deposition. Low pH and interaction with glycoaminoglycan help in deposition of amyloid.[8]

Clinical Types, Presentation and Diagnosis

1. Tracheobronchial Amyloidosis

Tracheobronchial amyloidosis is a rare disease. Here amyloid deposition typically occurs in the submucosa of trachea and main bronchi, sometimes extending to the level of segmental bronchi. Tracheobronchial amyloidosis usually occurs as an isolated airway involvement without that of lung parenchyma or other organs. Tracheobronchial involvement may be focal or diffuse, the later being more common.[9,10] Tracheobronchial amyloidosis has been associated with tracheobronchopathia osteochondroplastica though the causative relationship of these two rare conditions remains debatable.

Clinical presentation: Most cases have been reported in the fifth and sixth decades of life.[9] The presentation is predictable from the site of involvement: cough, dyspnea, recurrent hemoptysis and wheezing are common symptoms. Significant narrowing of airway can happen, leading to consequences like atelectasis and recurrent pneumonia.[11] Rarely, tracheobronchomalacia due to amyloidosis of the trachea has been reported.[12]

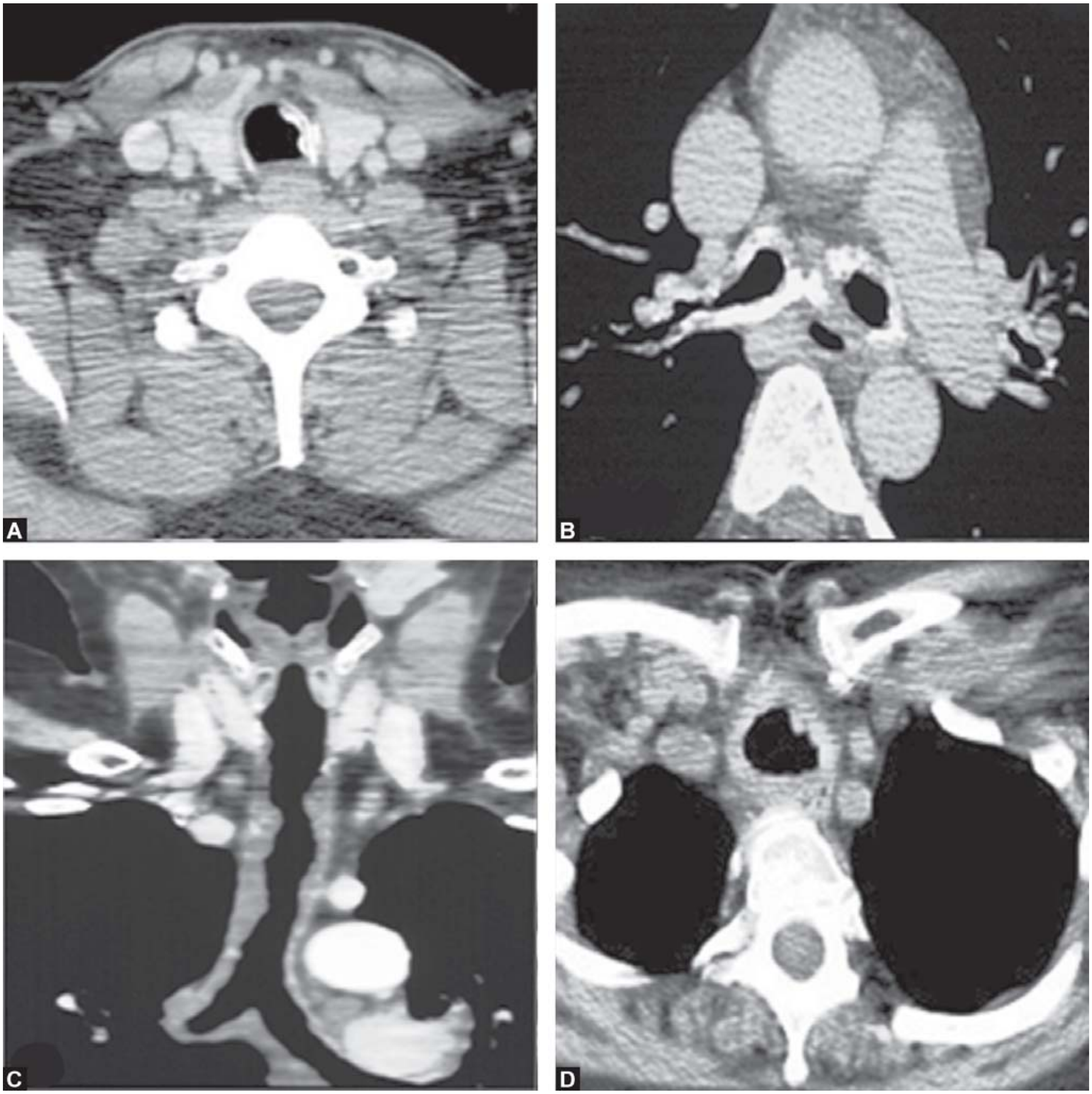
Diagnosis: The nonspecific clinical presentation of tracheobronchial amyloidosis can lead to delay in diagnosis. Often the disease is misdiagnosed as (refractory) asthma or chronic bronchitis for a long period of time.[11] Lung function tests may show evidence of large airway obstruction. Chest X-ray (CXR) and CT may show focal or diffuse thickening of the airway wall (Figs 98.1A and B), nodular and irregular narrowing of airway lumen (Fig. 98.1C), and localized nodule in the airway lumen (Fig. 98.1D). CXR can also show the consequences of airway obstruction like pneumonia, distal atelectasis or hyperinflation of lung distal to the obstruction.[10,13] CXR sometimes may be normal adding initial difficulty to the diagnosis.[14]

Bronchoscopy shows different endoscopic patterns: submucosal plaques, pseudotumor appearance, circumferential wall thickening; these are believed to represent different stages of the same process of amyloid deposition.[15] The deposits on bronchoscopy typically appear yellowish, often shiny and pale, with indistinct outline of cartilaginous rings and intact overlying mucosa (Fig. 98.2).[14] On macroscopic examination of the affected tissue, the amyloid deposits appear as irregular nodular masses or as diffuse sheets. Microscopically, the nodular masses or diffuse sheets are made of pink, amorphous, acellular material on hematoxylin and eosin (H and E) stain (hyaline deposits) (Fig. 98.3). Congo red staining shows apple-green birefringence under polarized light. Macrophages, foreign-body giant cells, microscopic calcifications, osseous metaplasia can be seen.[9] Submucosal blood vessels may also show amyloid deposition. Localized tracheobronchial amyloidosis is usually AL type, but AA type amyloid has been found in rare cases.[16]

2. Nodular Pulmonary Amyloidosis

In this type of pulmonary amyloidosis, nodular deposits of amyloid occur in pulmonary parenchyma, usually bilaterally at multiple sites. Nodular pulmonary amyloidosis is usually not associated with systemic amyloidosis. Presentation as a single nodular lesion/mass (amyloidoma) may also occur.[17]

Diagnosis: Average age of presentation is in the sixth decade of life. Nodular amyloid is commonly asymptomatic, often found incidentally on CXR or at autopsy.[9] Symptoms arise when a large mass produces its mechanical effects: patients present with cough and progressive dyspnea. Significant weight loss has also



Figs 98.1A to D: Tracheobronchial amyloidosis: A. Localized thickening of upper trachea; B. Diffuse thickening of tracheal wall at the level of carina; C. Sagittal section of trachea showing irregular narrowing of airway; D. Localized amyloid nodule in the airway lumen
(*Courtesy:* Dr Rakesh Shah, Consultant Radiologist, North Shore University Hospital, Manhasset, NY, USA [Figs 98.1A to C]
Dr Subha Ghosh, Consultant Radiologist, Ohio State University, Columbus, Ohio, USA [Fig. 98.1D])

been reported.[18] CXR and CT of the thorax show single or multiple pulmonary nodular opacities/masses of soft tissue density. These masses have irregular contour and are distributed diffusely, bilaterally and often asymmetrically.[18] Distribution of nodules may show lower lobe and subpleural preponderance. The size of most nodules ranges from 0.4 to 5 cm; an average nodule is ~3 cm in size and size up to 15 cm has been reported

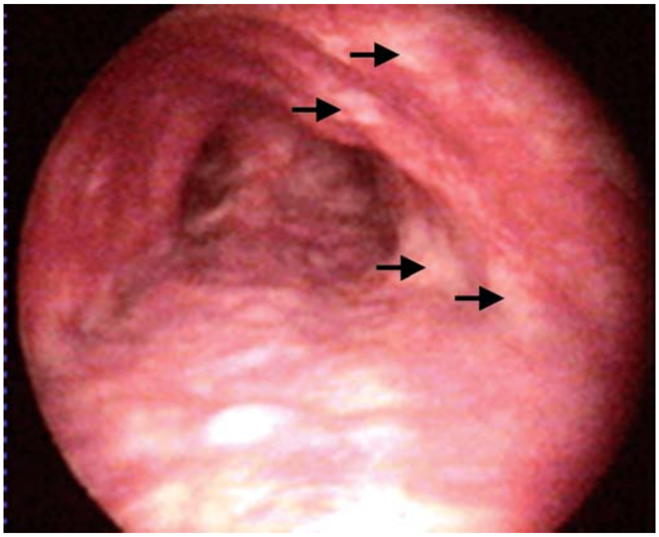


Fig. 98.2: Bronchoscopic view of tracheobronchial amyloidosis showing multiple yellowish, shiny submucosal deposits (marked with arrow)

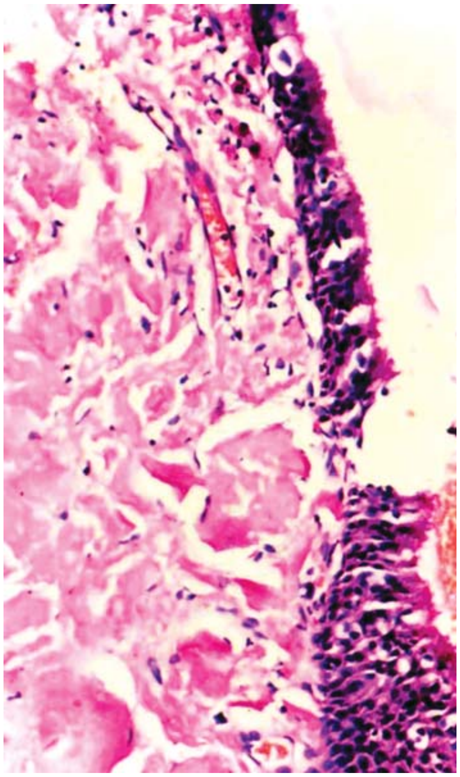


Fig. 98.3: Light microscopic appearance of a bronchoscopic biopsy specimen in a case of tracheobronchial amyloidosis. Diffuse sheets of pink, amorphous, acellular material are seen (hematoxylin and eosin [H and E] stain, 100X)
(*Courtesy:* Dr Ritesh Aggarwal, Assistant Professor, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India)

reported.[9,19] A solitary amyloidoma can grow unusually big with extension into the surrounding tissues[20] (Fig. 98.4). The nodular deposits may contain areas of calcification, may rarely cavitate.[21,22] Calcification is often subtle, apparent only on CT scan and can be the only clue to the diagnosis.

Nodular pulmonary amyloidosis has close radiological resemblance with primary/metastatic lung cancer. Therefore, biopsy is required to reach a diagnosis. Image-guided transthoracic fine needle aspiration (FNA) biopsy can be attempted, but the firm-to-hard consistency of deposits may cause difficulty in obtaining an adequate sample.[23] Bronchoscopic tissue sampling, including transbronchial lung biopsy, can give diagnosis in some cases.[2] Occasional report of accurate diagnosis with CT-guided bronchoscopic sampling can also be found.[24] However, serious adverse consequences have been reported in some cases following transbronchial biopsy, including reports of fatal pulmonary hemorrhage and arterial air embolism.[2,25] Open lung biopsy by thoracotomy or video-assisted thoracoscopy should often be the preferred approach for safe and adequate tissue sampling.

In pathological specimens, nodular amyloid deposits appear as irregular masses of eosinophilic amorphous material. Some nodules can have areas of ossification and/or calcification. Small arteries or veins adjacent to or within the lesions may contain amyloid. Clusters of plasma cells and giant cells are seen adjacent to or within the amyloid deposits (more frequently in the nodular parenchymal than in the tracheobronchial variant). A histological picture consistent with interstitial pneumonitis or granulomatous

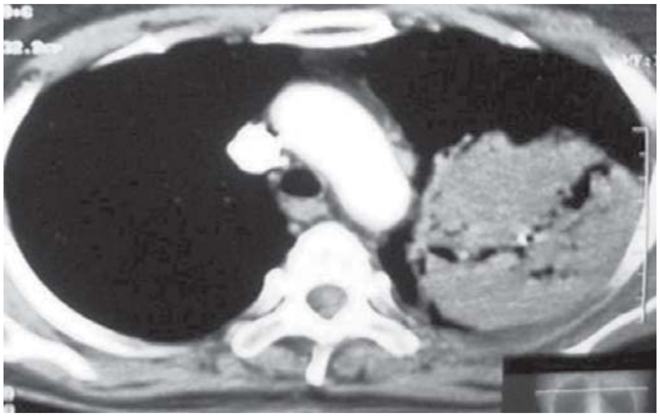


Fig. 98.4: Large solitary mass of amyloid deposit in the pulmonary parenchyma
(*Courtesy:* Dr Ritesh Aggarwal, Assistant Professor, Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India)

pneumonitis can be found in a small number of cases.[9] Immunohistochemistry usually reveals AL amyloid; amyloid composed predominantly of beta 2-microglobulin has also been described.[23]

Differential diagnoses include primary and secondary neoplasms and granulomatous disorders.[26] In cases of solitary nodule/mass, careful sectioning of pathological specimen is necessary to rule out any neoplastic process as amyloid deposition has been described in association with primary lung tumor.[27,28] Amyloid deposits are usually fluorodeoxyglucose positron emission tomography (FDG-PET) negative, a point which may be useful in diagnosis; false positive results are however known adding difficulty to the diagnosis.[29,30]

3. Diffuse Alveolar Septal Amyloidosis

In this pathological pattern of pulmonary involvement, the microscopic deposits of amyloid occur diffusely within the alveolar septae and the interstitial tissue. Interstitial/alveolar septal pulmonary amyloidosis is usually seen as a part of the systemic amyloidosis.[2] It is rare for primary/localized pulmonary amyloidosis to show a diffuse interstitial pattern and till 2009, only 11 such well documented cases have been reported in the literature.[31]

Clinical presentation: The patient may be asymptomatic or may present with progressive dyspnea. The severity of clinical symptoms depends on the extent the gas exchange zones, namely alveolar septae and capillaries are involved. Majority of these patients have significant cardiac involvement complicating the picture in many of these patients. Diffuse alveolar hemorrhage leading to fatality has been reported with this form of amyloidosis.[32]

Diagnosis: Pulmonary function tests reveal a restrictive physiology with impaired gas exchange that parallels with the extent and pattern of interstitial amyloid deposition. A high-resolution computed tomography (HRCT) scan of the thorax reveals interlobular septal thickening or irregular lines that frequently have a predominant basilar and peripheral distribution.[33] Small (2-4 mm in diameter), well defined nodules and confluent areas of consolidations can also be seen. Some nodules may show calcifications and some of the areas of consolidation may contain punctate foci of calcification, a subtle clue to the diagnosis. Radiological changes often predominate in the subpleural regions. Associated pleural effusion, mediastinal and hilar lymphadenopathy may be seen. Rarely, CT scan might reveal multiple cysts of variable size with surrounding high-density areas.[21,34-36]

Histopathologically, variable amount of amyloid deposition is found in the pulmonary interstitium: alveolar septa, capillaries, as well as in the wall of bronchioles, arterioles, venules and in lymphatic vessels.[37,38] Interstitial/septal amyloid deposit may be present as diffuse and uniform or as multiple small interstitial nodules.[9] Correlating with radiological findings, thickening of interlobular septa with amyloid deposition can be shown in histological specimens. Extensive deposits are also found beneath the visceral pleura. Areas of calcification and ossification are found within the affected areas.[35]

4. Pleural Disease

Pleural effusion is a rare manifestation of systemic amyloidosis. Significantly large, persistent pleural effusions have been reported in 6% cases in a large series of AL amyloidosis; less significant effusions are seen in ~10 to 15% cases.[38] Pleural effusions are not usually seen in secondary (AA) amyloidosis.[4,5] Cardiac involvement and congestive heart failure are common in AL amyloidosis. Pleural effusions may result from congestive heart failure; the pleural fluid in these cases is expected to be transudative in character. However, one-third of the persistent pleural effusions in primary amyloidosis are exudative, which cannot be explained by cardiac involvement alone.[39] Large persistent effusions are the result of direct involvement of the parietal pleura.[40] Apart from being exudative, cellular characteristics of the effusions do not have any distinctive feature to point to the diagnosis. Pleural infiltration by amyloid can be demonstrated by thoracoscopy and can be proven by pleural biopsy.[41-43] AL amyloidosis patients sometimes develop nephrotic syndrome and hypothyroidism, secondary to infiltration of the kidney and the thyroid gland respectively. Both nephrotic syndrome and hypothyroidism may contribute to pleural effusions in these patients, though their contribution remains debated.[39] Lymphatic infiltration with amyloid can lead to chylous effusion.[44]

5. Other Manifestations of Respiratory System Amyloidosis

Pulmonary hypertension has been known to develop in systemic amyloidosis with or without the presence of parenchymal lung involvement.[31,45,46] Deposition of amyloid in the pulmonary vasculature is responsible for this uncommon development.[47] Pulmonary hypertension has been described in primary systemic AL amyloidosis, as well as in AA amyloidosis related to familial Mediterranean fever (FMF).

Diffuse pulmonary hemorrhage has been described as a first manifestation of pulmonary amyloidosis. Amyloid angiopathy, involving small- and medium-sized pulmonary arteries, may cause ***pulmonary arterial dissection***, presenting with recurrent hemoptysis.[48] Rupture of an amyloid-involved vessel may cause ***pulmonary hematoma***.[49] Amyloid deposition in vessel wall may cause fragility and lead to the formation of ***arteriovenous fistula***.[50]

Involvement of nasopharynx, paranasal sinuses: Leads to chronic infections and contribute to obstructive sleep apnea.

Laryngeal amyloidosis: Laryngeal involvement causes long-standing hoarseness of voice. It may also cause airway obstruction. Amyloidosis localized to the larynx has been rarely reported to cause fatal upper respiratory tract hemorrhage.[51]

Mediastinal lymphadenopathy: Mediastinal, as well as unilateral or bilateral hilar lymphadenopathy can be seen in amyloidosis. Lymph node involvement is usually a part of systemic amyloidosis.[21] It is an unusual manifestation in localized pulmonary amyloidosis though hilar or mediastinal lymphadenopathy has been described in conjunction with tracheobronchial amyloidosis. Very rarely, mediastinal or hilar lymphadenopathy in the absence of pulmonary involvement, has been reported as the only manifestation of localized amyloidosis.[52] Lymph nodes involved in amyloidosis present homogeneous low attenuation and faint or stippled calcification.

Diaphragmatic paralysis: Diaphragm dysfunction has been reported in systemic amyloidosis as a result of infiltrative myopathy.[53,54] Alternatively, diaphragm paralysis may result from amyloid-induced mononeuritis multiplex.[55]

Treatment

A variety of management strategies, such as observation in selected cases, intermittent bronchoscopic intervention, surgical resection and external beam radiation are used in laryngotracheobronchial amyloidosis.[15] In a given case, the choice of treatment strategy depends on the extent of involvement, the size, location and appearance of the lesions, the functional consequences of amyloid deposition and the availability of expertise in a particular institution. Bronchoscopic procedures include the mechanical debulking/resection with/without dilatation, transmucosal Nd:YAG laser treatment (for pseudotumoral mass or circumferential thickening), carbon dioxide laser ablation (for submucosal lesions) and stent placement (after establishing patency of airway lumen).[15,56] Majority of the cases can be managed by bronchoscopic procedures. Open neck surgical approach for the management of laryngotracheal amyloidosis is rarely necessary.[57] External beam radiation has been successfully used in the treatment with functional improvement, as well as the regression of lesions.[58]

In patients with secondary systemic amyloidosis, treatment of the underlying inflammatory or chronic condition is recommended. The response to tumor necrosis factor α blockade has been described in patients with rheumatic diseases who developed systemic AA amyloidosis.[59-61] Sustained improvement in proteinuria and renal function has been consistently reported though no information is available about the efficacy of these agents for the pulmonary involvement. Patients with systemic amyloidosis, who have an underlying hematological condition like multiple myeloma, Waldenström's macroglobulinemia or other monoclonal gammopathies, need treatment for the underlying condition.

Various treatment options are available for primary systemic amyloidosis (AL amyloidosis) (Table 98.5). For decades, alkylating agents have been the mainstay of treatment, often in combination with high-dose dexamethasone (Table 98.5). Intermediate dose chemotherapy regimens, adapted from chemotherapy of multiple myeloma, have also been used with success. As the general prognosis of primary systemic amyloidosis remains poor, hematopoietic stem-cell transplantation (HSCT) has been advocated as one approach to achieve survival better than chemotherapy.[62,63] Caution should be exercised while interpreting the available data, particularly while choosing HSCT over chemotherapy. Patients who are considered eligible for HSCT comprise a good-risk population. This group of patients do relatively well with chemotherapy (median survival 42 months), substantially better than the expected median survival of 18 months for all patients with AL amyloidosis on chemotherapy.[64] Using a variety of chemotherapy or cytotoxic regimens, (adapted from multiple myeloma therapy) (Table 98.5), result comparable to HSCT (survival of ~ 60% after a median follow-up of > 20 months) were found.[65-67] Chemotherapy remains the first line management for primary systemic amyloidosis. In selected patients or in patients who fail to respond to chemotherapy, HSCT is a choice. Specific clinical or radiological response of pulmonary lesions to any form of treatment has scarcely been reported.[68] The optimal approach for treating isolated

TABLE 98.5: Treatment of primary systemic amyloidosis

Standard dose alkylating agents with dexamethasone
Monthly courses of oral melphalan (10 mg per square meter of body-surface area on days 1 to 4) plus high-dose oral dexamethasone (40 mg per day on days 1 to 4): for up to 18 treatment courses (12 courses if complete remission has been achieved).
High-dose melphalan with autologous hematopoietic stem cell transplantation (HSCT)
Melphalan, 200 mg per square meter given intravenously on day 0, and stem cells were infused on day 2.
Intermediate dose chemotherapy regimens (regimens adapted from multiple myeloma treatment)
Vincristine, adriamycin and dexamethasone (VAD) Cyclophosphamide, vincristine, adriamycin and methylprednisolone (C-VAMP) Intermediate-dose melphalan (IDM)

pulmonary interstitial amyloidosis is undefined. Colchicine has been tried. Symptomatic improvement with prednisone and azathioprine has been reported.[31]

Management of heart failure is the mainstay of treatment in the cases where the effusions result from heart failure. Refractory pleural effusions, secondary to direct amyloid involvement of pleura, pose a difficult therapeutic challenge. These patients should be managed with diuretic therapy and intermittent thoracentesis. When thoracentesis is required weekly or more frequently, measures of a more sustained nature should be adopted to prevent accumulation of pleural fluid. These measures include one of the following: tube thoracostomy and pleurodesis, video-assisted thoracoscopy with talc insufflations for pleurodesis, or placement of a drainage system that can be kept in place for long time and be intermittently drained at home (e.g. *Pleurx tube*). Recently, four patients reported with AL amyloidosis who presented with bilateral pleural effusions, refractory to diuretic therapy were treated with bevacizumab, an antivascular endothelial growth factor (VEGF) antibody.[69] Three of the four patients had improvement in their pleural effusions. Further studies are required to define the role of this novel agent in the management of amyloidosis-related pleural effusion.

Prognosis

The prognosis of pulmonary amyloidosis depends on the type and extent of lung involvement, as well as on the involvement of other major organs. In tracheobronchial amyloidosis, the prognosis is not always benign. Some patients die of respiratory failure or recurrent pneumonia secondary to bronchial obstruction.[9] Severe hemoptysis also remains an important complication. Recurrence of isolated endobronchial masses after resection is rare. Nodular pulmonary amyloidosis typically runs a benign course, generally has an excellent prognosis. Nodules grow slowly over years without any regression. Follow-up of cases over 6–20 years has been reported.[70-72] Occasionally, patients may develop large lesions producing space-occupying effects.

Long-term prognosis of patients with primary systemic amyloidosis remains poor. A median survival of 16 months was reported in the Mayo clinic series.[2] Pulmonary involvement in itself contributes to death in a small proportion of cases.[4,37] Many of the patients with primary amyloidosis have other major organ involvement, notably cardiac and renal involvement, causing death. Overall, the presence of pulmonary amyloidosis in patients with primary systemic amyloidosis portends a poor outcome, whether the pulmonary component of the disease is directly related to death or is simply a marker of an otherwise advanced disease.[2] In the rare presentation of alveolo-septal form of localized pulmonary amyloidosis, the prognosis is generally poor with death occurring from progressive respiratory failure within two years.

LYSOSOMAL STORAGE DISORDERS

Lysosomal storage disorders (LSDs) are a diverse group of hereditary metabolic disorders caused by defects in lysosomal function. Most commonly, these disorders result from mutations in genes that encode catabolic enzymes (e.g. lysosomal hydrolases) involved in the degradation of macromolecules. Failure to degrade macromolecules causes accumulation of the same in the cells leading to cellular dysfunction and progressive clinical manifestations. More than 45 diseases have been described till date, most being inherited in an autosomal recessive manner[73] (Table 98.6).

The clinical expression of LSDs is variable. The age of onset, the severity of symptoms and the pattern of organ involvement can vary markedly within a single disorder type or subtype. Clinical manifestations differ according to the residual enzyme function, genetic and environmental factors. Many of these disorders, e.g. Gaucher, Tay-Sachs, Pompe, metachromatic leukodystrophy, and GM1 gangliosidosis have infantile, juvenile and adult forms. Many LSDs have upper and/or lower respiratory tract involvement. A detailed description of all the entities is beyond the scope of this chapter. Respiratory involvement can occur in various LSDs

TABLE 98.6: Classification of lysosomal storage disorders (by affected lysosomal function)

Nature of defective lysosomal function	*Prototype disorder*
Defective metabolism of glycosaminoglycans	Mucopolysaccharidosis (MPS) I–IX
Defective degradation of glycan portion of glycoproteins	Aspartylglucosaminuria, fucosidosis, mannosidosis, Schindler disease, sialidosis type I
Defective degradation of sphingolipid components	Fabry disease, Farber disease, Gaucher disease (types I–III) GM1- gangliosidosis, GM2-gangliosidoses (Tay-Sachs disease, Sandhoff disease, GM2 activator disease), Krabbe disease, metachromatic leukodystrophy, Niemann-Pick disease (type A or B).
Defective degradation of glycogen	Pompe disease
Defective degradation of polypeptides	Pycnodysostosis
Defective degradation or transport of cholesterol, cholesterol esters, or other complex lipids	Ceroid lipofuscinosis, cholesterol ester storage disease, Niemann-Pick disease type C, Wolman's disease
Multiple deficiencies of lysosomal enzymes Multiple sulfatase	Galactosialidosis
Transport and trafficking defects	Cystinosis, mucolipidosis IV, sialic acid storage disorder, chylomicron retention disease, Hermansky-Pudlak syndrome (several forms), Chédiak-Higashi syndrome
Unknown defects	Geleophysic dysplasia, Marinesco-Sjögren syndrome

(Table 98.7), some of whom have been also reported in adult patients.[74]

Anderson-Fabry Disease (AFD)

Introduction

Fabry disease is an X-linked recessive disease as a result of the deficiency of the lysosomal enzyme α-galactosidase A (α-gal A). It has no ethnic predilection and occurs in about 1:117,000 live births. AFD leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide (GL-3), in many body tissues over a period of years or decades. Clinical manifestations include renal failure in about 30% of patients and cerebrovascular accidents in about 25% of patients. A 15-year follow-up of patients from AFD clinical and genetic register (UK) reported the median age of 21.9 years at diagnosis and median cumulative survival of 50 years.[75] Obligate carrier females have also been reported to have clinical manifestations with a high frequency.[76]

Pulmonary Manifestations

Respiratory symptoms, consistent with airway involvement, are common in AFD patients.[77] In a cohort of 25 consecutive male patients with AFD, 36% complained of dyspnea and 24% had cough and/or wheezing.[78] Hemoptysis has also been reported. Interstitial involvement can also occur in AFD.[79] In line with symptoms of airway disease, chronic airflow obstruction is commonly reported on spirometry in AFD patients and is said to be more common in those who smoke.[78,80] Other investigators have reported features consistent with small airway disease, in more than half of both men and women with AFD.[77] A reduced diffusion capacity (DL_{CO}) is also a common finding.

The disease manifestations can be explained by the deposition of GL-3 within various compartments of the lower respiratory tract. The airflow obstruction is thought to be due to fixed airway narrowing secondary to deposition of GL-3 in airway epithelial cells as has been demonstrated by presence of inclusion bodies in bronchoscopic biopsy specimens.[80] Pathologic evidence for pulmonary parenchymal and vascular involvement have also been reported; hemoptysis may result from such direct vascular involvement or from angiectatic lesions in bronchi.

Diagnosis

Chest X-ray (CXR) can be normal in many patients. In keeping with the occurrence of airway disease, some of the patients have CXR changes suggestive of emphysema with or without bulla.[80] Pneumothorax can also occur. HRCT findings of lung involvement in AFD have been infrequently reported. In a recent report, HRCT demonstrated bilateral mosaic attenuation pattern. Regions of both abnormally lucent and dense lung parenchyma were present, reflecting a combination of ground-glass opacity and air trapping.[81]

TABLE 98.7: Respiratory manifestations of lysosomal storage disorders

Disease	*Upper respiratory tract involvement*	*Lower respiratory tract involvement*
(MPS I) Disease* (Hurler, Hurler-Scheie, Scheie syndromes)	Chronic rhinitis and rhinorrhea Enlarged tongue, tonsils, adenoids Obstructive sleep apnea	Narrowing of trachea Thickened vocal cords Reduced lung volumes Recurrent respiratory infections Respiratory failure common cause of death
(MPS II) Disease* (Hunter syndrome)	Recurrent ear infections Upper airway obstruction Progressive hearing loss	Pulmonary hypertension
(MPS III) Disease* (Sanfilippo syndrome)	Airway obstruction common cause of death	
(MPS IV) Disease* (Morquio syndrome)	Upper airway obstruction	Restricted chest wall movement leads to restrictive ventilator defect
(MPS VI) Disease* (Maroteaux-Lamy syndrome)	Enlarged tongue	
(MPS VII) Disease* (Sly syndrome)		Chronic inflammatory lung disease Recurrent respiratory infections
Aspartylglycosaminuria*		Kyphoscoliosis Recurrent respiratory infections
Fucosidosis – Type I	Macroglossia	Recurrent lung infections
Mannosidosis*		Recurrent respiratory infections
Pompe disease*	Macroglossia Sleep apnea	Recurrent lung infections
Acid Sphingomyelinase Deficiency (Niemann-Pick Disease Types A and B*)		Alveolar proteinosis
Fabry disease*		Chronic airflow obstruction
Farber disease	Vocal cord infiltration Hoarseness of voice	Recurrent respiratory infections
Gaucher disease – Type I* (Non-neuronopathic)		Pulmonary infiltration Kyphoscoliosis Pulmonary hypertension Restrictive lung disease Hypoxia secondary to liver disease
Gaucher disease – Type II (Acute infantile neuronopathic)	Laryngospasm Apneic episodes	
Gaucher disease – Type III (Chronic neuronopathic)*		Pulmonary infiltration Kyphoscoliosis Pulmonary hypertension Restrictive lung disease
GM1 gangliosidosis – Type I (Infantile Form)		Dorsolumbar kyphoscoliosis Recurrent pneumonia
GM1 gangliosidosis – Type II (Infantile Form)		Recurrent pneumonia
Sandhoff disease – Type I Mucolipidosis II (I-Cell disease)	Loss of swallowing Recurrent and persistent upper respiratory tract infections	Recurrent aspiration and pneumonia

*Survival into adulthood known
Disease entities marked in bold are discussed in details in the text

In a patient known to have AFD, characteristic manifestations point to pulmonary involvement and a tissue diagnosis may not be warranted. Where needed, diagnosis can be confirmed by demonstrating typical lamellar inclusion bodies in bronchial biopsy or brushings.[78,80] Cells present in induced sputum may also show inclusion bodies clinching the diagnosis.[82] Whether similar inclusion bodies are present in AFD patients without clinical lung involvement is not known. In a patient with the evidence of interstitial lung disease, lung biopsy may be indicated to rule out other diagnoses.

Management

Enzyme replacement therapy (ERT) for AFD has been available since 2003. Agalsidase beta (Fabrazyme®, Genzyme Corp.) and agalsidase alfa (Replagal®, Shire) are approved in USA, Europe and some other countries for treatment of AFD. ERT has been shown to improve symptoms, as well as renal and cardiac function.[83,84] ERT with agalsidase alfa 0.2 mg/kg every other week (EOW) or agalsidase beta 1.0 mg/kg EOW is the standard of treatment for this disease. Controlled data about the effect of ERT on progression of pulmonary function abnormalities are either scant or absent. Isolated case reports have shown significant improvement in radiological abnormalities and spirometry on ERT.[79] Renal involvement and neuropathy usually dominate the clinical picture in AFD; it can be anticipated that pulmonary involvement alone will rarely be the sole indication for ERT.

Gaucher Disease

Introduction

Gaucher disease is an autosomal recessive disorder as a result of the deficiency of the lysosomal enzyme glucocerebrosidase. It is the most prevalent lysosomal storage disorder. Gaucher disease leads to the accumulation of the lipid glucocerebroside within the lysosomes of the monocyte-macrophage system. Lipid-engorged cells (Gaucher cells) accumulate and cause organ dysfunction. Age of the onset of symptoms and their severity is variable. At an incidence of 1 in 40–60,000 live births, type I is the most common type. Type 1 is panethnic, but has higher frequency among Ashkenazi Jews. Type 1 Gaucher disease patients have normal life-expectancy and may present for the first time in adult life. Type III presents in late childhood/early adolescence and has more severe and rapidly progressive visceral disease. Type II disease rarely survives beyond the age of two years.

Pulmonary Manifestations

Pulmonary involvement has been reported in both type I and type III Gaucher disease, is more rare in type I and more severe in type III.[85] The frequency of symptomatic pulmonary involvement varies in literature from uncommon to common presentation.[86,87] Clinical picture is characterized by gradual onset and progression of dyspnea that in some cases culminates to respiratory failure and death. (Lung involvement is the second most common cause of death in type III Gaucher disease). Pulmonary involvement occurs due to infiltration by the Gaucher cells giving a pattern of interstitial lung disease (ILD). Pulmonary hypertension (PAH) has been reported in a significant proportion of adult patients and may be particularly severe, life-threatening in those who have had splenectomy for the management of the disease.[88] PAH in Gaucher disease can result from chronic hypoxemia secondary to interstitial disease, secondary to liver disease or due to long bone infarction and fracture with pulmonary emboli. Severe pulmonary hypertension can also occur in these patients primarily due to pulmonary capillary blockage by Gaucher cells, in absence of significant parenchymal involvement.[89] Other intrathoracic manifestations of Gaucher disease include: enlarged hilar and mediastinal lymph nodes that can sometimes lead to bronchial obstruction; increased incidence of pulmonary infections and hypoxemia due to intrapulmonary arterial-venous shunts in patients with severe hepatic disease. Large hepatosplenomegaly can cause the elevation of diaphragm and contribute to dyspnea.

Diagnosis

The chest radiograph may be abnormal with or without symptoms and show bilateral diffuse reticulonodular or miliary opacities. HRCT shows bilateral irregular interlobular, as well as intralobular septal thickening. The interstitial changes are more common in lower lung zones. Irregular costal margin and fissures indicate subpleural interstitial thickening. Additional ground glass opacities reflect interstitial and alveolar space disease.[90,91] Other reported HRCT findings include consolidation, alveolar opacities and bronchial wall thickening.[92] Additional findings also may include prominent pulmonary arteries as a result of the PAH. Osteopenia, cortical thinning and the widening of medullary spaces of clavicles and ribs can also be evident on the CXR.

Diagnosis is established by showing deficient glucocerebrosidase activity in peripheral blood leukocytes. In patients with respiratory involvement, bronchoalveolar lavage (BAL) reveals Gaucher cells;[93] these cells resemble macrophages with eccentric, small, oval nuclei and abundant cytoplasm with the characteristic "rumpled tissue paper" appearance. Gaucher cells stain strongly positive with periodic acid-Schiff stain. Electron microscopy reveals lysosomes containing the characteristic twisted tubular structures. Lung biopsy specimens also reveal similar cells. Lung biopsy may not be needed in known patients of Gaucher disease with typical respiratory manifestations.

Pathologic examination of the lungs reveal massive infiltration of alveolar septal walls, interstitial spaces in a lymphatic distribution, perivascular septal regions by Gaucher cells. Clumps of these cells also fill alveolar spaces and obliterate functional air exchanging tissue. In some cases, interstitial fibrosis may result. Alveolar hemorrhage and multiple pulmonary emboli are also seen in some cases.[94] In patients with PAH, apart from the characteristic arterial/arteriolar changes associated with PAH, the histological sections of lung disclose widespread plugging of the lumina of precapillary arterioles and alveolar capillaries by Gaucher cells.[89,95]

Management

Gaucher disease is the first LSD for which macrophage-targeted ERT was introduced in clinical practice (in 1991). Two modified forms of the enzyme β-glucocerebrosidase are in use: Alglucerase (Ceredase®, Genzyme Corporation, Cambridge, Massachusetts) and the recombinant analog imiglucerase (Cerezyme®, Genzyme Corporation). With imiglucerase, majority of the patients initiate therapy with doses ranging from 30 to 60 U/kg bodyweight given every fortnight. ERT is started in early childhood and has been found to be safe and effective in reducing organomegaly, skeletal complications and in improving hematological parameters.[96-98] Improvement in clinical signs of pulmonary disease, increased sense of well-being, stabilization of lung function, stabilization or improvement in chest radiological changes and improvement in lung pathology have been reported on ERT.[87,99] Lungs may be slow to respond to ERT in some patients and in some cases, pulmonary changes may be irreversible. In recent years, substrate reduction therapy (SRT) has come in practice in type I Gaucher disease; these medications (e.g. Miglustat, a small iminosugar), given orally, act to reduce substrate load either by inhibiting its synthesis or enhancing the residual activity of the endogenous mutant enzyme. The effect of SRT on lung disease is unknown.[100]

Niemann-Pick Disease

Introduction

Niemann-Pick disease (type A and B) is due to the deficiency of the enzyme acid sphingomyelinase (ASM). When ASM is deficient, sphingomyelin and cholesterol accumulate in lysosomes. Clinical manifestations are due to fat deposition in one or more organs. ASM deficiency can present along a continuum of severity. Severe ASM deficiency is associated with the type A phenotype (neuronopathic form presenting in infancy, death before 5 years of age). Non-neuronopathic ASM deficiency can present at any age and historically has been classified as Niemann-Pick disease type B phenotype. Niemann-Pick type C is a genetically distinct disorder resulting from defective intracellular trafficking of cholesterol and secondary accumulation of glycosphingolipids. Niemann-Pick disease is pan-ethnic though type A has higher frequency among Ashkenazi Jews; the incidence is 1 in 248,000 live births.

Pulmonary Manifestations

Pulmonary involvement has been reported in all types of Niemann-Pick disease.[101-103] Pulmonary symptoms result from alveolar lipoproteinosis. Pulmonary disease has been best described in type B disease. Respiratory manifestations may present at a variable age and rarely may be the initial presentation of this disease.[104,105] In the largest reported cohort of patients with type B disease, (59 patients, $\leq$ 6 years of age, 50% >18 years of age), shortness of breath and respiratory infections were common symptoms.[101] Various bleeding manifestations are common in this disease and hemoptysis and hemothorax have been reported. Cyanosis, clubbing, rales and wheezing may be present on physical examination. Pulmonary function tests are abnormal in vast majority of patients with type B disease, including those who have no symptoms.

Diagnosis

CXR shows reticulonodular opacities with the areas of ground glass haziness, often out of proportion to clinical manifestations.[104] HRCT shows variable combination of septal thickening and ground glass, diffuse and homogeneous.[102,105,106] The radiological evidence of interstitial lung disease has been reported to be present in nearly all patients with type B Niemann-Pick disease.[107]

Diagnosis of Niemann-Pick disease is based on the deficiency of ASM activity in peripheral leukocytes or in cultured skin fibroblasts/lymphocytes in the presence of characteristic clinical features. BAL shows numerous foamy macrophages (Niemann-Pick cells), helps to establish diagnosis and avoid lung biopsy in many patients.[102] On lung biopsy, finely vacuolated foamy macrophages are seen to fill the alveolar space along with the thickening of alveolar septa. Foamy macrophages also fill the lymphatic space around peripheral bronchioles, pulmonary artery branches and the interstitial tissues in subpleural area and interlobular septa. Pneumocytes and Clara cells remain unaffected.[102] Foamy changes have also been seen in ciliated epithelial cells. Inflammation and fibrosis are minimal and pulmonary architecture is usually preserved. In short, the histological picture can be described as diffuse endogenous lipoid pneumonia or alveolar proteinosis.[105]

Management

No specific therapy is available for ASM deficiency. Both ERT and gene therapy have shown promising results in the mouse model. Clinical trial of ERT in Niemann-Pick type disease is currently undergoing. Slow and inexorable progress is the natural history of respiratory disease. Treatment with whole lung lavage has been described with clinical improvement in isolated case reports.[105,108]

Hermansky-Pudlak Syndrome

Introduction

Hermansky-Pudlak Syndrome (HPS) is an autosomal recessive disorder characterized by the triad of oculocutaneous albinism, bleeding diathesis (secondary to defect in platelet function) and (in some cases) lysosomal accumulation of ceroid lipofuscin. Eight human subtypes have been described, each one resulting from mutation in one of eight different human genes. HPS has been described in many different ethnic groups; HPS1 is the most frequently described subtype; it is particularly common in individuals from North West Puerto Rico and accounts for approximately 50% of non-Puerto Rican cases. Mutations in both HPS1 and HPS4 genes have been described in Indian patients.[109,110]

Pathogenesis

The function of HPS genes is thought to involve intracellular vesicle formation and trafficking. The mutations of HPS genes cause defective formation, trafficking or function of intracellular lysosome-related organelles, e.g. melanosomes, platelet dense granules and lamellar bodies in alveolar type II pneumocytes.[111] A suggested mechanism for lung disease is that intracellular disruption of type II pneumocytes by ceroid deposition triggers a cascade of inflammation, cytokine production and fibroblast proliferation, leading to fibrosis. Interaction with external/environmental noxious stimuli has also been postulated to contribute to the development of fibrosis.

Pulmonary Manifestations

HPS causes interstitial lung disease. Pulmonary involvement has been described in HPS1 and HPS4.[109,112] Studies exploring pulmonary involvement in other subtypes of HPS are lacking. Lung fibrosis typically develops in the second or third decade of life in HPS1. In a series of 38 patients with HPS1, 61% had the onset of pulmonary symptoms at the mean age of 35 years.[113] However, a wide individual variability in clinical presentation and pulmonary function is known. Clinical presentation is akin to usual interstitial pneumonia: exertional dyspnea and dry cough are the usual presenting symptoms; physical examination is conspicuous for clubbing and velcro crepitations.[114]

Pulmonary function tests reveal restrictive physiology with reduced DL_{CO}. CXR shows bilateral reticulonodular opacities. HRCT scan shows septal thickening, ground glass pattern and mild reticulation in early cases; in the more advanced stages of disease, moderate to severe reticulation, traction bronchiectasis, subpleural cysts, and peribronchovascular thickening are seen. The changes have fairly even distribution within the lung zones with peripheral predominance.[115]

Diagnosis

This diagnosis can be suspected when a young patient presents with pulmonary fibrosis and shows typical ocular features, albinism and platelet dysfunction. Absence of platelet dense bodies on electron microscopy has been described as a rapid and reliable method of diagnosing HPS.[116] The diagnosis can also be established by the genotyping of DNA samples or the demonstration of ceroid accumulation in pathological specimens. Pathological examination of the lungs shows a picture of pulmonary fibrosis, architectural distortion and diffuse lymphocytic infiltration; in addition, a distinctive feature is the presence of large vacuolated histiocytes and pneumocytes containing periodic acid–Schiff (PAS) positive fine and coarse brown pigment within areas of interstitial fibrosis.[117] Numerous giant lamellar bodies can be seen in the macrophages and type II pneumocytes by ultrastructural examination. The fibrosis is also unevenly distributed without any subpleural or peribronchial predilection.

Management

Antifibrotic agent, pirfenidone has been tried in pulmonary fibrosis of HPS. Pirfenidone appears to slow progression of the disease when started at a stage when good residual function is still left.[118] As is true in many other chronic lung diseases, measures like the avoidance of smoking and environmental tobacco smoke, prompt treatment of respiratory infections, and administration of influenza and pneumococcal vaccines are recommended to preserve residual lung function.[113] In HPS patients with end-stage lung fibrosis, lung transplantation has been used successfully.[119]

Pulmonary fibrosis in HPS is usually fatal in fourth or fifth decade and accounts for death in ~50% of HPS patients.

Lipoid Pneumonia

Introduction

Lipoid pneumonia is a pattern of pathological involvement of lungs characterized by prominent deposition/filling of alveolar spaces with lipoid material. It can be called exogenous when the source of the aspirated lipoid material is from external sources and endogenous when the lipid deposition occurs without an exogenous source. Also called "cholesterol pneumonia," endogenous lipoid pneumonia typically occurs from accumulation of lipid-filled macrophages, surfactant and eosinophilic proteinaceous material derived from degenerating cells, in the alveoli distal to the bronchial obstruction. Diffuse intra-alveolar deposition of lipoprotein material, either as an idiopathic process or in the association of systemic diseases, e.g. chronic myeloid leukemia, is better termed pulmonary alveolar proteinosis (PAP). In this section, we will limit our discussion to exogenous lipoid pneumonia.

Pathogenesis

Exogenous lipoid pneumonia is an uncommon condition that occurs as a result of aspiration or inhalation of lipids: mineral oils (hydrocarbons obtained from petroleum), vegetable-based oils or animal fats. Mineral oils and vegetable-based oils cause milder inflammatory reactions with local encapsulation and fibrosis; animal fats, on the other hand, are hydrolyzed by lung lipases and the resultant free fatty acids trigger a severe inflammatory reaction, both in the alveolar space and the interlobular septa. Progression to fibrosis and end-stage lung disease may occur.

Risk Factors

Exogenous lipoid pneumonia has been reported in two settings: ingestion of paraffin for chronic constipation and the use of oily nasal preparations for rhinopharyngeal obstruction (often as a part of folk remedies).[120] In both scenarios, it involves aspiration of mineral oil that cannot be cleared by the lungs. Patients with the high risk of aspiration, due to anatomic or functional alterations of swallowing, such as patients with achalasia, gastro-esophageal reflux, scleroderma, Zenker diverticulum, and neurological and psychiatric disorders, etc. are at the increased risk of exogenous lipoid pneumonia. Accidental aspiration of isoparaffin and the development of exogenous lipoid pneumonia have also been reported as a peril of fire eating as a recreational activity.[121,122] Exogenous lipoid pneumonia, usually in the chronic form, has been described in a variety of industrial occupations involving the lubrication and cleaning of machinery and the spraying of pesticides or paints. It has also been reported as a result of embolization following rectal or subcutaneous administration of mineral oils. Rarely, it has been reported as a consequence of substance abuse, e.g. the inhalation of crack cocaine mixed with petroleum jelly or smoking of weed oil.[123,124]

Clinical Presentation

The clinical presentation depends on the volume and acuity of the aspiration episode(s). Acute exogenous lipoid pneumonia results as a consequence of aspiration of large amount of oil/hydrocarbons, e.g. accidental poisoning in children. Here the presentation is with acute respiratory symptoms: cough, respiratory distress and low-grade fever. Repeated aspirations of small amounts of lipids result in the chronic form of exogenous lipoid pneumonia. Here the onset of symptoms is insidious with chronic cough and/or dyspnea; fever, weight loss, chest-pain and hemoptysis are less common at presentation.[120,125] Often the presentation is that of nonresolving pneumonia. Sometimes, the patient may be present with chronic fibrosis. Auscultation of lungs may be normal or may reveal crepitations or wheezes. Lung function can be normal or may show a restrictive pattern, with reduced DL_{CO}.

Imaging Features

Different radiological patterns can be seen in the cases of lipoid pneumonia. In acute cases, radiological changes develop within the first few hours and usually within 24 hours. CXR and CT scan show: a. focal or multifocal consolidation with air bronchogram; b. areas of ground glass haziness; c. CT lesions typically with negative attenuation values (HU<0); d. pneumatoceles (as a late complication); e. pneumomediastinum, pneumothorax, and pleural effusions (rarely). The changes predominate in lower and middle lobes and are segmental or lobar in distribution. The radiologic manifestations of acute exogenous lipoid pneumonia improve or resolve over a variable period of time. Chronic lipoid pneumonia may show: a. multiple areas of low-attenuation consolidation (Figs 98.5A to D); b. areas of ground glass with septal thickening giving rise to a "crazy pavement" pattern; c. single or multiple nodules or masses resembling primary or metastatic lung cancer; d. predominant peribronchovascular and lower lobe distribution; e. architectural distribution and fibrosis in late cases.[126-130] False positive result with ^{18}F fluorodeoxy-D-glucose (FDG) positron emission tomography (PET) scan has been reported and may raise the suspicion of lung cancer.[128,131] The radiological manifestations of chronic lipoid pneumonia remain stable or slowly improve over time if exposure can be halted.

Diagnosis

Making a diagnosis of lipoid pneumonia requires a high degree of clinical suspicion and meticulous history taking. Diagnosis is difficult as the aspiration episodes are often unrecognized and clinical and radiological features mimic many other pulmonary diseases. On CT scan, the demonstration of fat-density areas within the lesions is considered diagnostic of lipoid pneumonia. Diagnosis can be confirmed by BAL. Fat globules are found in the bronchoalveolar fluid; cytological examination of the BAL fluid shows presence of lipid laden foamy macrophages.[132] Lung biopsy specimens show alveoli filled with macrophages containing lipid vacuoles (Fig. 98.6). Advanced lesions show larger lipid vacuoles surrounded by inflammatory infiltrates. Formation of giant cells and fibrosis are also seen.[133]

Management

Prompt identification and prevention of further aspiration prevent the progression of the disease, and in some cases allow resolution.[120,134] Anecdotal case reports of improvement with steroids are there; the beneficial effects in these cases may be attributed to the effect of steroids on the inflammatory process in lipoid pneumonia.[135-137] Similar results, however, have not been supported in data from large series.[120] Bronchoscopy with therapeutic BAL for the clearance of mineral oil from the lung parenchyma has been reported as the treatment for this condition. This strategy can lead to improvement in lung function, can prevent fibrosis and reduce the morbidity from lipoid pneumonia. Use of a fat emulsifier (sorbitan monooleate) during the lung lavage has also been reported.[138-140] BAL may not be effective in all cases, particularly in the chronic ones; each individual case should be carefully reviewed to decide whether therapeutic lavage will be effective.[120] The prognosis is generally good in most of the cases. However, complications like fibrosis, lung abscess formation, pleural effusion, bronchopulmonary fistula and bacterial/mycobacterial/fungal superinfection may occur. Infections with mycobacterial species like *M chelonae* and *M fortuitum* and fungal pathogens like *Aspergillus fumigates, Nocardia species,*[141,142] have been reported. These infections should be looked for when appropriate and treated.

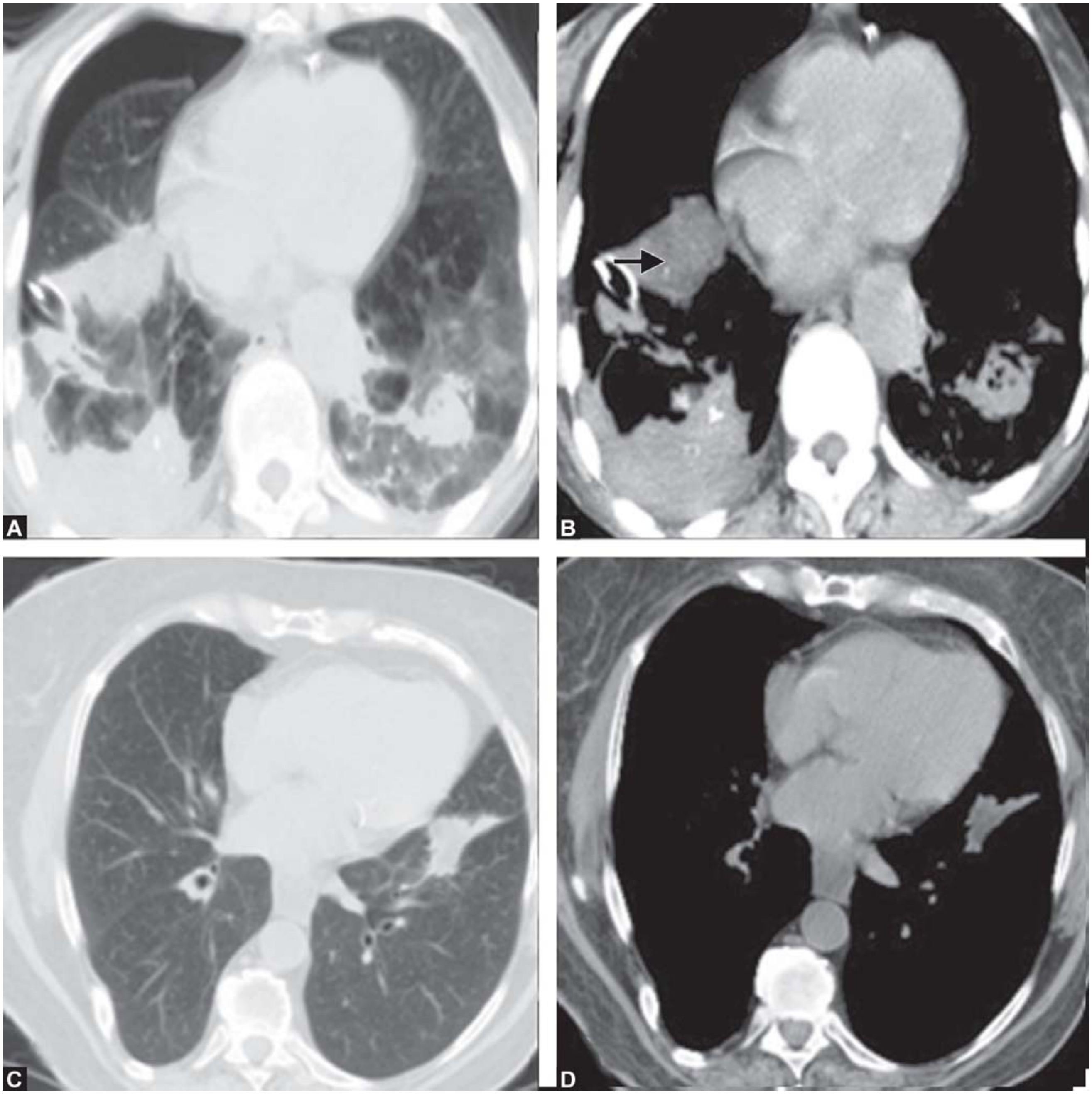
Idiopathic Pulmonary Hemosiderosis

Introduction

Idiopathic pulmonary hemosiderosis (IPH) is an uncommon disease of unknown etiology characterized by the repetitive episodes of diffuse alveolar hemorrhage (DAH). The causes of DAH are diverse and other causes need to be excluded before a diagnosis of IPH can be reached.

Pathogenesis

The etiology of IPH remains unknown. Several theories have been proposed.[143] Familial clustering has been reported, which may suggest the inheritance of a rare genetic defect, predisposition and common exposure to environmental antigens. Suggestions of an autoimmune pathogenesis are based on indirect evidences like the presence of circulating immune complexes and the development of other autoimmune diseases in many patients of IPH who survive for more than a decade. An allergic theory has been proposed based on presence of antibodies against cow milk and coexistence with celiac disease.[144,145] Reports of the potential association of IPH and exposure to insecticides or fungal toxins have never been conclusively proven. A metabolic role of toxic oxidative radicals is likely to perpetuate lung



Figs 98.5A to D: CT scan appearance of lipoid pneumonia: A. Lung window showing multiple bilateral areas of alveolar consolidation/nodule. (*Note:* Right pneumothorax following CT guided lung biopsy); B. Mediastinal window showing an area of low attenuation within the consolidation (arrow); C. Small area of consolidation in left upper lobe; D. Mediastinal window from the same case showing an area of low attenuation. (*Courtesy:* Dr Linda Haramati, Professor of Radiology, Albert Einstein College of Medicine, Bronx, New York, USA [Figs 98.5 A and B]. Dr Rakesh Shah, Consultant radiologist, North Shore University Hospital, Manhasset, New York, USA [Figs 98.5C and D])

pathology in IPH. Alveolar macrophages have only a limited capacity for iron metabolism. After an episode of DAH, alveolar macrophage apparatus becomes exhausted and excess free iron can be present in the alveoli; within the alveoli, the free iron leads to the formation of highly reactive hydroxyl radicals, eventually leading to damage to alveolar structure and fibrosis.[146,147]

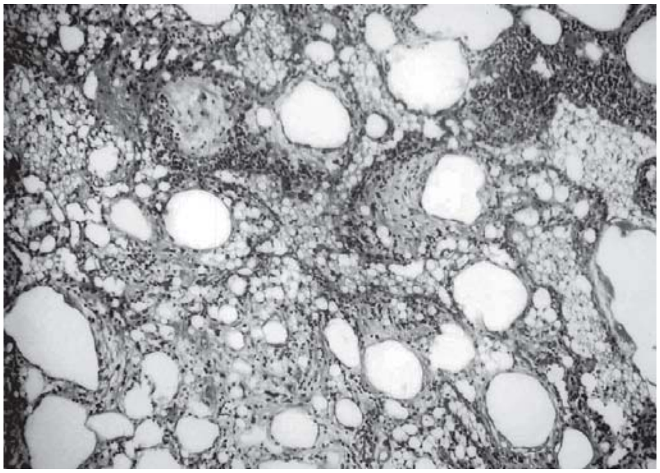


Fig. 98.6: Lung biopsy showing an area of lipoid pneumonia with large vacuoles surrounded by histiocytes in the interstitium (From *Reference 128* with permission) [hematoxylin and eosin stain; magnification: 100X]

Clinical Presentation

About 80% of all cases of IPH occur in children, most of them being diagnosed in the first decade of life.[148] The rest of the cases are diagnosed in young adults, some of which may have remained undiagnosed till the adulthood.[143] Among adult patients, slight male preponderance is found. The clinical presentation widely varies. Some patients have a fulminant presentation with catastrophic DAH and respiratory failure. Some patients are present with the nonspecific symptoms of chronic cough and dyspnea. Recurrent hemoptysis is yet another presentation.[149] Patients may be present with symptomatic or asymptomatic anemia without any respiratory symptoms.[150] All adult patients report hemoptysis at some point of time. As the alveolar hemorrhage is intermittent, the waxing and waning of symptoms are usual in the clinical course. Exacerbations can occur during the tapering of steroids/immunosuppressive therapy. Other factors causing exacerbations are not clearly known. Fulminant DAH has been reported in the peripartum period.[151]

Pulmonary function tests reveal a pattern of restrictive ventilatory defect. Increased DL_{CO} is the hallmark abnormality in pulmonary function tests during an acute episode of DAH. When chronic changes of the disease, e.g. fibrosis sets in, DL_{CO} is low or normal.[152,153]

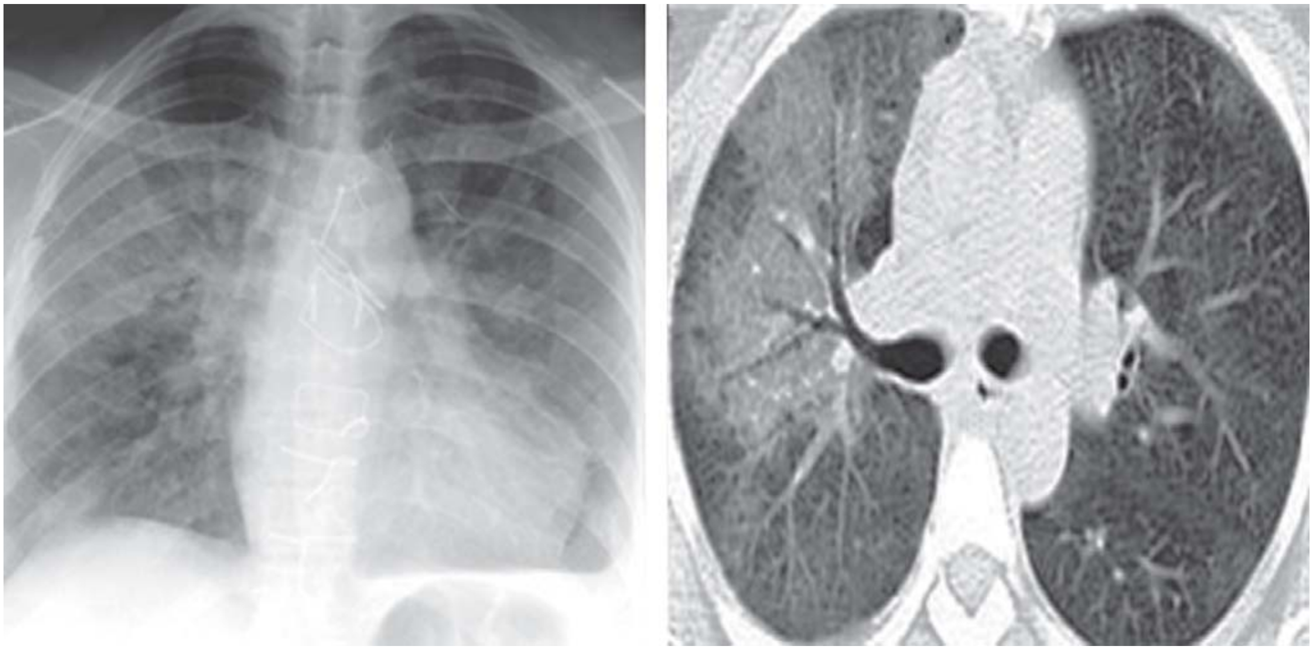
Laboratory and Radiological Features

Investigations often reveal hypochromic microcytic anemia, a reflection of repeated DAH, binding of iron with pulmonary hemosiderin (an unusable form) and iron loss in the sputum. Plasma ferritin level does not reflect the iron deficiency state, it is normal or elevated as a result of alveolar synthesis and subsequent release into the circulation of ferritin.[154] Bone marrow examination is consistent with an iron deficiency state. During or few days before an episode of bleeding, peripheral blood neutrophilia and eosinophilia may be seen.[155] During an acute phase of IPH, CXR reveals diffuse alveolar opacities and HRCT reveals bilateral ground glass opacities (Figs 98.7A and B). After multiple episodes of bleeding, chronic changes, evident as reticulonodular interstitial shadows, are seen on HRCT. Variable amount of fibrosis eventually develops.[156-158]

Diagnosis

Proof of intrapulmonary hemorrhage is an essential part of diagnosis of IPH. History of repeated episodes of cough, dyspnea and hemoptysis along with a consistent picture on CXR and HRCT, point towards the diagnosis. The demonstration of hemosiderin-laden macrophages in the sputum or in the BAL fluid confirms alveolar hemorrhage. Sometimes, the pulmonary hemorrhage is occult and the patient presents with iron deficiency anemia only; a comprehensive investigation of the cause is required before a diagnosis of IPH is suspected and established.[150,155] Serological studies for the markers of autoimmune diseases, e.g. antinuclear factor (ANF), antidouble-stranded DNA, antineutrophilic cytoplasmic antibody (ANCA, both perinuclear and cytoplasmic variants), antiglomerular basement membrane (GBM) antibody, antiphospholipid antibodies, IgG and IgE cow's milk antibodies and rheumatoid factor (RF) are negative.

A lung biopsy is required to rule out other causes of DAH. Transbronchial lung biopsy may be tried initially, if inadequate, video-assisted thoracoscopic biopsy or open lung biopsy can be obtained to get adequate tissue for study. Characteristic light microscopic features of IPH include: 1. the presence of intact or minimally fragmented erythrocytes in the distal airways and alveoli, an indication of recent alveolar hemorrhage; 2. hemosiderin-laden macrophages as an evidence of recurrent alveolar hemorrhage; 3. absence of vasculitis, granuloma, vascular malformation, neoplasm, infections, pulmonary infarct or evidence of any other lung disease. Thickening of the alveolar septae with the evidence of interstitial fibrosis is seen in the longstanding cases. Immunofluorescence and immunohistochemistry studies do not show any immunoglobulin or immune complex deposition, an important step to rule out autoimmune diseases causing



Figs 98.7A and B: Idiopathic pulmonary hemosiderosis: CXR and CT scan showing bilateral ground glass opacity (*Courtesy:* Dr Linda Haramati, Professor of Radiology, Albert Einstein College of Medicine, Bronx, New York, USA.)

DAH.[159,160] Some authors suggest that celiac disease should be routinely looked for in patients with IPH.[144]

Management

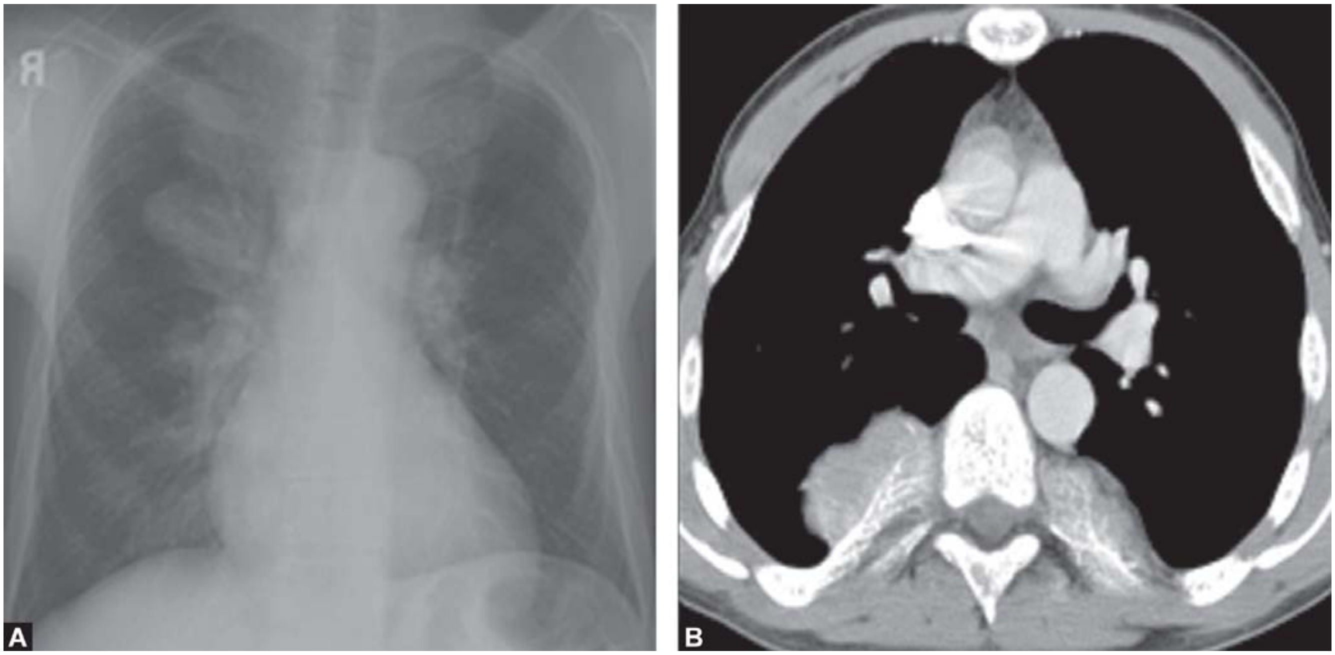
Systemic glucocorticoids remain the mainstay of treatment. Occasional reports of the successful use of inhaled corticosteroids are there, but the strength of evidence is not sufficient to support their use as a routine therapy.[143,161] Treatment, when started during an acute phase, helps to control symptoms and reduce mortality. Once started during the acute phase, steroids are continued till the new pulmonary infiltrates have resolved. A slow taper-off over a few months follows, if symptoms do not recur. Corticosteroids, when chronically administered, reduce the number of acute episodes and the occurrence of pulmonary fibrosis.[162,163] The indefinite administration of glucocorticoids, however, may lead to troublesome adverse effects; in some cases, symptoms may not be adequately controlled by corticosteroids. As maintenance therapy, various immunosuppressive agents, e.g. azathioprine, cyclophosphamide and chloroquine have been tried with or without corticosteroids, with variable success.[149,159,164-167] Cyclophosphamide infusion has been tried with success as a salvage therapy in IPH exacerbation with life-threatening DAH.[168] IPH patients, who had advanced chronic lung disease requiring lung transplantation, had recurrence of disease in the transplanted lung.[169]

Prognosis

IPH patients have substantial mortality from acute, severe DAH and significant morbidity from the recurrent episodes of bleeding and chronic lung disease. Prognosis and mortality vary in the reported literature.[163,170,171] In general, better outcome has been reported when prolonged immunosuppressive therapy has been used.[163] Prognosis is better in adult patients than in children and adolescents. No other clinical or biological parameter predicts prognosis in IPH.

Intrathoracic Extramedullary Hematopoiesis

In many hematological disorders, such as thalassemia, sickle-cell anemia, hereditary spherocytosis, polycythemia vera and myelofibrosis, intense compensatory hematopoiesis leads to the formation of foci of extramedullary hematopoiesis. Extramedullary hematopoiesis can be present within the thoracic cavity, described most frequently in patients with sickle-cell anemia and thalassemia.[172,173] Intrathoracic extramedullary hematopoiesis appears as paravertebral and/or paracostal masses. Formation of these masses occurs from the extrusion from the bone marrow through the cortex. A common site in the thorax is the costovertebral junction leading to a paraspinal mass. These masses have smooth, sharply defined margins, may be unilateral or bilateral in distribution (Figs 98.8A and B). No erosion of the adjacent



Figs 98.8A and B: Extramedullary intrathoracic hematopoiesis. CXR and CT scan showing bilateral multiple paraspinal soft tissue density opacities (*Courtesy:* Dr Rakesh Shah, Consultant radiologist, North Shore University Hospital, Manhasset, NY, US)

bone is seen. The masses may show initial rapid growth and subsequently remain stable in size. The patients usually do not have any symptoms attributable to the masses.[174]

Occasional cases with symptoms due to mass effect from the large foci of extramedullary hematopoiesis and other complications, e.g. exudative pleural effusion, hemothorax have been described.[172,175,176] In the case of presentation as intrathoracic masses, classic location and clinical setting make the diagnosis obvious; invasive diagnostic studies should be avoided. In symptomatic cases, a variety of treatment options may be tried. Blood transfusion (hypertransfusion) and hydroxyurea have been used with improvement in symptoms and should be the first line of treatment.[172,175] In cases where the lesions do not respond to the above, radiotherapy and surgical resection remain other treatment options. Pleural effusion and hemothorax are managed with pleural drainage and pleurodesis.[177]

Neurofibromatosis

Von Recklinghausen's disease or neurofibromatosis type 1 (NF) is an autosomal dominant disorder with characteristic neurocutaneous manifestations. Neurofibromatosis causes ILD. In an analysis of 64 cases of ILD in neurofibromatosis patients, the mean age of presentation of 50 years and a male preponderance was reported.[178] Most NF patients with lung involvement by ILD report dyspnea. Pulmonary function tests show an obstructive pattern with reduced DL_{CO}. CXR and HRCT show bilateral cystic lesions with upper lobe predominance.[179] Other radiological findings include ground-glass opacities, bibasilar subpleural reticular opacities and bullae. On pathological specimens, the involvement is patchy; areas of normal lung alternate with the areas of interstitial involvement. In the involved areas, the alveolar septae demonstrate lymphoplasmacytic inflammation and fibrosis consistent with nonspecific idiopathic pneumonia (NSIP) pattern. The etiological role of smoking in NF related ILD is debated, it has been suggested that smoking is the actual risk factor for the development and severity of ILD in NF patients.[180,181]

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Section

12

DISORDERS DUE TO ENVIRONMENTAL AND CLIMATE FACTORS

SK Jindal

99

Outdoor Air Pollution and Respiratory Health

Sara Maio, Sandra Baldacci, Marzia Simoni, Fabio Cibella, Giovanni Viegi

INTRODUCTION

According to the Department of Chronic Diseases and Health Promotion of the World Health Organization (WHO), main chronic diseases include cardiovascular diseases (30% of projected total worldwide deaths in 2005), cancer (13%), chronic respiratory diseases (7%) and diabetes (2%). Chronic diseases are often defined as problems of ageing communities mainly caused by tobacco use, unhealthy diet and physical inactivity.[1] According to WHO, in Europe 86% of deaths are caused by chronic diseases.[2] However, chronic diseases are a large problem in low-income countries also (especially among those who do not have the resources to improve the quality of life). Recent evidence highlighted that deaths from cardiopulmonary diseases and lung cancer occur at earlier ages in low- and middle-income countries, where prevention is not a priority. It has been estimated that 35 million people died in 2005 due to stroke, cancer, and heart, respiratory and other chronic diseases. Only 20% of these deaths were in high-income countries, while 80% were in low- and middle-income countries.[3]

In an estimate of the proportions of total deaths and disability-adjusted life years (DALYs) lost in India, it was estimated that 53% of deaths were caused by chronic diseases, compared with 61% of deaths over the world, in 2005. Moreover, chronic diseases caused 44% of DALYs.[4] Compared to India, China showed higher estimates for chronic diseases mortality (80%) and DALYs (70%); there was the highest rate of death from chronic disease in middle-aged people.[5]

Using the WHO 2002 mortality estimates as a baseline, globally, about 58 million people died of chronic diseases in 2005.[3] This value is projected to rise to 64 million in 2015. The distribution of these deaths across three major cause groups showed a mortality of 30% for communicable, maternal, perinatal conditions, and nutritional deficiencies, of 61% for chronic and noncommunicable diseases and of 9% for injuries. In detail, respiratory diseases are the third leading single-cause of death worldwide (7%).[3]

OUTDOOR AIR POLLUTION EFFECTS

Air pollution represents an important risk factor for respiratory diseases. The statement of the American Thoracic Society published in the year 2000 was aimed at enlisting the respiratory health effects of air pollution, emphasizing the interpretation of the epidemiological evidence. The statement recognized the spectrum of responses to air pollution, which has been characterized as a pyramid, with the most common consequences of exposure (increased prevalence and incidence of respiratory symptoms/diseases, reduction of lung function, etc.) at the base and mortality, the least common and most severe consequence, at the tip.[6]

At the population level, respiratory diseases and related mortality have been increasingly associated with exposure to air pollutants. In the last years, the research about the effects of particulate matter (PM) with aerodynamic diameter <10 µm (PM_{10}) or <2.5 µm ($PM_{2.5}$) in relation to death for cardiopulmonary causes, originated much interest in the scientific community.

There is now firm evidence that PM, at low levels, has major effects on respiratory and on cardiovascular system, that traffic is a major source of harmful PM and

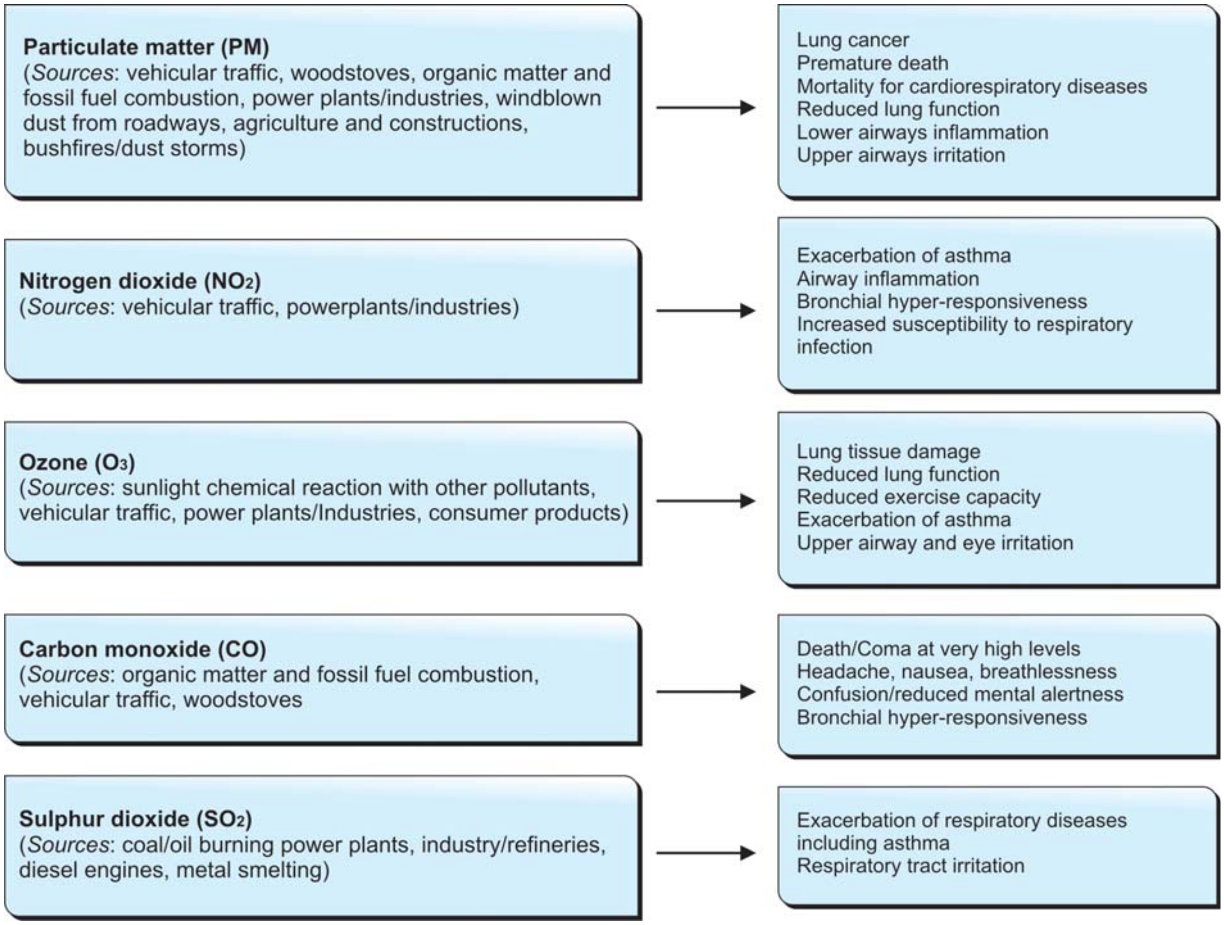
Particulate matter (PM)
(Sources: vehicular traffic, woodstoves, organic matter and fossil fuel combustion, power plants/industries, windblown dust from roadways, agriculture and constructions, bushfires/dust storms)
Lung cancer
Premature death
Mortality for cardiorespiratory diseases
Reduced lung function
Lower airways inflammation
Upper airways irritation
Nitrogen dioxide (NO2)
(Sources: vehicular traffic, powerplants/industries)
Exacerbation of asthma
Airway inflammation
Bronchial hyper-responsiveness
Increased susceptibility to respiratory infection
Ozone (O3)
(Sources: sunlight chemical reaction with other pollutants, vehicular traffic, power plants/Industries, consumer products)
Lung tissue damage
Reduced lung function
Reduced exercise capacity
Exacerbation of asthma
Upper airway and eye irritation
Carbon monoxide (CO)
(Sources: organic matter and fossil fuel combustion, vehicular traffic, woodstoves
Death/Coma at very high levels
Headache, nausea, breathlessness
Confusion/reduced mental alertness
Bronchial hyper-responsiveness
Sulphur dioxide (SO2)
(Sources: coal/oil burning power plants, industry/refineries, diesel engines, metal smelting)
Exacerbation of respiratory diseases including asthma
Respiratory tract irritation

Fig. 99.1: Main respiratory health effects by common outdoor pollutants

that public health improves in areas where PM pollution has been reduced (Fig. 99.1). Other important air pollutants are: "black smoke (particulates produced by fossil fuel) (BS)", carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen oxides (NO_x) (products coming from vehicular-traffic and combustion processes), and ozone (O_3) (originated by photochemical reactions correlated to urban traffic) (Fig. 99.1).

Long-Term Effects

Many epidemiological surveys have shown that the long-term exposure to outdoor air pollutants is strongly associated with detrimental effects on respiratory health. In particular, a 16 year follow-up study carried out in US metropolitan areas on over half million people has evidenced that each 10 $\mu g/m^3$ elevation in fine particulate air pollution ($PM_{2.5}$) was associated with approximately a 6%, 9%, and 14%, increased risk of all-cause, cardiopulmonary and lung cancer mortality, respectively[7] (Table 99.1).

An European confirmation of the association between long-term air pollution exposure and cardiopulmonary mortality comes from a Dutch cohort (n=4492), where cardiopulmonary mortality was associated with living near a major road (relative risk 1.95, 95% CI 1.09–3.52) and, less consistently, with the estimated ambient background concentration (relative risk 1.34, 95% CI 0.68–2.64)[8] (Table 99.1).

The results of the investigation, the concentration-response relation of NO_2, PM_{10} and $PM_{2.5}$ with cause-specific mortality among all inhabitants of Oslo (Norway) suggest that the elderly and patients with chronic obstructive pulmonary disease (COPD) may have an increased risk of mortality at lower levels of pollutants with respect to general population.[9] Similarly, the results of study on the relation between long-term exposure to traffic air pollution and lung

TABLE 99.1: Long-term effects of outdoor air pollution (mortality and lung function)

Study	*Population sample investigated*	*Health outcome*	*Exposure*	*Measures (95% CI)*
Pope CA, 2002[7]	500.000 adults United States	Mortality: all-cause cardiopulmonary lung cancer	$PM_{2.5}$ (μg/m^3)	RR for an increase of 10 μg/m^3 of $PM_{2.5}$: 1.06 (1.02-1.11) 1.09 (1.03-1.16) 1.14 (1.04-1.23)
Hoek G, 2002[8]	4,492 subjects (55-69 years) Netherlands	Cardiopulmonary mortality	Living near major road	RR: 1.95 (1.09-3.52)
Gauderman WJ, 2004[12]	1,759 children (10-18 years) California	Clinical decrease of FEV_1	NO_2 (ppb) $PM_{2.5}$ (μg/m^3)	Correlation between average level, over eight-year period, of pollutants and low FEV_1
Shikowski T, 2005[10]	4,757 women (55 years) Germany	Pulmonary function and COPD	NO_2 (μg/m^3) PM_{10} (μg/m^3)	OR for an IQR range increase of pollutants (16 μg/m^3 NO_2; 7 μg/m^3 PM_{10}): 1.43 (1.23-1.66) 1.33 (1.03-1.72)
Gauderman W, 2007[11]	3,677 children California	Lung-function growth	Living near a freeway (500 m)	FEV_1: –81 mL, (–143 to –18) MMEF: –127 mL/s, (–243 to –11)
Rosenlund M, 2009[13]	1,195 children (9-14 years) Rome	Lung function	NO_2 (μg/m^3)	Changes for 10 μg/m^3 $NO_{2:}$ FEV_1/FVC: -0.62% (–1.05 to –0.19) FEF_{25-75}: -62 mL/s (–102 to –21) PEF: -85 mL/s (–135 to –35)

RR, relative risk; OR, odds ratio; PM_{10} and $PM_{2.5}$, particulate matter with aerodynamic diameter <10 μm and <2.5 μm respectively; NO_2, nitrogen dioxide; MMEF, maximum midexpiratory flow rate; FEF_{25-75}, forced expiratory flow between 25 and 75% of forced vital capacity; PEF, peak expiratory flow; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile; 95% CI, 95% confidence interval

function and exacerbations of COPD, showed that exacerbations of COPD were associated with a 7 μg/m^3 increase in five years mean of PM_{10} (interquartile range) [odds ratio (OR) 1.33, 95% CI 1.03–1.72] and with a 16 μg/m^3 increase in five years mean of NO_2 (interquartile range) (OR 1.43, 95% CI 1.23–1.66). Moreover, women living less than 100 meters from a busy road also had a significantly decreased lung function; among them, COPD was 1.79 times more likely (95% CI 1.06–3.02) than for those living farther away[10] (Table 99.1).

Analogous results were found in a sample of about 3,000 Californian children: those who lived within 500 m of a freeway had substantial deficits in 8-year growth of forced expiratory volume in one second (FEV_1) and maximum midexpiratory flow rate, compared with children who lived at least 1,500 m from a freeway[11] (Table 99.1).

The same research group following up children from the age of 10 to 18 years indicated that the current levels of air pollution have chronic adverse effects on lung development, leading to clinically significant deficits in maximal attained FEV_1 level as children reach adulthood, especially in boys. In particular there was a significant positive correlation between the deficit in the FEV_1 attained at the age of 18 years and the average level of exposure to NO_2 and $PM_{2.5}$[12] (Table 99.1).. In Italy, a strong association between estimated NO_2 exposure per 10 μg/m^3 increase and lung function decrease in children exposed to traffic-related air pollution was observed.[13] The exposure to air pollution is also associated with allergic respiratory symptoms/diseases. The detrimental effects of living near busy streets on respiratory health were confirmed by the results of the Swiss Cohort Study on Air Pollution and

Lung Diseases in Adults (SAPALDIA): living within 20 m of a main street increased the risks of regular phlegm by 15% (95% CI 1.00–1.31) and wheezing with breathing problems by 34% (95% CI 1.00–1.79) in never smokers[14] (Table 99.2).

More recently, associations between residential traffic and asthma and COPD in adults in southern Sweden were examined; the results showed that living within 100 m of a heavy road was associated with the prevalence of asthma diagnosis (OR 1.40, 95% CI 1.04–1.89), and

TABLE 99.2: Long-term effects of outdoor air pollution (respiratory symptoms/diseases)

Study	*Population sample investigated*	*Health outcome*	*Exposure*	*Measures (95% CI)*
Mi YH, 2006[19]	1,414 children (13-14 years) China	Current asthma	NO_2 (μg/m^3)	OR for an increase of 10 μg/m^3 of NO_2: 1.44 (1.06-1.95)
Hwang BF, 2006[20]	32,143 schoolchildren Taiwan	Allergic rhinitis		OR for 10 ppb change of SO2, NOx, and 100 ppb change of CO:
			SO_2 (ppb)	1.43 (1.25-1.64)
			CO (ppb)	1.05 (1.04-1.07)
			NO_x (ppb)	1.11 (1.08-1.15).
Bayer-Oglesby L, 2006[14]	8,407 subjects Switzerland	Phlegm	Living near major road (20 m)	OR: 1.15 (1.00-1.31)
		Wheezing with breathing problems (in never smokers)		1.34 (1.00-1.79)
Annesi-Maesano I, 2007[18]	5,000 schoolchildren France		$PM_{2.5}$ (μg/m^3)	OR for an increase of 10 μg/m^3 of $PM_{2.5}$:
		Asthma		1.31 (1.01-1.66)
		Atopic asthma		1.58 (1.17-2.14)
Brauer M, 2007[21]	4,000 children (0-4 years) Netherlands			OR for an IQR range increase in annual average concentration:
		Wheeze	NO_2 (μg/m^3)	1.19 (1.05-1.34)
			$PM_{2.5}$ (μg/m^3)	1.22 (1.06-1.41)
		Asthma	NO_2 (μg/m^3)	1.28 (1.04-1.56)
			$PM_{2.5}$ (μg/m^3)	1.32 (1.04-1.69)
Padhi BK, 2008[16]	750 adults India	Asthma diagnosis	Living near major road (0.5 Km)	OR: 3.57 (3.00-3.95)
			Living near major road (1 km)	3.00 (2.85-3.50)
Lindgren A, 2009[15]	9,316 subjects (18-77 years) Sweden		Living near major road (100 m)	OR:
		Asthma diagnosis		1.40 (1.04-1.89)
		COPD diagnosis		1.64 (1.11-2.41)
Maio S, 2009[17]	2,760 subjects (8-74 years) Italy	Increased bronchial responsiveness	Urban residence	OR: 1.41 (1.13-1.76)
Migliore E, 2009[22]	33,632 children (6-7 yrs) and adolescents (13-14 years) Italy		Living in zone with:	OR:
		Asthma symptoms	continuous cars transit	1.16 (1.00-1.33)
		Cough or phlegm		1.32 (1.08-1.63)
		Asthma symptoms	continuous trucks transit	1.27 (1.08-1.50)
		Cough or phlegm		1.67 (1.36-2.06)

OR, odds ratio; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide; NO_x, nitrogen oxide; COPD, chronic obstructive pulmonary disease; IQR, interquartile; 95% CI, 95% confidence interval

COPD diagnosis (OR 1.64, 95% CI 1.11–2.41)[15] (Table 99.2). A recent study assessed the association between exposure to air pollutants in a suburban area of India and the prevalence of asthma and respiratory disorders. Compared to subjects staying 5.0 km away from a main road, those subjects living within 0.5 km and 1.0 km showed an OR for doctor-diagnosed asthma of 3.57 (95% CI 3.00–3.95), and 3.00 (95% CI 2.85–3.50), respectively. The authors concluded highlighting the necessity to perform prospective studies considering the continuing rise in motorized vehicle use in India[16] (Table 99.2).

A study performed on two general population samples living in Northern Italy (rural area) and Central Italy (urban area) (areas with mean annual levels of total suspended particulate of 54 µg/m^3 and 94 µg/m^3, and values of sulfur dioxide of 8 µg/m^3 and 15 µg/m^3, respectively) pointed out that people living in urban area have an higher risk of having increased bronchial responsiveness (OR 1.41, CI 95% 1.13–1.76) with respect to people living in the rural area[17] (Table 99.2). A study in about 5,000 school children, living in six French cities, showed an important association between living in residential settings with $PM_{2.5}$ concentrations exceeding 10 µg/m^3 and asthma (OR 1.31, 95% CI 1.04–1.66) and atopic asthma (OR 1.58, 95% CI 1.17–2.14); this association was strengthened in long-term residents (current address for at least 8 years)[18] (Table 99.2).

Similar results were found in about 1,400 school children living in Shanghai for current asthma for 10 µg/m^3 increase in NO_2[19] and in 32,143 Taiwanese school children showing the prevalence of allergic rhinitis to be significantly associated with SO_2[20] (Table 99.2).

This results were confirmed in a Dutch birth cohort (n = 4000) that reported significant association between outdoor concentrations of traffic-related air pollutants ($PM_{2.5}$ and NO_2) and wheeze and asthma developed during the first four years of life[21] (Table 99.2). Recently, an Italian multicenter study (SIDRIA-2) showed independent association between car/truck traffic and current asthma symptoms and cough or phlegm; the stronger associations were found with truck traffic[22] (Table 99.2).

Short-Term Effects

Scientific evidence of the health effects of air pollution is not limited to studies of long-term exposure. In several cities throughout the world, consistent associations emerged between daily mortality, hospital admissions, emergency department (ED) visits and air pollutants concentration during the same or the previous few days. For the warm season, an increase in the 8-hour ozone concentration by 10 µg/m^3 was associated with a 0.31% (95% CI 0.17–0.52) increase in the total daily number of deaths, 0.46% (95% CI 0.22–0.73) in the number of cardiovascular deaths and 1.13% (95% CI 0.74–1.51) in the number of respiratory deaths[23] (Table 99.3).

In a study on the effect of $PM_{2.5}$ exposure on mortality in the nine cities of California, USA, for every increase of 15 µg/m^3 of $PM_{2.5}$, there was an increase of 0.61% (95% CI 0.18–1.04), 0.70% (95% CI 0.07–1.33) and 2.05% (95% CI 0.02–4.12) of total, cardiovascular and respiratory mortality, respectively[24] (Table 99.3). More recently, a time-series study of the acute effect of $PM_{2.5}$ and PM coarse on the increased risk of death for all causes, cardiovascular disease and respiratory diseases for the years 1999-2005 in 112 US cities showed a 0.98% increase (95% CI 0.751.22) in total mortality, a 0.85% increase (95% CI 0.461.24) in cardiovascular and a 1.68% increase (95% CI 1.04-2.33) in respiratory mortality for a 10-µg/m^3 increase in 2-day averaged $\mathbf{PM_{2.5}}$[25] (Table 99.3).

The association between daily air pollution levels ($PM_{10,}$ PNC–particle number concentration –CO, NO_2, O_3) and the occurrence of fatal, non-hospitalized coronary events was evaluated (referred the association); the association was statistically significant for PNC, PM_{10} and CO. The effect was stronger among people over 65 years of age, but was not limited to a group with specific comorbidity, even if there was a major risk in subjects with COPD[26] (Table 99.3).

The MISA study (the Italian Meta-analysis of Short-term effect of Air pollution) dealt with the effect of the exposure to air pollution in 15 Italian cities, summing up to 9.1 million inhabitants at the 2001 census. The results showed an increase of mortality for all natural causes associated to the increase of air pollutants concentration. Similar findings were found for cardiorespiratory mortality and hospital admissions for respiratory and cardiac diseases[27] (Table 99.3).

In Shanghai, China, a time-series analysis to assess the effects of major air pollutants and daily mortality, was also conducted. In the single-pollutant models, an increase of 10 µg/m^3 of PM_{10}, SO_2, NO_2 was associated with mortality from all causes and from cardiopulmonary diseases; a significant effect was found on daily mortality for NO_2 and SO_2 after adjusting for PM_{10}, in the multipollutants model[28] (Table 99.3). Another study performed in Shanghai assessed the association between outdoor air pollutants (PM_{10}, SO_2, and NO_2) and total hospital outpatient visits. In particular, for lag 3 (pollutant concentration level three days before

TABLE 99.3: Short-term effects of outdoor air pollution (mortality)

Study	*Population sample investigated*	*Health outcome*	*Exposure*	*Measures (95% CI)*
Biggeri A, 2004[27]	9.1 million subjects 15 Italian cities (MISA)	Daily mortality: total		Increase % for an increase of 10 μg/m^3 of NO_2 and PM_{10} and of 1 μg/m^3 of CO:
			NO_2 (μg/m^3)	0.6 (0.3-0.9)
			PM_{10} (μg/m^3)	0.31 (0.2-0.7)
			CO (mg/m^3)	1.2 (0.6-1.7)
Gryparis A, 2004[23]	> 50 million adults 23 European cities (APHEA 2)	Daily mortality:	O_3 (μg/m^3)	Increase % of mortality for an increase of 10 μg/m^3 of O_3:
		total		0.31 (0.17-0.52)
		respiratory		1.13 (0.74-1.51)
		cardiovascular		0.46 (0.22-0.73)
Forastiere F, 2005[26]	5,144 subjects died out of hospital Italy (Rome)	Fatal, nonhospitalized coronary events		Increase % in risk for IQR range increase of pollutants (27.8 particles/cm^3 PNC; 1.2 μg/m^3 CO):
			PNC (particles/cm^3)	7.6 (2.0-13.6)
			CO (μg/m^3)	6.5 (1.0-12.3)
Ostro B, 2007[24]	> 22 million adults 9 American cities	Daily mortality:	$PM_{2.5}$ (μg/m^3)	Increase % in risk for an increase of 15 μg/m^3 of $PM_{2.5}$:
		total		0.61 (0.18-1.04)
		respiratory		2.05 (0.02-4.12)
		cardiovascular		0.70 (0.07-1.33)
Chen G, 2008[28]	Residents in nine urban districts of Shanghai (China)	Daily mortality:		Increase % for an increase of 10 μg/m^3 of air pollutants :
		total	PM_{10} (μg/m^3)	0.26 (0.14-0.37)
		cardiovascular		0.27 (0.10-0.44)
		total	SO_2 (μg/m^3)	0.95 (0.62-1.28)
		respiratory		1.37 (0.51-2.23)
		cardiovascular		0.91 (0.42-1.41)
		total	NO_2 (μg/m^3)	0.97 (0.66-1.27)
		respiratory		1.22 (0.42-2.01)
		cardiovascular		1.01 (0.55-1.47)
Zanobetti A, 2009[25]	5,609,349 total deaths, 112 US cities	Daily mortality:	$PM_{2.5}$ (μg/m^3)	Increase % for an increase of 10 μg/m^3 of $PM_{2.5}$ in 2-day average:
		total		0.98 (0.75-1.22)
		respiratory		1.68 (1.04-2.33)
		cardiovascular		0.85 (0.46-1.24)

PM_{10} and $PM_{2.5}$, particulate matter with aerodynamic diameter <10 μm and <2.5 μm respectively; PNC, particle number concentration; NO_2, nitrogen dioxide; O_3, ozone; CO, carbon monoxide; IQR, interquartile; 95% CI, 95% confidence interval

the events), a 10 μg/m^3 increase in concentration of PM_{10}, SO_2 and NO_2 corresponded to 0.11% (95% CI – 0.03-0.26%), 0.34% (95% CI 0.06-0.61%) and 0.55% (95% CI 0.14-0.97%) increase of outpatient visits[29] (Table 99.4). Data of daily emergency hospital admissions was assessed for COPD in 15 major hospitals in Hong Kong and indices of air pollutants like SO_2, NO_2, O_3, PM_{10} and $PM_{2.5}$: relative risks for admission for every 10 μg/m^3 increase were 1.007, 1.026, 1.034, 1.024 and 1.031, respectively[30] (Table 99.4).

For estimating risks of cardiovascular and respiratory hospital admissions associated with short-term exposure to $PM_{2.5}$, a national database comprising daily time-series data on hospital admission rates for 204 US urban counties (population >200,000) was analyzed for the years 1999–2002. There was a significant increase in the hospitalization rate for COPD and respiratory tract infections per each 10 µg/m^3 increase of $PM_{2.5}$ in the elderly[31] (Table 99.4). The association between gaseous pollution and hospitalization for COPD among elderly people living in Vancouver, British Columbia, Canada (1994–1998) was examined. The combined relative risk for an increase of interquartile range of 7-days, average level of NO_2, CO, O_3 and SO_2, on COPD hospitalization was 1.21[32] (Table 99.4).

A recent study performed in Canada showed an association between outdoor air pollution levels and ED visits for asthma. In particular, an increase in the interquartile range of the 5-day average for NO_2 levels was associated with a 20% increase in the number of ED visits, whilst an increase in the interquartile range of the same day average for $PM_{2.5}$ levels was associated with a 12% increase in the number of ED visits, among subjects over 75 years[33] (Table 99.4). A similar study was conducted in 15 major hospitals of Hong Kong, finding a relative risk for asthma hospitalization of about 1.02 for every 10 µg/m^3 increase in NO_2, O_3 and $PM_{2.5}$, in subjects of age 15–65 years; the younger age group (0–14 years) tended to have a higher RR for each 10 µg/m^3 increase in pollutants than, those aged 15–65 years[34] (Table 99.4).

Another important time-series analysis was conducted on about 400,000 ED visits to 14 hospitals in seven Canadian cities. Associations were examined between CO, NO_2, O_3, SO_2, PM_{10} and $PM_{2.5}$, and visits for cardiovascular and respiratory diseases. 24-hour average concentrations of CO and NO_2 (lag 0 days) showed associations with increase in visits for myocardial infarction/angina (2.1%, 95% CI 0.0–4.2% and 2.6%, 95% CI 0.2–5.0%, respectively); O_3 (lag 2 days) was most consistently associated with increases in asthma visits (3.2%, 95% CI 0.3–6.2%)[35] (Table 99.4).

The association between hospital admission for cardiovascular and respiratory diseases and daily levels of $PM_{2.5}$ chemical components in 119 US urban communities for 12 million Medicare enrollees ($\geq$ 65 years of age) was investigated. In multiple-pollutant models, an interquartile range (IQR) increase, in elemental carbon was associated with a 0.80% increase in the risk of same-day cardiovascular admissions, and an IQR increase in organic carbon matter was associated with a 1.01% increase in the risk of respiratory admissions on the same day[36] (Table 99.4). A similar relationship was found for pneumonia; a significantly elevated rate of pneumonia hospitalizations was seen in subjects over 65 years, associated with BS, $PM_{2.5}$ and CO.[37] Another study, conducted in 36 US cities on respiratory hospital admissions in the elderly in the period 1986–1999, assessed that, during the warm season, a 5-ppb increase in O_3 was associated with a 0.42% increase in pneumonia admissions. Also, a 10 µg/m^3 increase in PM_{10} during the warm season resulted in a 0.79% increase in pneumonia admissions[38] (Table 99.4).

With regard to the association between outdoor air pollution and tuberculosis (TB), the exposure to PM-associated transition metals, e.g. iron, producing oxidative stress in the lung, could adversely affect the progression of TB. Only few studies of outdoor air pollution and TB have been reported, indicating that outdoor air pollution might have a negative impact on TB infection and/or progression of disease.[39]

Prevention

There are clear evidences on the benefits of exposure reductions. More than 70% of chronic bronchitis cases could be prevented, if the prevalence rates of active smoking, environmental tobacco smoke and PM_{10} annual mean were reduced to 5%, 2.5%, and 5 µg/m^3, respectively.[40] Moreover, a Swiss recent study showed that a decline of 10 µg/m^3 of PM_{10}, over an 11-year period, reduced the annual rate of decline in FEV_1 by 9% and of the FEF_{25-75} by 16%.[41]

Previously, an association of the prolonged reduction in ozone, due to the traffic changes in Atlanta, Georgia, USA, during the 1996 Summer Olympic Games, was shown with significantly lower rates of childhood asthma events. These data provide support for efforts to reduce air pollution and improve health via reductions in motor vehicle traffic.[42] A rather moderate decline of air pollution levels in the 1990s in Switzerland was associated with a reduction in respiratory symptoms and diseases in school children. The results showed a decline of the prevalence of chronic cough, bronchitis, common cold, nocturnal dry cough and conjunctivitis symptoms.[43] A more recent study assessed whether, a ban on diesel-powered motor vehicles in Lebanon reduced emergency respiratory admissions for children (< 17 years of age) in Beirut. A significant reduction in admissions for asthma and upper respiratory tract infection from one year, pre-ban to one year, post-ban has been recorded.

TABLE 99.4: Short-term effects of outdoor air pollution (hospital admissions and emergency department visits)

Study	*Population sample investigated*	*Health outcome*	*Exposure*	*Measures (95% CI)*
Yang Q, 2005[32]	6.027 adults hospitalized for COPD Vancouver (Canada)	Daily COPD hospitalization		RR for IQR range increase of 7-days average level of pollutants (5.5 ppb NO_2; 0.3 ppm CO):
			NO_2 (ppb)	1.11 (1.04-1.20)
			CO* (ppm)	1.08 (1.02-1.13)
Dominici F, 2006[31]	> 200.000 subjects (>65 years) 204 US cities	Hospital admission:	$PM_{2.5}$* (µg/m^3)	Increase % in risk for an increase of 10 µg/m^3 of $PM_{2.5}$:
		COPD		0.91 (0.18-1.64)
		respiratory tract infection		0.92 (0.41-1.43)
Zanobetti A, 2006[37]	25.000 patients ($\geq$65 years) Boston	Pneumonia hospital admission		Increase % of risk for an increase in the difference 90th-10th percentile of pollutants (2.05 µg/m^3 BS; 17.14 µg/m^3 $PM_{2.5}$; 0.48 ppm CO):
			BS (µg/m^3)	10.76 (4.54-15.89)
			$PM_{2.5}$ (µg/m^3)	6.48 (1.13-11.43)
			CO* (ppm)	5.45 (1.10-9.51)
Medina-Ramon M, 2006[38]	Subjects $\geq$65 years 36 US cities	Pneumonia hospital admission		Increase % of risk for an increase of 5 ppb of O_3 and 10 µg/m^3 of PM_{10}:
			O_3* (ppb)	0.42 (0.29-0.55)
			PM_{10} * (µg/m^3)	0.79 (0.45-1.13)
Ko FWS, 2007[30]	Adults 15 hospitals of Hong Kong	COPD hospital admission		RR* for an increase of 10 µg/m^3 of pollutants
			SO_2 (µg/m^3)	1.01 (1.00-1.01)
			NO_2 (µg/m^3)	1.03 (1.02-1.03)
			O_3 (µg/m^3)	1.03 (1.03-1.04)
			PM_{10} (µg/m^3)	1.02 (1.02-1.03)
			$PM_{2.5}$ (µg/m^3)	1.03 (1.03-1.04)
Ko FWS, 2007[34]	Subjects 0-14 years 15 hospitals of Hong Kong	Asthma hospital admission		RR for an increase of 10 µg/m^3 of pollutants:
			NO_2 (µg/m^3)	1.04 (1.03-1.05)
			O_3 (µg/m^3)	1.04 (1.03-1.05)
			PM_{10} (µg/m^3)	1.02 (1.02-1.03)
			$PM_{2.5}$ (µg/m^3)	1.02 (1.01-1.03)
Villeneuve PJ, 2007[33]	Subjects $\geq$75 years Canada	ED visits for asthma		OR for an increase of IQR range of pollutants (13.5 ppb NO_2; 6.3 µg/m^3 $PM_{2.5}$):
			NO_2* (ppb)	1.20 (1.04-1.38)
			$PM_{2.5}$ (µg/m^3)	1.12 (1.01-1.23)
Cao J, 2009[29]	Adults Shanghai (China)	Total hospital outpatient visits		Increase % in risk for an increase of 10 µg/m^3 of pollutants:
			PM_{10} (µg/m^3)	0.11 (-0.03-0.26)
			SO_2 (µg/m^3)	0.34 (0.06-0.61)
			NO_2 (µg/m^3)	0.55 (0.14-0.97)

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Study	*Population sample investigated*	*Health outcome*	*Exposure*	*Measures (95% CI)*
Peng RD, 2009[36]	12 million subjects ($\geq$65 year) 119 US urban communities	Hospital admission: respiratory cardiovascular	EOC of $PM_{2.5}$ EC of $PM_{2.5}$	Increase % in risk for an increase of the IQR range of air pollutant (3.18 μg/m^3 EOC; 0.40 μg/m^3 EC): 1.01 (0.04-1.98) 0.8 (0.34-1.27)
Stieb DM, 2009[35]	ED visits in 14 hospitals of seven Canadian cities	ED visits for asthma	O_3	Increase % in risk for daily average air pollution: 3.2 (0.3-6.2)

*PM_{10} and $PM_{2.5}$, particulate matter with aerodynamic diameter <10 μm and <2.5 μm respectively; BS, black smoke; CO, carbon monoxide; O_3, ozone; NO_2, nitrogen dioxide; 95% CI 95%, confidence interval; OR, odds ratio; RR, relative risk; EOC, elemental organic carbon; EC, elemental carbon; ED, emergency department visits; IQR, interquartile; 95% CI, 95% confidence interval

Unfortunately, this finding is weakened by the absence of evidence from air quality monitoring and speciation of particulate matter, which are lacking in most developing countries.[44]

There is little direct evidence that diminished particulate air pollution concentrations would lead to reductions in death rates. A study reported the effect of air pollution controls (i.e. the ban on coal sales) on particulate air pollution and death rates in Dublin: in connection with a decline in average BS concentrations of 35.6 μg/m^3 (70%), decreases of adjusted non-trauma death rates (5.7%), respiratory deaths (15.5%), and cardiovascular deaths (10.3%) were shown.[45] A recent confirmation comes from the Harvard Six Cities adult cohort study that showed an association between reduced $PM_{2.5}$ concentrations and reduced mortality risk: RR 0.73 (95% CI 0.57–0.95) for total mortality, RR 0.69 (95% CI 0.46–1.01) for cardiovascular mortality and RR 0.43 (95% CI 0.16–1.13) for respiratory mortality.[46]

Conclusion

Although outdoor air pollution levels are highest in the cities of developing countries, few studies took into account the association between air pollutants exposure and respiratory health in these realities; indeed, studies performed in other countries indicate the detrimental effects of air pollution on respiratory health also below the reference values of air quality, especially in susceptible population like, children and elderly. For this reason, national and international respiratory societies, respiratory physicians, as well as public health professionals, should advocace for a cleaner environment.

According to the 2007 ERS position paper about particulate matter, science and European Union (EU) policy,[47] neither the $PM_{2.5}$ annual average of 25 μg/m^3 nor the target value proposed by EU Parliament on September 26, 2006 (20 μg/m^3) are sufficient to adequately protect public health. Indeed, there is sufficient epidemiological evidence pointing to the necessity of promulgating air pollution standards in both developed and underdeveloped countries, which set the long-term air quality guideline for $PM_{2.5}$ to 10 μg/m^3.[48] Implementation of strategies, which allow to respect stringent air pollution standards require more resources, but the health benefits gained from the reduction of air pollution clearly outweigh these costs.

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Indoor Air Pollution and Respiratory Health

Marzia Simoni, Sara Maio, Sandra Baldacci, Fabio Cibella, Giovanni Viegi

INTRODUCTION

Indoor environments contribute significantly to total human exposure to air pollutants. Exposures occur in places where people spend time and globally, people spend the majority of their time indoors. The same quantity of a pollutant causes more exposure when, released indoors than outdoors. For some pollutants, indoor exposure probably dominates the global human exposure. Approximate estimates indicate that about 85% of all global Particulate Matter (PM) pollution occurs indoors.[1] Some pollutants may be 2–5 fold more concentrated inside, than outside the buildings; furthermore, indoor pollutants may have an important biological impact even at low concentrations over long exposure periods.

Indoor Air Pollution (IAP) represents a substantial risk for human health, particularly for children (their defense mechanisms are still evolving, and they inhale a higher volume of air per body weight than adults), elderly people, subjects with cardiorespiratory diseases, subjects at higher risk for specific exposures, or for the socioeconomically deprived.[2] The largest health impacts occur among the poorest and the most vulnerable populations, such as those living in Low-Middle-Income Countries (LMIC), especially in Least-Developed Countries (LDC), where people suffer from the conditions of extreme poverty; conflicts and wars; lack of political and social stability; and often the authoritarian form of government.[3]

Indoor exposure mainly occurs at home and in workplaces/schools, but also in day care centers, social recreation settings, or microenvironments, such as cars, buses, trains, subways and airplanes.

Indoor Pollutants and Related Sources

Anthropogenic agents and allergens are two common groups of indoor pollutants (Fig. 100.1). Most indoor pollutants derive from anthropogenic activity (combustion processes, redecorating/remodeling/repair or cleaning activity). The main sources are two: Combustion of solid fuels for cooking/heating, and Environmental Tobacco Smoke (ETS).[3]

Biomass fuel is the primary source of domestic fuel in developing nations, frequently burnt in the households in open fire or inefficient stoves. The consequence is a large production of smoke, containing many substances harmful for health (PM, carbon monoxide, nitrogen oxides, polycyclic organic hydrocarbons, etc.), derived from incomplete combustion. In houses where biomass fuels and coal are used, PM levels may be 10–50 times higher than the guideline values for good Indoor Air Quality (IAQ). About 3 billion people (almost half of the humanity) rely on solid fuels for cooking/heating, with little or no access to the modern forms of energy. The World Health Organization (WHO) reports that, globally, about 1.5 billion people have no access to electricity, and more than 80% of them live in sub-Saharan Africa and South Asia. In Chad, Liberia, and Burundi, 95% of people lack electricity access, as well as 62% in Haiti, and 25% in South Africa (but only 2% in Brazil and less than 1% in Mauritius). Only 27% of people relying on solid fuels use improved cooking stoves (6% in LDC and sub-Saharan Africa). Traditional biomass, such as wood, charcoal and dung is much more commonly used in rural than in urban areas.[3]

Environmental tobacco smoke (ETS) is the largest contributor to indoor PM in buildings where, people

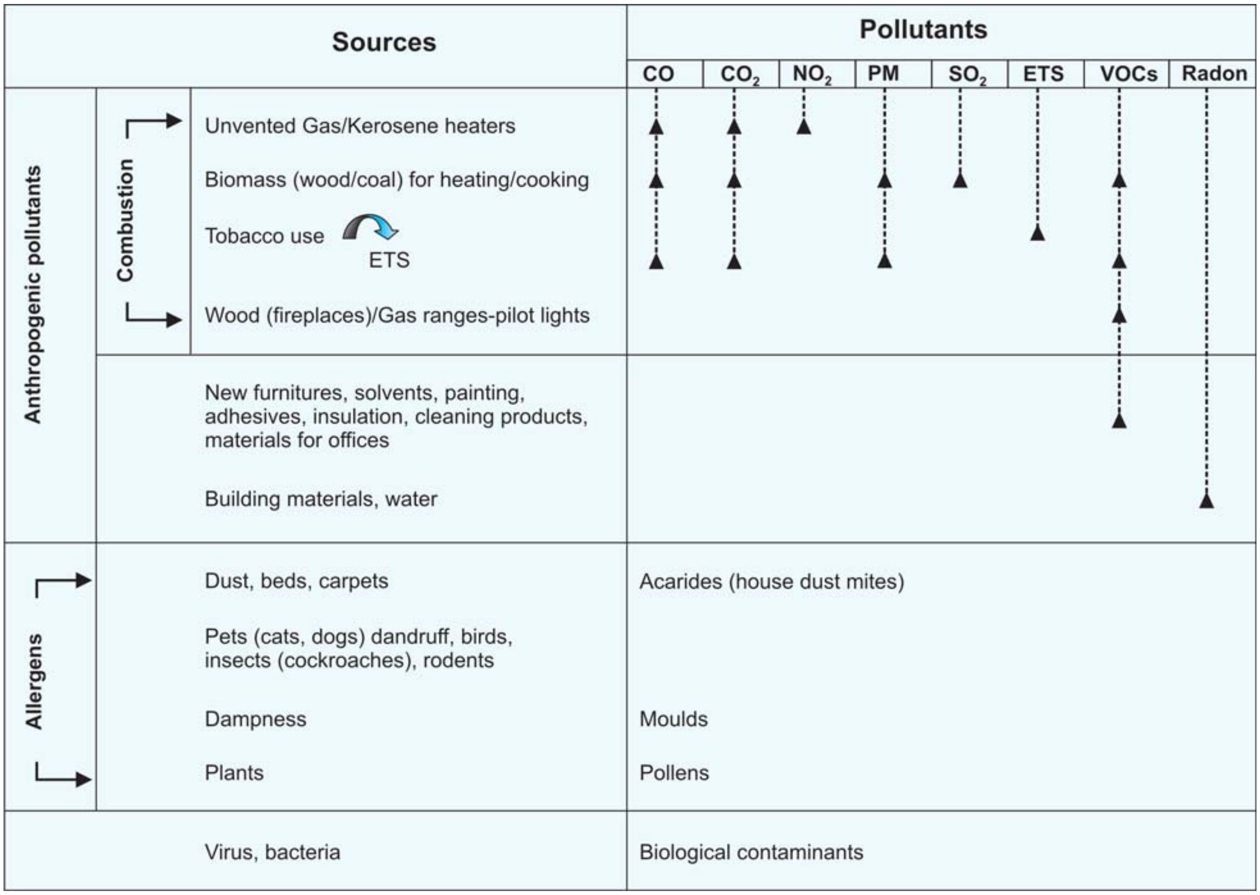
Sources
Pollutants
CO
CO2
NO2
PM
SO2
ETS
VOCs
Radon
Anthropogenic pollutants
Combustion
Unvented Gas/Kerosene heaters
Biomass (wood/coal) for heating/cooking
Tobacco use
ETS
Wood (fireplaces)/Gas ranges-pilot lights
New furnitures, solvents, painting, adhesives, insulation, cleaning products, materials for offices
Building materials, water
Allergens
Dust, beds, carpets
Acarides (house dust mites)
Pets (cats, dogs) dandruff, birds, insects (cockroaches), rodents
Dampness
Moulds
Plants
Pollens
Virus, bacteria
Biological contaminants

Fig. 100.1: Main indoor pollutants and related sources (CO and CO_2, carbon oxides; NO_2, nitrogen dioxide; PM, particulate; SO_2, sulphur oxide; ETS, environmental tobacco smoke; VOCs: volatile organic compounds)

smoke, accounting for up to 50-90% of the total PM concentration. WHO estimates around 1.3 billion smokers in the world (84% in developing countries).[4] About 40% of smokers in the world live in China and India. In the developed countries, people are stopping smoking, while in the developing countries, tobacco sales are on the rise. More than 20% of low-income countries have no (or no recent/no representative) national smoking prevalence data for adults or youth. Globally, about one third of adults are regularly exposed to ETS.[5] The global prevalence of ETS exposure among young people is still high. In 2008, 43% of adolescents were living in homes where, other people smoke[5] (Fig. 100.2).

Indoor Pollutants and Health Effects

The scientific interest for IAP and possible effect on human health began in early 80s and keeps increasing. Poor IAQ poses a risk to the health of over half of the world's population, especially affecting the poor people. IAP results as the eighth most important risk factor, being responsible for 2.7% of the global burden of disease (between 1.5 and 2 million deaths yearly).[6] There is consistent evidence that the exposure to IAP increases the risk for several respiratory/allergic symptoms/diseases[6,7] (Fig. 100.3).

Health Effects From Biomass Exposure

From a global point of view, the health consequences of IAP from biomass fuels are comparable to those of tobacco use.[8] Never smoker Mexican women exposed to wood smoke have a five-fold risk for chronic bronchitis and chronic airflow obstruction as compared to the unexposed.[9] Never smoker women exposed domestically to biomass develop Chronic Obstructive Pulmonary Disease (COPD) with clinical characteristics, quality of life, and increased mortality similar in degree to that of tobacco smokers.[10]

The exposure to biomass fuels is strongly poverty-related, consequently is a major health concern in the

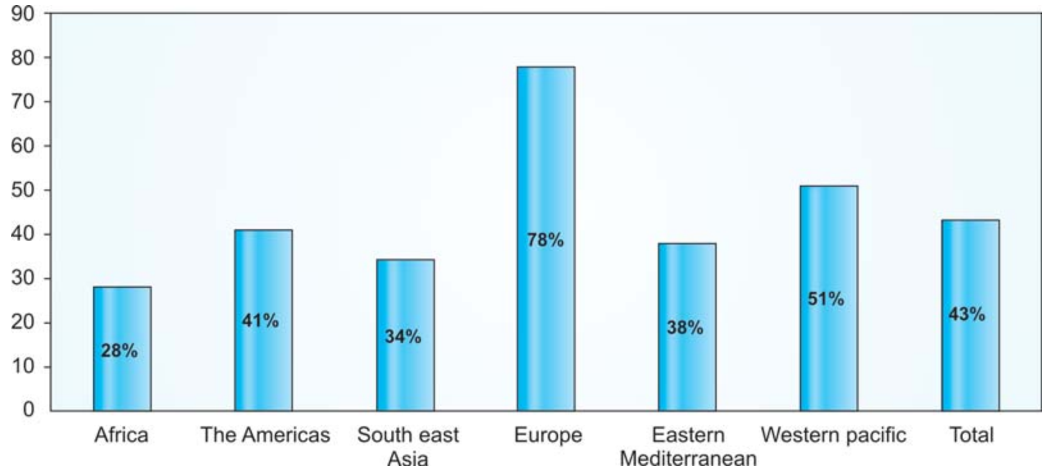

Fig. 100.2: Prevalence of passive smoking exposure in 13–15 years aged, by geographic area. Original data are from World Health Organization[5]

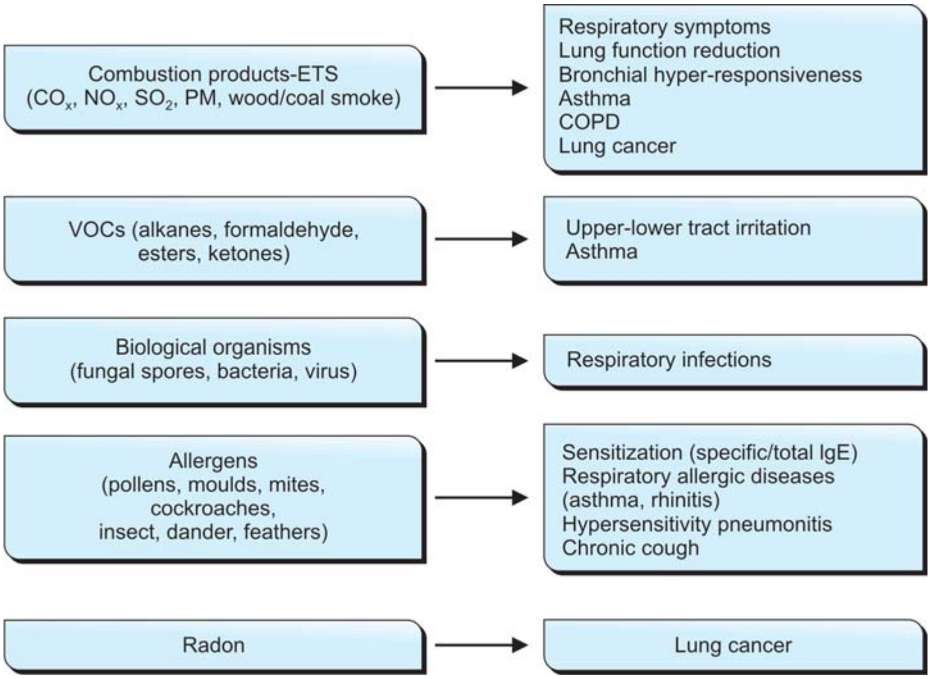
Combustion products-ETS
(CO$_x$, NO$_x$, SO$_2$, PM, wood/coal smoke)
Respiratory symptoms
Lung function reduction
Bronchial hyper-responsiveness
Asthma
COPD
Lung cancer
VOCs (alkanes, formaldehyde, esters, ketones)
Upper-lower tract irritation
Asthma
Biological organisms
(fungal spores, bacteria, virus)
Respiratory infections
Allergens
(pollens, moulds, mites, cockroaches, insect, dander, feathers)
Sensitization (specific/total IgE)
Respiratory allergic diseases
(asthma, rhinitis)
Hypersensitivity pneumonitis
Chronic cough
Radon
Lung cancer

Fig. 100.3: Main respiratory health effects of common indoor pollutants

developing world, especially for children and women, who generally spend much time in the kitchen for cooking.

The strongest evidence of biomass burning effect, concerns acute lower respiratory infections (ALRI, i.e. pneumonia), in children, and COPD and lung cancer in adults. WHO[3] estimates the use of solid fuel to be responsible for about 2 million deaths per year from these diseases (3.3% of all deaths, globally). More than 99% of these deaths occur in developing countries (Fig. 100.4). The fraction of deaths from these three diseases, which can be attributed to solid fuel, is 38% in all developing countries. More than 50% of deaths occur in LDC and sub-Saharan Africa (Fig. 100.5). About 60% of deaths from COPD and lung cancers, attributable to solid fuels, occur in women (Fig. 100.6). A recent Chinese study suggests, for the first time that indoor air pollution from unvented coal burning is an important risk factor for pneumonia death, also in adults.[11]

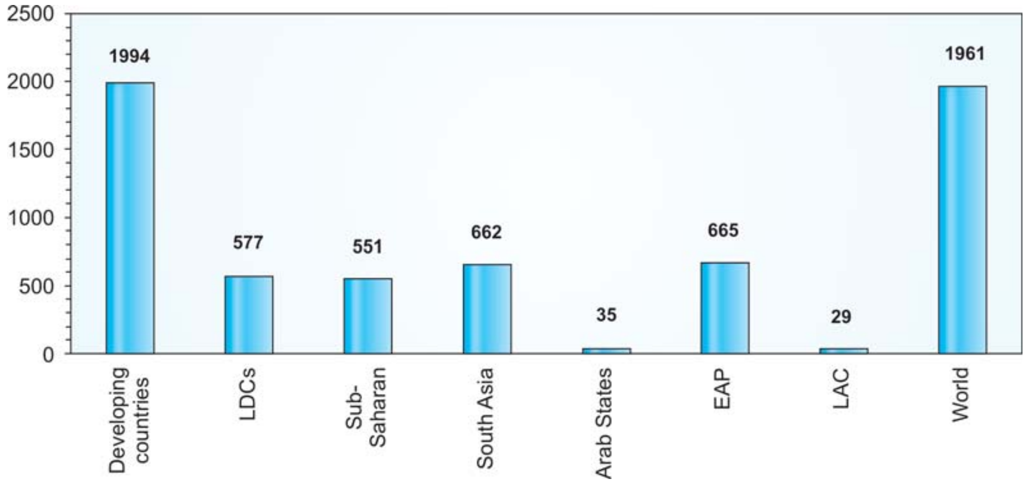

Fig. 100.4: Number ('000) of deaths from pneumonia, COPD, and lung cancer. LDCs, Least Developed Countries; EAP, East Asia and the Pacific; LAC, Latin America and the Caribbean. Original data are from World Health Organization[3]

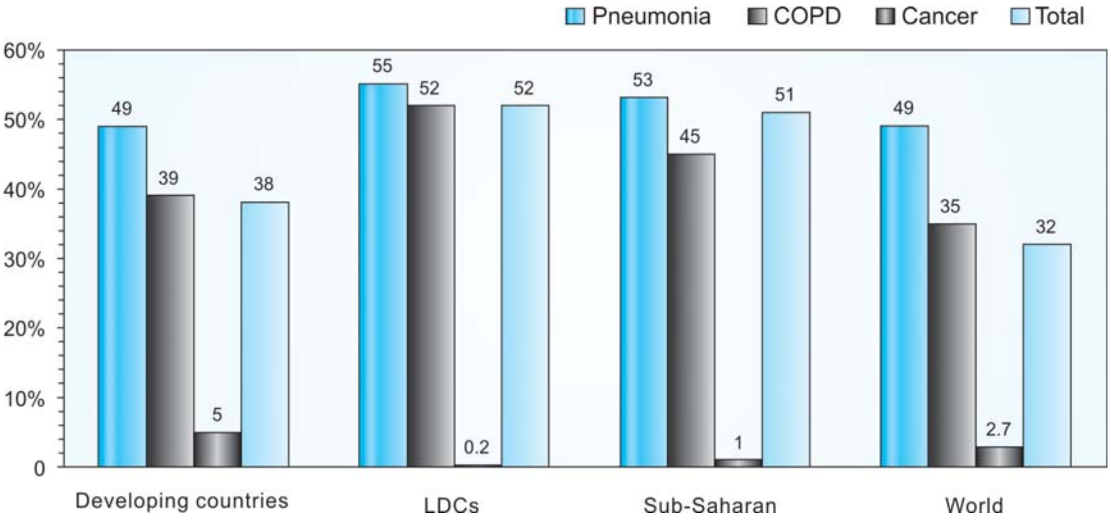

Fig. 100.5: Percent of deaths attributable to solid fuel, by disease. LDCs, Least Developed Countries. Original data are from World Health Organization[3]

The association of biomass burning with ALRI, in children of less than 5 years yields a Relative Risk (RR) of 2.3 (95% Confidence Interval, CI, 1.9–2.7), while RRs for COPD from biomass exposure and lung cancer from coal smoke exposure, in women, are 3.2 (2.3–4.8), and 1.9 (1.1–3.5), respectively.[12] In South Africa, Zimbabwe, Nigeria, Tanzania, Gambia, Brazil, India, Argentina, Nepal and Kenya, children exposed to biomass fuel have a risk for ALRI two to three times higher than unexposed or less exposed (ORs range from 2.2 to even 9.9).[13] Ezzati and Kammen, in 2001, evaluated for the first time, data on exposure-response relationships between PM and incidence of ALRI, in children and adults living in rural Kenya: the trend of increasing risk with higher levels of exposure was highly significant.[14]

Moderate evidence has been found for the associations of biomass exposure with COPD in men (RR 1.8, 1.0–3.2), asthma in children (RR 1.6, 1.0–2.5), asthma and tuberculosis in all (RR 1.2, 1.0–1.5, and RR 1.5, 1.0–1.4, respectively), and lung cancer in women (RR 1.5, 1.0–2.1). Coal exposure is also moderately related to lung cancer in men (RR 1.5, 1.0–2.5).[12] A meta-analysis on data from Africa, Latin America and China,[15] as well as epidemiological studies performed in India,[16-18] Tanzania,[19] China,[20,21] Ecuador,[22] Zimbabwe,[23,24] Iran,[25] and Bangladesh,[26] show

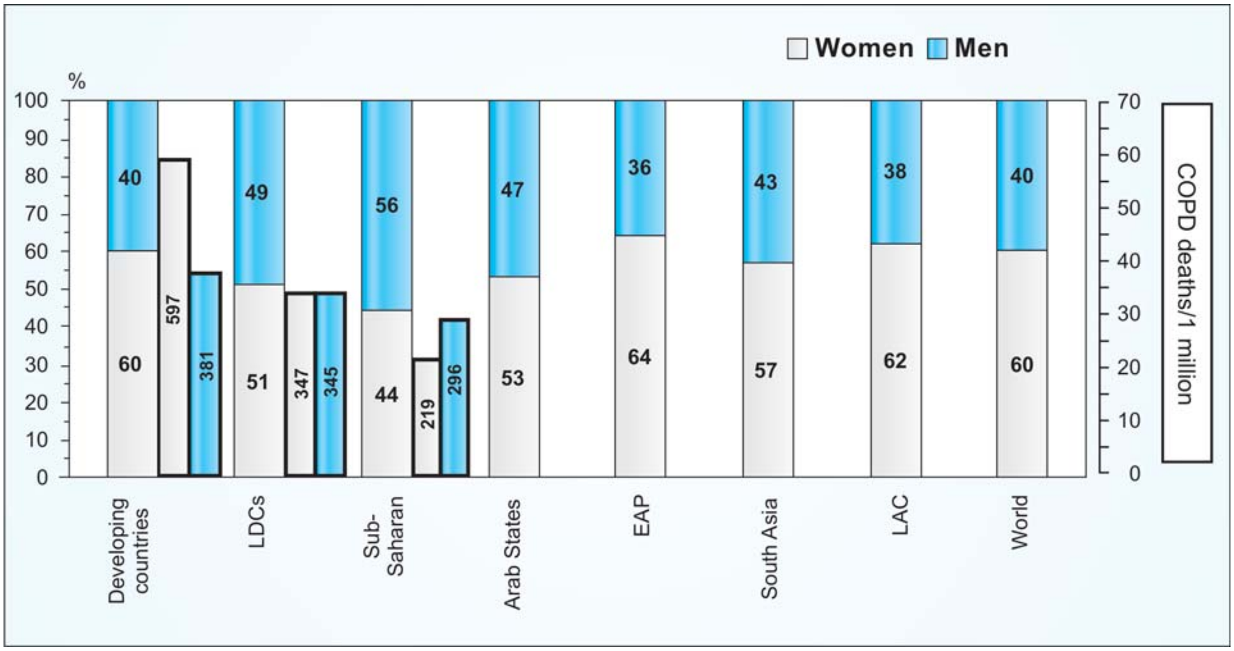

Fig. 100.6: Distribution (%) of deaths for COPD and cancer attributable to solid fuel in women and men, and rate per 1 million people of COPD deaths attributable to solid fuel, by gender. LDCs, Least Developed Countries; EAP, East Asia and the Pacific; LAC, Latin America and the Caribbean. Original data are from World Health Organization[3]

associations between biomass fuel use and acute respiratory illnesses, respiratory symptoms (including persistent cough/phlegm, shortness of breath, chest tightness, wheezing or whistling chest), or impaired lung function (Table 100.1).

In 2006, the Working Group (WG) of the International Agency for Research on Cancer (IARC) concluded that indoor emissions from household combustion of coal are "carcinogenic to humans (Group 1)," and those from household combustion of biomass fuel (mainly wood) are "probably carcinogenic to humans (Group 2A)."[27]

Health Effects of ETS

Environmental tobacco smoke kills 600,000 people each year,[5] and is linked to several acute and long-term adverse respiratory effects, including lung cancer and tuberculosis. There exists a pooled risk for chronic cough in men (OR 1.60, 95% CI 1.22–2.10) and women (1.68, 1.17–2.34) exposed to ETS.[28] Women have higher risk for ETS exposure than men, and many respiratory symptoms/diseases have been related to smoke exposure from husbands.[29]

There is also strong evidence that ETS exposure, in adults, is related to new-onset asthma,[30] and that exacerbates preexisting COPD and asthma, as also confirmed by an Indian study, where adults exposed to ETS showed higher prevalence of asthma and asthma exacerbation than unexposed ones.[31]

In children, there is a consistent evidence of adverse effects from parental smoking for wheezing [ORs ranging from 1.17, 95% CI 1.02–1.33 (early exposure) to 1.25, 1.14–1.37 (fetal exposure)], asthma (mean OR 1.18, 1.08–1.28, for mother's smoking during pregnancy), and bronchitis (mean OR 1.10, for early or current passive smoking).[32] Through a meta-analysis, which also included African countries, the pooled OR for asthma in children was reported as 1.37 (1.15–1.64).[33] Another meta-analysis on the relationship between parental smoking and ALRI in children (38 studies from 14 European and non-European countries) estimated a pooled OR of 1.57 (1.42–1.74) for children with both parents smoking, 1.72 (1.55–1.91), and 1.29 (1.16–1.44), for children with either the mother or the father smoking, respectively.[34]

There are very few reports on the health effects from ETS exposure in the LMIC. Most studies concern Indian samples (Table 100.2). Most studies concern Indian samples. In Indian adolescents, passive smoking was associated with an increased risk of asthma, and with a variety of respiratory symptoms, with ORs ranging

TABLE 100.1: Association between biomass fuel use and respiratory disorders in developing countries

Author (sample)	*Country (sample)*	*Exposure*	*Health outcome**	*Measures†*
Dherani M, 2008[15]	Africa, Latin America, China (children)	Unprocessed solid fuel	Pneumonia	OR (95% CI):1.78 (1.45-2.18)
Tielsch JM, 2009[16]	India (infants)	Wood/dung fuel	ARI	RR (95% CI):1.34 (1.09-1.64)
Padhi BK, 2008[17]	Rural India (children)	Biomass fuel	Asthma	OR (95% CI):2.20 (1.16-4.19)
Kilabuko JH, 2007[19]	Tanzania (women/children)	Biomass fuel	ARI	OR (95% CI):5.5 (3.6-8.5)
Liu S, 2007[20]	China (women)	Biomass fuel	FEV_1/FVC<0.70	OR (95% CI):3.11 (1.63-5.94)
Rinne ST, 2006[22]	Ecuador (children)	Biomass fuel vs GPL	FEV_1; FVC	$^{\beta}$(95% CI):-0.39 (-0.78, -0.01) -0.41 (-0.76, -0.07)
Mishra V, 2003[23]	Zimbabwe (infants)	Wood fuel vs GPL/natural gas/ electricity	ARI	OR (95% CI):2.20 (1.16–4.19)
Golshan M, 2002[25]	Iran (women)	Biomass fuel	Chronic Bronchitis	OR (95% CI):2.91 (2.08-4.40)

* ARI, acute respiratory illnesses; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity;

† OR, Odds Ratio; CI, Confidence Interval; RR, relative risk, β, linear regression coefficient

TABLE 100.2: Association between environmental tobacco smoke (ETS) exposure and respiratory disorders in developing countries

Author (sample)	*Country (sample)*	*Exposure*	*Health outcome**	*Measures†*
Leung CC, 2010[43]	China (women)	ETS at home	COPD	OR (95% CI):1.43 (1.16-1.77)
Tielsch JM, 2009[16]	India (infants)	ETS	ARI	RR (95% CI):1.21 (1.06-1.39)
Pokharel PK, 2001[35]	India (children)	ETS	Asthma	OR (95% CI):3.33 (1.85-7.65)
Gupta D, 2001[31]	India (adolescents)	ETS	Asthma	OR (95% CI):1.78 (1.33-2.31)
Rinne ST, 2006[22]	Ecuador (children)	ETS	FEV_1, FVC	$^{\beta}$(95% CI): -0.65 (-1.00, -0.25) -0.45 (-0.77, -0.13)
Rapiti E, 1994[41]	India (adults)	ETS during childhood	Lung cancer	OR (95% CI):3.9 (1.9-8.2)
Jin C, 1993[37]	China (infants)	ETS	Bronchitis and Pneumonia	RR
		1-9 cig/day		1.3
		10-19 cig/day		1.7
		20-39 cig/day		2.0

* COPD, chronic obstructive pulmonary disease; ARI, acute respiratory illnesses; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity;

† OR, Odds Ratio; CI, Confidence Interval; RR, relative risk, β, linear regression coefficient.

from 1.60 to 2.25.[31] Yet, in India ETS exposure increased approximately three-fold the risk for asthma in schoolchildren,[35] and affected pulmonary function, even if only in children exposed also to biomass fuels.[36] A significant inverse association of ETS exposure with pulmonary function was found among children living in Ecuador.[22] Recently, ETS exposure was a significant risk factor for acute respiratory illnesses in Indian infants.[16] Dose-response effects have been found for bronchitis and pneumonia in Chinese infants, as well.[37]

The causal role of ETS exposure in lung cancer development is well-established. ETS is classified as a class A carcinogen, responsible for about 20% of lung cancers in nonsmokers. The pooled risk from spousal smoking for lung cancer in never smokers is OR 1.18 (1.01–1.37) [for ever exposure] and 1.23 (1.01–1.51) [for long-term exposure]. Similar ORs are seen for ETS exposure in the workplace and in social settings [1.16, 0.99–1.36 (for ever exposure) and 1.27, 1.03–1.57 (for long-term exposure)].[38] Through a meta-analysis that also includes data of China, Japan and Taiwan, RRs for lung cancer are 1.20 (1.13–1.92) in nonsmoker women ever exposed to husband's ETS, and 1.16 (1.05–1.28) in those ever exposed to ETS at work.[39] RRs for lung cancer in never-smoking women exposed to husband's smoking were evaluated: 1.15 (1.03–1.28) in North America, 1.31 (1.16–1.48) in Asia, and 1.31 (1.24–1.52) in Europe.[40] In India, the risk for lung cancer was found to be about four-fold higher in those exposed to ETS during childhood (the highest risk was found for women), and increased with increasing number of smokers and duration of exposure (Table 100.2). In this study, lung cancer was weakly related to ETS exposure at the workplace, with a dose-response effect by the number of years of exposure; interestingly, a positive association between ETS exposure in vehicles and lung cancer in nonsmokers was also found.[41] In Morocco, passive smoking increased the risk of lung cancer, but not significantly (OR 1.36, 0.71–2.62).[42]

Less known is the link between ETS and tuberculosis. A recent cohort study on 15,486 never-smoking married women (age 65 to 74 years), performed in China (where the prevalence of current smokers is 60% in men and only 4% in women), shows that women exposed to ETS at home have higher risk for COPD (Table 100.2), and more likely develop tuberculosis (hazard ratio 1.49, 95% CI 1.01–2.19).[43]

Other Indoor Exposures

Dampness/moulds are present in 10 to 50% of houses in affluent countries. Although few data are available, the magnitude of the problem appears similar in LMIC. The exposures to building dampness and moulds are associated with approximately 30 to 50% increase in a variety of respiratory and asthma-related health outcomes (asthma diagnosis/development, upper respiratory tract symptoms, cough, wheeze, dyspnea, bronchitis, allergic rhinitis and respiratory infections).[44] In a Chinese subtropical area, dampness at home was very common and was a strong predictor of respiratory symptoms, in children: the risk by dampness/moulds exposure was OR 1.37 (1.03–1.83) [for allergic rhinitis] and 5.74 (2.20–14.95) for cough].[45]

The exposure to Volatile Organic Compound (VOCs) in developing countries is likely related to the wood smoke from cooking/heating that, contains also VOCs, such as, aldehydes (e.g. formaldehyde). Many studies indicate health effects from very low levels of VOCs exposure, commonly found at the population level. The exposure to VOCs may result in, effects ranging from irritation to cancer.

In children, ORs for asthma diagnosis range from 1.2 to 2.9.[46] Many of the effects reported in children are also seen in adults. An increasing concern is addressed to exposure to VOCs from cleaning activity, which involves both the general population and a large fraction of workers, and constitutes a risk factor for asthma.

Occupational Exposure

Occupational exposure, which will be treated extensively in other parts of this book, deserves a brief comment herein. It does not involve the general population, but it is important for specific groups of workers, that can be exposed indoors to inorganic dust, wood dust, fumes, gases and cleaning agents.

Occupational exposure is an important risk factor for respiratory health independently of tobacco smoke. The population attributable risk for occupational asthma is quite similar in the developed and the developing countries with rapid industrialization (13% to 15%), and lower in other developing countries (6%).[47] However, occupational asthma remains under-recognized, especially in LMIC.

The median population attributable risk for either chronic bronchitis or airflow obstruction in different countries, including China, ranges from 15% to 19%.[48] In Iran, among the employees of cement and ceramic industries, exposed workers to raw materials showed significantly higher prevalence of cough, phlegm, dyspnea and wheezing; in the cement industry, only exposed workers showed abnormal findings at chest X-ray.[49,50]

The highest risk in developing countries seems to be related to cleaning agents and pesticide exposure.[47] In Saudi Arabia, in chemical fertilizer producing factories, the workers exposed to the high levels of ammonia had a significantly higher relative risk for cough (3.48, 1.84–6.57), wheezing (5.01, 2.38–10.57), phlegm (3.75, 1.97–7.11), dyspnea (4.57, 2.37–8.81), and bronchial asthma (4.32, 2.08–8.98).[51] In Pakistani wood industries, the increased duration of wood dust exposure resulted significantly and inversely related to peak expiratory flow.[52]

Among cancers linked to occupational exposures, lung cancer is the most common. Recent extrapolation from cohort studies on miners, suggests radon as the second leading cause of lung cancer death after tobacco smoke.[53] In India, the lifetime risk of lung cancer due to indoor radon exposure, for the total population, of three studied areas, was 0.67%.[54]

PREVENTION AND CONCLUSIONS

Programs and public health initiatives to reduce exposures to indoor air pollution need to be adopted in LMIC. Among Chinese coal users, a stove improvement (higher ventilation by installing a chimney) was associated with a 50% reduction in pneumonia deaths.[11] In Guatemala, among Mayan women, all using traditional indoor open fires, the use of a chimney woodstove (plancha) significantly reduced carbon monoxide exposure by 61.6%, and the risk for all respiratory symptoms: the reduction was statistically significant for wheeze (RR 0.42, 95% CI 0.25-0.70). The number of respiratory symptoms reported by the women at each follow-up point was also significantly reduced by the "plancha" (OR 0.7, 95% CI 0.50-0.97). However, no significant effects on lung function were found after 12–18 months.[55]

The efforts to reduce the exposure or to introduce new energy technologies should take into account, the impact from interventions in the terms of dose-response relationships with health effects.[56] A study performed in Kenya indicates that, although improved woodstoves substantially reduce exposure, in many cases they offer smaller health benefits than a transition to charcoal, which can reduce the exposure to very low levels.[14] It is commonly suggested that biomass fuel should be replaced by fossil fuel, as pollution levels are believed to be higher with biomass fuel. However, in Bangladesh, the use of fossil fuels instead of biomass fuel did not necessarily improve the children's health.[27]

Smoke-free policies decrease ETS exposure by 80 to 90% in high-exposure settings. About 50% of countries in the world have at least minimal tobacco control policies in public places, but only 9% include also bars and restaurants, and 65 countries have no smoke-free policies on a national level. Even if the total global population covered by comprehensive smoke-free laws increased from 3.1% in 2007 to 5.4% in 2008 (due to new policies adopted in Colombia, Djibouti, Guatemala, Mauritius, Panama, Turkey and Zambia, in 2008), about two thirds of low-income countries (as well as two thirds of middle-income and half of high-income countries) have the lowest level of protection.

It is to point out that tobacco control is underfunded, especially in low-income countries, where the public spending for tobacco control is about $ 0.001 per capita "versus" about $1 in high-income countries.[4] Although it is impossible to directly ban passive smoking in private dwellings, a thorough health education campaign should be permanently implemented by health professionals, targeting primarily the parents of asthmatic children and relatives of cardiopulmonary patients.

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Environmental Risk Factors for Respiratory Disease

Kalpana Balakrishnan

INTRODUCTION

The assessment of health risks from exposure to environmental air pollutants is a challenging task and involves integrating evidences from a broad range of disciplines including epidemiology, animal toxicology and human inhalation studies. The most comprehensive consolidation of this evidence was performed by the World Health Organization (WHO) as a part of the Comparative Risk Assessment exercise (WHO, 2002, 2004 and 2005) that not only estimated respiratory disease burdens but identified major contributing risk factors. Accordingly, 80 million people were estimated to have moderate-to-severe chronic obstructive pulmonary Disease (COPD). More than three million people died of COPD in 2005, which corresponds to 5% of all deaths globally. Although most of the information available on COPD prevalence, morbidity and mortality comes from high income countries, it is now known that almost 90% of COPD deaths occur in low- and middle-income countries. Acute respiratory infections (ARIs) account for about two million deaths each year and ranks first among causes of Disability-Adjusted Life Years (DALYs) lost in developing countries (94.6 million, 6.3% of total).

The most important environmental risk factors that contribute to this burden included exposures to indoor and outdoor air pollutants, allergens and occupational exposures (Table 101.1). These risk factors interact significantly with other lifestyle risk factors, including smoking, unhealthy diets, obesity and physical inactivity as well as genetic risk factors to modify attributable disease burdens. This chapter provides a brief description of the major environmental risk factors with respect to their sources, nature/chemical composition and prevalence of exposures among populations. Brief descriptions of epidemiological evidence of health effects and disease burdens are also provided (details of clinical manifestations and management may be found described in other chapters).

ENVIRONMENTAL RISK FACTORS

Outdoor Air Pollution

Sources and Composition

Outdoor air pollutants include two major categories viz those that are directly released into the atmosphere (primary air pollutants) and those that are formed after release in the atmosphere (secondary air pollutants). The physical state of pollutants (such as gaseous or particulate matter), the geographic location and distribution of sources determine levels of pollutions that may be found in the local, urban, regional and global scales.

Primary air pollutants include sulfur dioxide, oxides of nitrogen, carbon monoxide, volatile organic compounds, carbonaceous and non-carbonaceous primary particles. The main source of sulfur dioxide is the combustion of fuels containing sulfur. Fossil fuels and most notably coal and oil contain varying amounts of sulfur, according to their source but typically from 1% to 5%. On combustion, the sulfur in the fuel is converted to sulfur dioxide. In a process parallel to that of sulfur dioxide production during fuel combustion, nitrogen in fuels is also converted to oxides of nitrogen in the combustion process. The majority of nitrogen oxides

TABLE 101.1: Disability-adjusted life years (DALYs) (in millions) attributable to various risk factors, by level of socioeconomic development and sex, 2000 across world regions

	High mortality developing country		*Low mortality developing country*		*Developed country*	
	Males	*Females*	*Males*	*Females*	*Males*	*Females*
Total DALYs	421 (% of total)	412 (% of total)	223 (% of total)	185 (% of total)	118 (% of total)	97 (% of total)
Tobacco	3.4	0.6	6.2	1.3	17.1	6.2
Indoor smoke form solid fuels	3.7	3.6	1.5	2.3	0.2	0.3
Urban air pollution	0.4	0.3	1.0	0.9	0.6	0.5
Occupational airborne particulates	0.1	<0.1	0.87	0.1	0.4	0.1

(*Source:* WHO, 2002)

formed are emitted as nitric oxide, NO. A smaller amount, typically 5% of NO_x is emitted as primary nitrogen dioxide, NO_2, whilst the major proportion of atmospheric nitrogen dioxide is a secondary product of atmospheric chemistry. Carbon monoxide is formed by the incomplete combustion of carbon-containing fuels, e.g. combustion of fuel in vehicles. Volatile Organic Compounds (VOC) encompasses a very wide range of hydrocarbons, oxygenates, halogenates and other carbon compounds existing in the atmosphere in the vapor phase and are released upon evaporation of fuel as well as combustion. Particles are primarily generated by purely mechanical processes such as grinding or abrasion of surfaces and comprises of material in the solid or liquid phase suspended within the atmosphere. Such particles can be either primary or secondary and have a wide range of sizes. Newly formed secondary particles can be as small as 1 to 2 nanometers in diameter ($1\ nm = 10^{-9}\ m$) whilst coarse dust and sea salt particles can be as large as 100 micrometers ($1\ \mu m = 10^{-6}\ m$) or one tenth of a millimeter in diameter. However, the very large particles have a short atmospheric existence, tending to fall out rapidly through gravity and wind-driven impaction processes, and in practice there are few particles in the atmosphere exceeding 20 μm diameter except very close to sources of emission. Particles emitted from burning fossil fuels, coal and biomass may be emitted as carbonaceous particles that contain carbon, both in the elemental form and as organic compounds of low volatility or as non-carbonaceous primary particles (largely made of mineral material freed from a fuel such as coal in a combustion source and carried into the atmosphere with the flue gases). Particulate air pollutants have very diverse chemical composition and particle sizes which are highly dependent upon their source. Figure 101.1 illustrates the range of sizes (on a logarithmic scale) together with the ranges where certain important components are typically encountered.

Secondary air pollutants arise from chemical reactions of primary pollutants in the atmosphere, often involving natural components of the environment such as oxygen and water. Prominent secondary pollutants in the air include ozone, oxides of nitrogen and secondary particulate matter such as sulfates and nitrates.

Ambient Concentrations and Human Exposures

Exposures to air pollution are largely determined by the concentration of air pollutants in the environment where people spend their time and the amount of time they spend within them. Different methods of exposure assessment have been established that give qualitatively

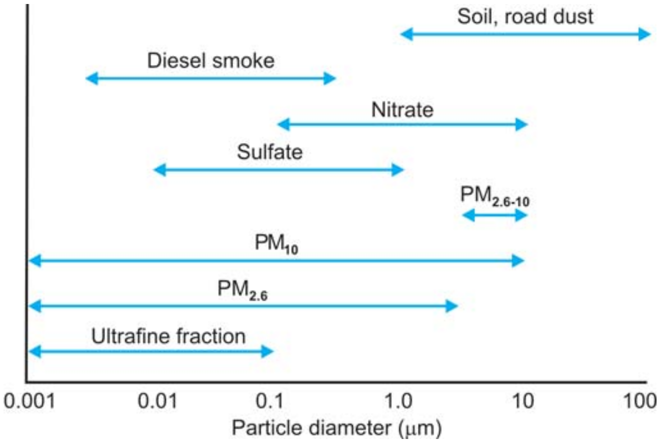

Fig. 101.1: Size range of air borne particles, showing the health related ultrafine, PM_2 and PM_{10} fractions, and the typical size range of some major components (*Source:* WHO, 2006)

different exposure estimates and differ in respect to precision, cost, feasibility and other factors. Among those methods are the fixed site measurements of ambient air pollutants, the modeled estimates of pollutant concentrations as well as personal measurements of exposure. Air quality measurements using fixed monitors that measure ambient concentrations of certain indicator pollutants (often termed criteria air pollutants) remain most widely used method to estimate human exposures. Such measurements during the last decade have shown air pollution problems in many major urban areas of the world. Some typical annual average concentrations of select criteria air pollutants across world cities shown in Figures 101.2 to 101.5, illustrate the regional differences in concentrations with rapidly developing countries of Asia facing the largest challenges.

Over the last decade, many cities have stepped efforts to provide a gridded network of air pollution monitors that operate throughout the year providing a more reliable estimate of population exposure together with

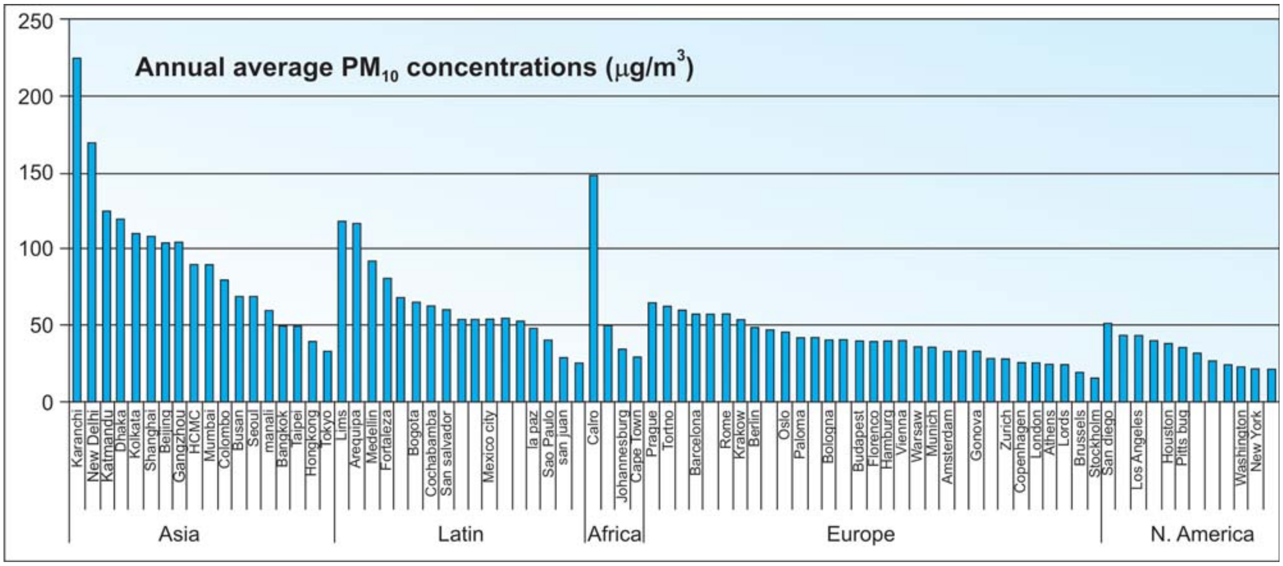

Fig. 101.2: Annual average PM_{10} concentrations observed in selected cities worldwide between 2000 to 2004 (*Source:* WHO, 2006)

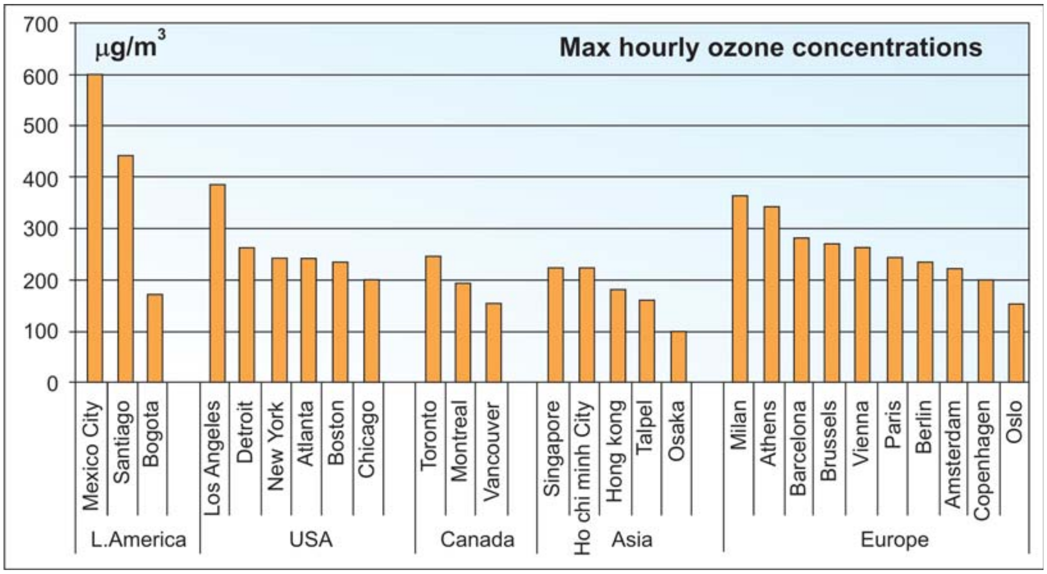

Fig. 101.3: Annual average O_3 concentrations observed in selected cities worldwide between 2000-2004 (*Source:* WHO, 2006)

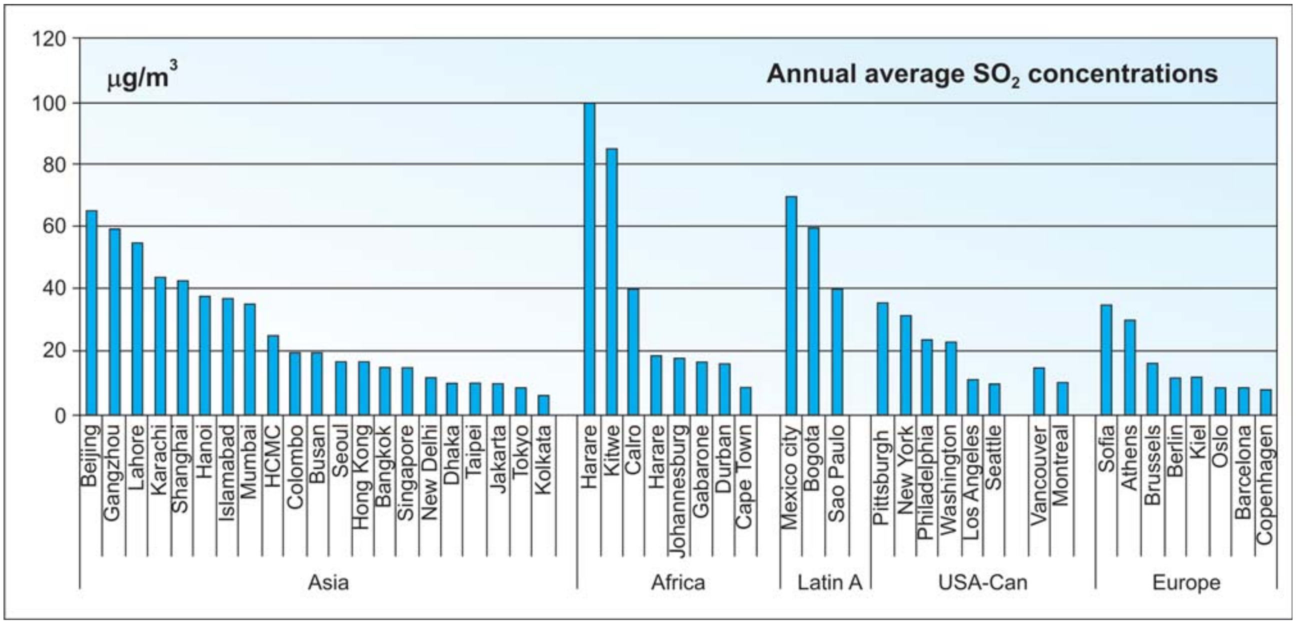

Fig. 101.4: Annual average SO_2 concentrations observed in selected cities worldwide between 2000-2004 (*Source:* WHO, 2006)

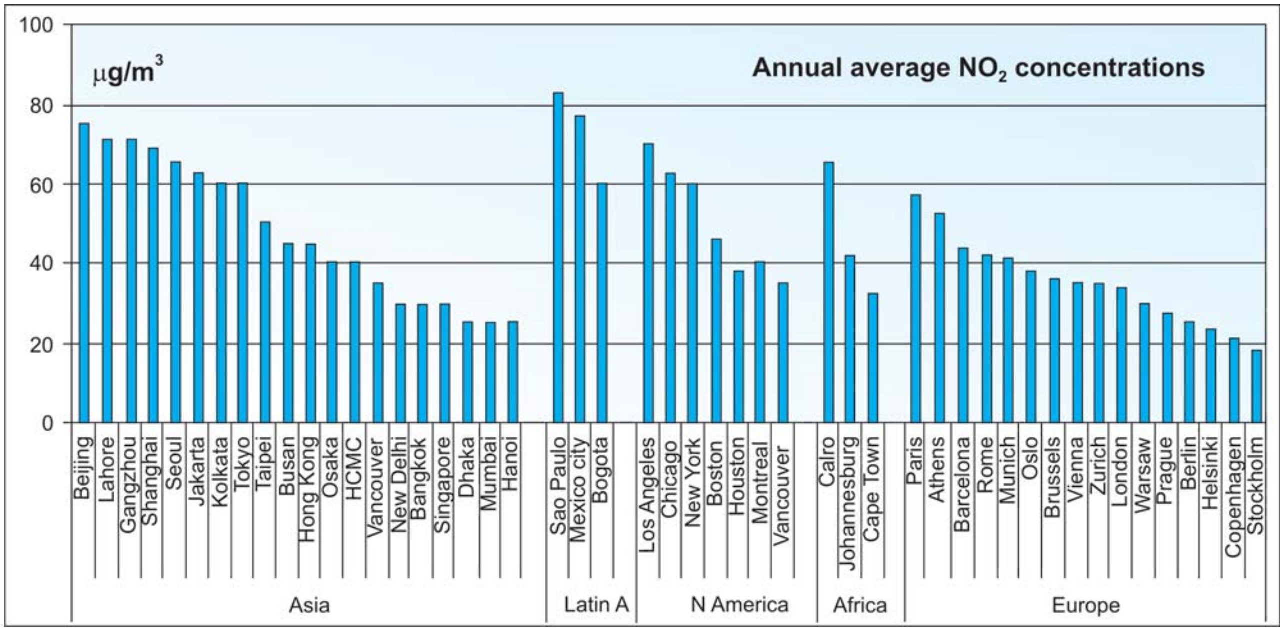

Fig. 101.5: Annual average NO_2 concentrations observed in selected cities worldwide between 2000-2004 (*Source:* WHO, 2006)

accompanying intra-city spatial/temporal differentials. The data has also become more easily accessible with many local pollution control agencies providing concurrent information on their websites. An example of data available through the Indian Central Pollution Control Board is provided in Figure 101.6.

Health Effects of Outdoor Air Pollution

There is now a wide body of literature available that documents health effects from criteria air pollutants in the urban outdoors. The earliest comprehensive consolidation of the evidence was provided by the first edition of the WHO Air Quality Guidelines for Europe

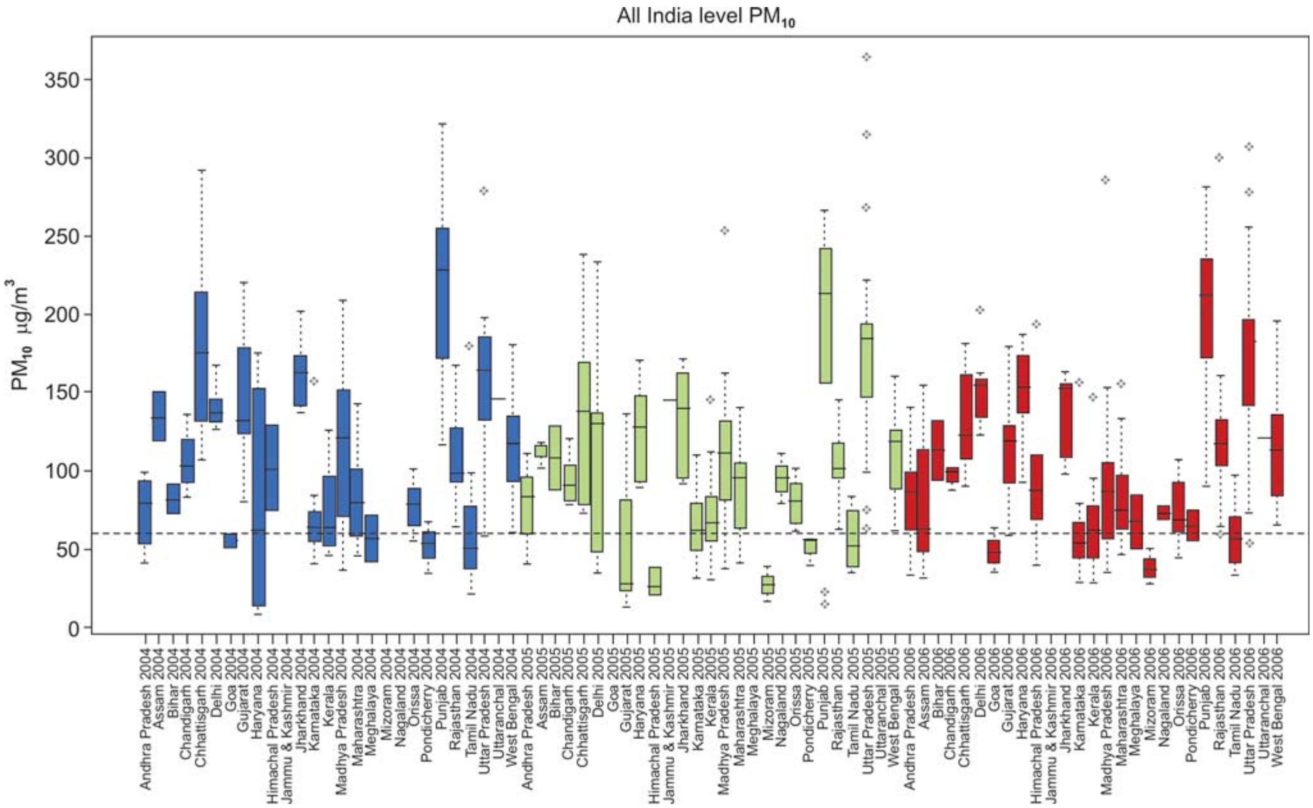

Fig. 101.6: Distribution of daily average concentrations of PM$_{10}$ across 126 cities in 25 states and 4 union territories in India over a 3 year period (2004-blue; 2005-green; 2006-red) shown as box-plots (*Source:* Central Pollution Control Board, Govt. of India)

(WHO, 1987). This summarized scientific knowledge on the health hazards related to 28 most common air pollutants, providing a uniform basis for risk assessment of air pollution to the national authorities responsible for protecting populations from adverse effects of pollution. In the early 1990s, the growing body of knowledge allowed WHO to initiate the process of revising the Guidelines in 2000, summarizing risk characterization of 37 pollutants (AQG, 2000). The American Thoracic Society (ATS, 2000) provided the guidance on definitions of what constitute an adverse effect of outdoor air pollution (Fig. 101.7). While most of the literature generated in this period focused on respiratory and cardiovascular events attributed to short- and long-term exposures, a new generation of studies is suggesting that the occurrence of effects is not limited to these outcomes. An expanded list of outcomes reported in literature is listed in Table 101.2. The WHO lead “Comparative Risk Assessment” (WHO, 2002) pointed out that while largest burden of disease attributable to outdoor air pollution is borne by regions of the world besides Europe and North America, most studies that informed this estimation came from this region. Considerable uncertainties remained in extrapolating exposure—response relationships to regions where the exposure is often an order of magnitude higher. The newly formulated WHO Air Quality Guidelines (AQG, 2006) recognizing this wide disparity in exposure levels, has provided interim targets that all regions of the world should attempt to reach in the near–term with the guideline values serving as a benchmark, where minimal impacts may be expected to occur.

Indoor Air Pollution

Household Solid Fuel Combustion

Nature and sources: Nearly three billion people, mostly in the least developed and developing countries are estimated to rely on solid fuels such as biomass (wood, agricultural residues and animal dung), charcoal and coal for cooking and other household energy needs. Solid fuels in these households is often used in inefficient and poorly vented combustion devices that results in bulk of the fuel energy being emitted and wasted as toxic products of incomplete combustion. Further, their use in small and poorly ventilated kitchens in close proximity to household members, on a daily basis over many years often spanning entire life times, creates an exposure situation that is significantly detrimental to health of all family members, in particular for women and children who spend the largest fraction of time within or near the kitchen.

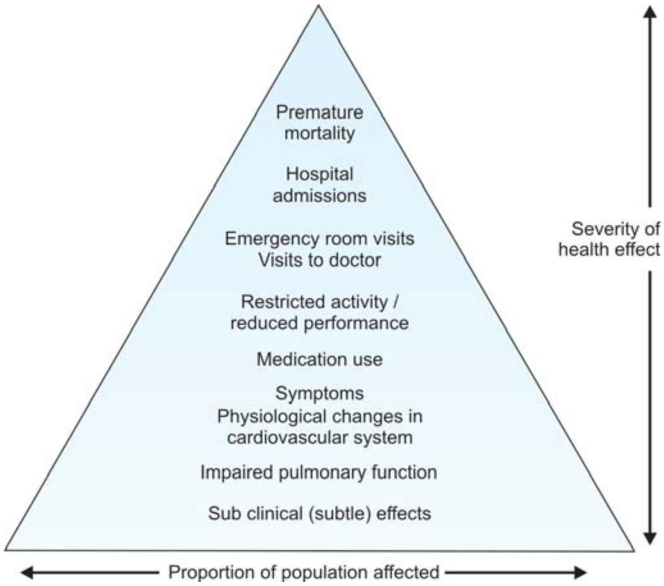
Premature mortality
Hospital admissions
Emergency room visits
Visits to doctor
Restricted activity / reduced performance
Medication use
Symptoms
Physiological changes in cardiovascular system
Impaired pulmonary function
Sub clinical (subtle) effects
Severity of health effect
Proportion of population affected

Fig. 101.7: Pyramid of health effects associated with air pollution (*Source:* ATS, 2000)

TABLE 101.2 Health effects attributed to outdoor air pollution

Effects attributed to short-term exposures

- Daily mortality
- Respiratory and cardiovascular hospital admissions
- Respiratory and cardiovascular emergency room visits
- Respiratory and cardiovascular primary care visits
- Use of respiratory and cardiovascular medications
- Days of restricted activities
- Work absenteeism
- School days missed
- Acute symptoms (wheezing, coughing, phlegm production, respiratory infections)
- Physiologic changes (e.g. lung function)

Effects attributed to long-term exposures

- Mortality due to cardiovascular and respiratory disease
- Chronic respiratory diseases incidence and prevalence (asthma, COPD, chronic pathological changes)
- Chronic changes in physiologic functions
- Lung cancer
- Chronic cardiovascular disease
- Intrauterine growth restriction (term low birth weight, intrauterine growth retardation, small for gestational age)

Source: Adapted from WHO, 2000b

Several demographic surveys conducted in developing countries, especially over the last decade, have started to collect information on household fuel use. According to a recent UNDP review (UNDP, 2009), some 129 countries have data available on fuel use including access to modern fuels and fuels used for cooking. India and China together account for nearly half the global population, that uses solid fuels for cooking (27 and 25% respectively), followed by sub-Saharan Africa. Wood is the predominant type of solid fuel used although in many surveys the distinction between wood, woodchips and agricultural residues is not clearly made. Although, among developing countries nearly 40% rely on modern fuel gas, which is uncommon among the least developed countries. Other fuel use is concentrated in certain countries, e.g. charcoal in sub-Saharan Africa, coal in China, dung in India, kerosene in Djibouti and electricity in South Africa.

Emissions from combustion of household fuels: Within communities, there exists a great deal of diversity in types and quantities of household fuels used. Further, the nature of devices deployed to burn these fuels and conditions of combustion (such as temperature, air flow, shape of the combustion chamber) have major implications for the specific nature of emissions within a household. Under ideal conditions complete combustion of carbon would produce only carbondioxide and water. However, virtually all configurations of solid fuel use emit substantial quantities of Products of Incomplete Combustion (PICs) as conditions for efficient combustion of these fuels are difficult to achieve in typical household stoves. These include respirable particulate matter, gases such as carbon monoxide and nitrogen-dioxide, organic compounds including saturated hydrocarbons, polycyclic aromatic hydrocarbons including benzo(a)pyrene, alcohols, phenols, quinones/semi-quinones and chlorinated acids such as methylene chloride and dioxins. Combustion of coal in addition to the above pollutants may release oxides of sulfur and heavy metal contaminants including arsenic and fluorine. On an average, a typical solid fuel stove converts 6 to 20% of the fuel carbon into toxic substances. At least 28 pollutants have been shown to be toxic in animal studies and some 14 carcinogenic compounds, six cilia-toxic and mucus coagulating agents and 4- co-carcinogenic or cancer-promoting agents have been identified (Table 101.3).

In a recently concluded assessment by IARC, indoor emissions from household combustion of coal has been classified as being "carcinogenic to humans" (Group 1 carcinogen based on sufficient human and experimental evidence) while indoor emissions from household combustion of biomass fuel (mainly wood) has been classified as "probably carcinogenic to humans" (Group 2A carcinogen on the basis of limited evidence of carcinogenicity of biomass combustion emissions (mainly from wood) in humans and experimental animals; sufficient evidence of carcinogenicity of wood-smoke extracts in experimental animals; and strong evidence of mutagenicity) (Straif et al, 2007).

Exposures to health damaging pollutants from combustion of household fuels: Well over a hundred studies over the last two decades have assessed levels of indoor air pollutants in households using solid fuels. The methods employed range from collection of questionnaire based information to quantitative measurements of household level exposures. A global database that documents results from these measurements across some 70 studies from developing countries of Asia, Latin America, Africa and China (if reported in English) has been available as a WHO IAP database (WHO, 2005). Although a great majority of studies have performed single pollutant measurements on a cross sectional sample of households, select studies have made important contributions to examining temporal, spatial or multi-pollutant patterns, in addition to day-to-day or seasonal variability in concentrations and exposures (Saksena et al, 1992; Balakrishnan et al, 2002; Ezzati et al, 2000; Gongli, 2004). A few have also developed models to examine the differential contributions of household level determinants and validate the use of simpler household level indicators (that are relatively easy to collect) as a proxy for household level exposures (Balakrishnan, 2004; Bruce, 2004). The 2005 version of WHO Global IAP database is now being updated to serve as a background for the revised burden of disease assessments for solid fuel use. To date, data from nearly 107 studies has been abstracted in this updated database and provides information on measured concentrations of indoor air pollutants related to solid fuel use from around 30 countries spread over all WHO regions (Balakrishnan et al, 2009).

Particulate matter of various size fractions has been measured, most often followed by carbon monoxide. Other air toxics have seldom been reported. While earlier studies measured Total Suspended Particulate (TSP) matter over short sampling durations during cooking, many recent studies report results of PM_{10} or $PM_{2.5}$ over 24 hour periods. All solid fuel using households experience concentrations 2 to 5 folds (upto 10 folds) higher than available 24 hour WHO Air Quality Guidelines (AQG) for PM_{10} and $PM_{2.5}$. Even gas using households in rural areas barely meet the AQG values presumably due a high background of outdoor air pollution resulting from venting/dispersion of solid fuel smoke from solid fuel using households. Figure 101.8

TABLE 101.3: Toxic pollutants from solid fuel combustion and potential for toxicity

Pollutant	*Known toxicological characteristics*
1. Particulates (PM_{10}, $PM_{2.5}$)	Bronchial irritation, inflammation increased reactivity, reduced mucociliary clearance, reduced macrophage response
2. Carbon monoxide	Reduced oxygen delivery to tissues due to formation of carboxy-hemoglobin
3. Nitrogen dioxide (relatively small amounts from low temperature combustion)	Bronchial reactivity, increased susceptibility to bacterial and viral lung infections
4. Sulfur dioxide (relatively small amount from most biofuels)	Bronchial reactivity (other toxic end points common to particulate fractions)
5. Organic air pollutants Formaldehyde 1,3 butadiene Benzene Acetaldehyde Phenols Pyrene Benzopyrene Benzo(a)pyrene Dibenzopyrenes Dibenzocarbazoles Cresols	Carcinogenicity Co-carcinogenicity Mucus coagulation, cilia toxicity Increased allergic sensitization Increased airway reactivity

(*Source:* Balakrishnan, 2004)

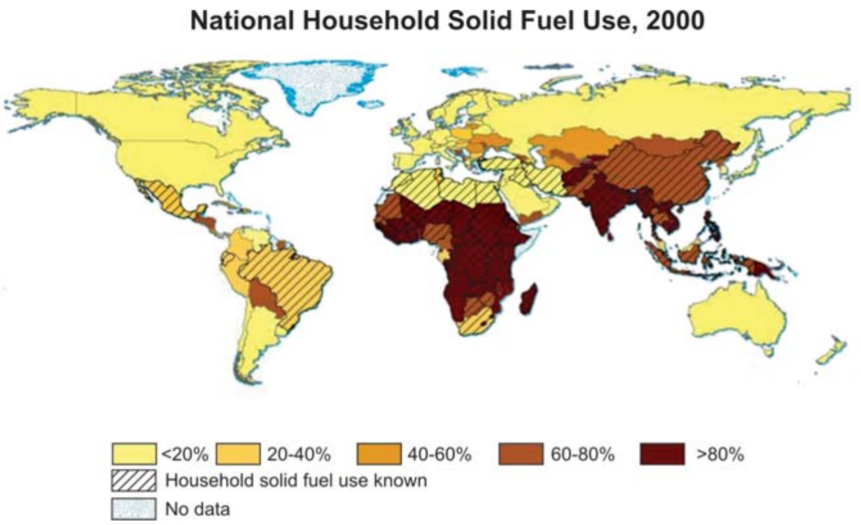
National Household Solid Fuel Use, 2000
<20%
20-40%
40-60%
60-80%
>80%
Household solid fuel use known
No data

Fig. 101.8: Global prevalence of household solid fuel use (*Source:* WHO, 2002)

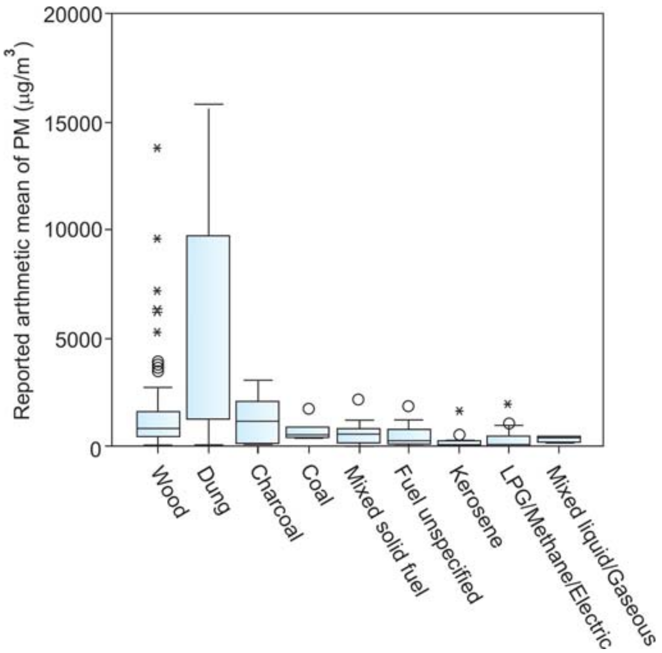

Fig. 101.9: Distribution of reported arithmetic mean of particulate matter concentrations across studies (including all size fractions and sampling durations) in households using solid fuels in traditional stoves [Balakrishnan et al, 2010 (personal communication)]

shows the global distribution of solid fuel use while Figure 101.9 and Table 101.4 show the distribution of reported mean (arithmetic) values of particulate matter across various types of fuels in rural/urban studies (available in the global IAP database) that include all sampling durations and size fractions. As tabulated, the median values in liquid or gaseous fuel using households are observed to be 5 to 10 fold lower than what is reported in solid fuel using households. When compared in nested paired measurements, the levels in gaseous fuel using households is often 10 to 20 fold lower than experienced in corresponding solid fuel using households. Peak values in dung and coal using households have occasionally been observed to be 100 fold higher than corresponding gas using households.

Health effects and disease burden attributable to use of solid fuels: Evidence for health effects associated with exposure to smoke from combustion of biomass fuels was provided initially by studies on outdoor air pollution as well as by studies dealing with exposure to environmental tobacco smoke. Criteria documents for outdoor air pollutants published by the USEPA (USEPA, 1997) for example detail the effects of many components also found in wood smoke including particulate matter, carbon monoxide, oxides of sulfur and nitrogen, and polycyclic aromatic hydrocarbons.

Considerable scientific understanding now exists about aerodynamic properties of the particles that govern their penetration and deposition in the respiratory tract. The health effects of particles deposited in the airway depend on the defense mechanisms of the lung such as aerodynamic filtration, mucociliary clearance and in situ detoxification. Since most particulate matter in biomass fuel smoke is less than 3 µm in diameter, it is likely to reach the deepest portions of the respiratory tract and alter defense mechanisms. Several biomass fuel combustion products may also impair the mucociliary activity and reduce the clearance capacity of the lung resulting in increased residence time of inhaled particles, including

TABLE 101.4: Distribution of reported particulate matter concentrations in solid fuel using households (form studies available in the Global IAP database)

Type of fuel	*Mean*	*Median*	*SD*
Wood	2097.42	858.00	3892.85
Dung	7755.93	2619.00	11999.90
Charcoal	3926.11	1190.00	8395.52
Coal	820.20	533.00	579.43
Mixed solid fuel	590.70	575.00	455.51
Fuel unspecified	537.10	298.00	565.68
Kerosene	269.94	100.00	422.10
LPG/ Methane /Electricity	316.01	139.00	371.08
Mixed Liquid/ Gaseous fuel	375.75	397.67	148.61
Total	1408.90	500.00	3869.69

microorganisms. In situ detoxification, the main mechanism of defense in the deepest non-ciliated portions of the lung may also be compromised by exposure to components of biomass fuel smoke (Demarest, 1997).

Some of the earliest epidemiological evidences linking indoor air pollution from biomass combustion with respiratory health came from studies carried out in Nepal and India in the mid-1980s. Since then there have been a number of new studies, especially on women who cook with these fuels and young children. While a rigorous epidemiological framework that uses all criteria for establishing causality (such as the use of Bradford Hill's criteria) cannot be created from available studies, strong associations have been reported for a select set of health outcomes. These outcomes were used by WHO to prepare the first burden of disease estimates attributable to the household use of solid fuels in 2000. Since limited quantitative exposure estimates are available across multiple world regions (especially in developing countries where such exposures predominate), it was not possible to use a conventional exposure–response approach for these calculations. Instead, reported use of solid fuels was used as an indicator to stratify households as exposed versus not exposed in health studies. The odds ratios computed from these studies were then applied at a national/regional level where routinely collected demographic surveys provided fuel use information to allow burden of disease estimates (wherever fuel use information was not available it was modeled using econometric information).

For computing disease burdens associated with solid fuel use, estimates of relative risk obtained from epidemiological studies have been combined in meta-analyses for the three disease end-points for which there is strong evidence of an association with use of solid fuels viz. Acute Lower Respiratory Infection (ALRI) in children aged less than 5 years, COPD and lung cancer (only for use of coal). The WHO led CRA exercise estimates that more than 1.6 million deaths and over 38.5 million DALYs were attributable to indoor smoke from solid fuels in 2000 (Table 101.5). Cooking with solid fuels is thus responsible for a significant proportion, about 3%, of the global burden of disease. These risks are comparable to risks from tobacco and only exceeded by malnutrition (16%), unsafe water and sanitation (9%) and unsafe sex (4%).

Allergens in the Indoor Environment

Nature and sources: Allergens in built environments pertain mainly to microbial pollution involving hundreds of species of bacteria and fungi as well as protozoans and dust mites that grow when sufficient moisture is available. These agents are responsible for a large variety of respiratory symptoms, allergies and immunological reactions and have also been associated with asthma. They may be transported into buildings through active and passive ventilation or through contact with materials or clothing. They are found ubiquitously in all indoor environments including those without moisture but growth conditions become favorable only in the presence of water and nutrients (such as human scales for dust mites, plant, animal and other organic matter for fungi and bacteria) that abound indoors and especially in poorly ventilated moist spaces.

Classes of allergens produces by these organisms include proteases (such as Derp I and II produced by dust mites), enzymatic glycopeptides (such as those produced by IgG and IgE inducing fungi), endotoxins

TABLE 101.5: Numbers and rates of deaths and DALYs per million population attributable to indoor air pollution from solid fuel use, for all causes (pneumonia, COPD, lung cancer), 2004

	Attributable deaths per year		*Attributable DALYs per year*	
	Number (000)	*Per 1 million population*	*Number (in millions)*	*Per 1 million population*
Developing countries	1,944	378	40.5	7,878
LDCs	577	771	18.4	24,606
Sub-Saharan Africa	551	781	18	25,590
South Asia	662	423	14.2	9,075
Arab States	35	114	1.1	3,489
East Asia and pacific	665	341	6.5	3,308
Latin America and Caribbean	29	54	0.7	1,334
World	1,961	305	41	6,374

Source: UNDP Report, 2009

(produced by gram-negative bacteria), fungal glucans, mycotoxins and volatile organics (produced by some fungi). Dampness and inadequate ventilation also favor the growth of bacteria and promote survival of viruses that are responsible for a range of respiratory infections.

Human exposures: The assessment of human exposure to allergens has been limited by the lack of routine monitoring methods to quantify allergen loads. While dampness is the most commonly used indicator of exposure, there is considerable variation and subjectivity on how dampness could be related to concentrations of microbes. There are many distinct challenges in assessment of indoor concentrations of microorganisms as well. Levels at which microorganisms may become hazardous may vary by several orders of magnitude between pathogenic and non-pathogenic species. Sampling inactivates many sensitive organisms while others such as spores are relatively robust. Sensitivity and specificity of methods to identify and count microbes are not uniform across species. Consequently, widely different concentrations have been reported even while using well-established methods (e.g. the *Limulus* amebocyte lysate assay for measuring bacterial endotoxins). Despite these limitations, culture and non-culture based analytical methods have been used in conjunction with active or passive to assess bioaerosol loads in many indoor environments. Most of such assessments have shown concentrations to be several folds higher in damp indoor spaces as compared to well ventilated dry indoor environments.

Health effects: In a recent assessment conducted by WHO to develop guidelines for indoor air quality related to dampness (WHO, 2009), reviews were performed to evaluate the epidemiological, toxicological and clinical evidence for association of dampness with respiratory ill-health. Although exposures to microbial agents have been quantified in some studies, these data were found to be too sparse to allow their use in health effects studies with the exception of select clinical studies. Most health effects have thus been observed in relation to prevalence of dampness. Key results of the meta-analyses of epidemiological studies are summarized in Table 101.6. In addition, the WHO review also provides details of studies to estimate the strength of toxicological and clinical evidence. These are summarized in Table 101.7.

Air Pollutants in the Occupational Environment

Several categories of air pollutants in the occupational environment have been well known and are well recognized to be causative agents for a wide range of respiratory health impairments ranging from respiratory symptoms, COPD and fibrotic lung diseases to lung cancer and asthma. These include airborne particulates in the form of mineral/organic dusts and fibers as well as occupational carcinogens such as solvents.

Well established guidelines for exposure assessment and medical surveillance are widely available through the numerous local and international regulations and publications of agencies such as the WHO, International Labor Organization and National Institute for Occupational Safety and Health (USA). These include agents such as asbestos, silica, cotton dust, heavy metals and volatile organic compounds. To reproduce such widely available information for agents would be redundant and instead descriptions of some newly emerging concerns are provided.

TABLE 101.6: Key results of the meta-analyses of Fisk, Lei-Gomez and Mendell (WHO, 2009)

Outcome	*Participants*	*No. of studies*	*Odds ratio (95%CI)*	*Estimated % increase in outcome in houses with visible dampness, mould or mould odor*
Upper respiratory tract symptoms	All	13	1.70 (1.44-2.00)	52
Cough	All	18	1.67 (1.49-1.86)	50
	Adults	6	1.52 (1.18-1.96)	—
	Children	12	1.75 (1.56-1.96)	—
Wheeze	All	22	1.50 (1.38-1.64)	44
	Adults	5	1.39 (1.04-1.85)	—
	Children	17	1.53 (1.39-1.68)	—
Current asthma	All	10	1.56 (1.30-1.86)	50
Ever-diagnosed asthma	All	8	1.37 (1.23-1.53)	33
Asthma development	All	4	1.34 (0.86-2.10)	30

TABLE 101.7: Strength of evidence for various health outcomes related to dampness (as an indicator of indoor microbial contamination), (WHO, 2009)

Strength of Evidence		*Health Effects*
Sufficient	Epidemiological	Asthma development, asthma exacerbation, current asthma, respiratory infections (except otitis media), upper respiratory tract symptoms,cough, wheeze and dyspnea
	Clinical	Hypersensitivity pneumonitis, allergic alveolitis and mould infections in susceptible individuals and inhalation fevers
Suggestive	Epidemiological	Allergic Rhinitis and Bronchitis
	Toxicological	Inflammation, cytotoxicity, immunosuppression
Inadequate		Lung function, allergy, atopy

Some examples of newly recognized occupational lung disease include flock worker's lung, hypersensitivity pneumonitis associated with biocontaminated synthetic metal working fluids, Severe Acute Respiratory Syndrome (SARS), asthma associated with 3-Amino-5-Mercapto-1,2,4-Triazole (AMT) in herbicide manufacture and bronchiolitis obliterans from flavoring chemicals. Nano-materials represent a particularly challenging class of occupational respiratory hazards as little is known about their disposition in the body following exposures. Table 101.8 provides a listing of some newly recognized respiratory hazards in the occupational environment and associated clinical conditions. While the occupational etiology for these risk factors have been established on the basis of a detailed history of exposure, little is known about the quantitative exposure levels or the mechanisms underlying disease causation. A general description of the exposure situations and clinical conditions are therefore provided for selected agents.

Bronchiolitis obliterans linked to the small-molecular-weight chemical diacetyl is frequently referred to as "popcorn lung disease" as the first outbreak of cases were noted among manufacturing workers in a popcorn plant where diacetyl was being used to produce butter-like flavoring. "Flock-worker's lung" represents another emerging occupational respiratory disease reported amongst workers dealing with flock made of nylon, polyethylene, polypropylene and rayon. Short length synthetic fibers produced by rotary or guillotine blades and cleaning operations are known to be most prevalent exposure circumstance. The use of a series of commercial products with waterproofing components (Table 101.8) has been associated with outbreaks of a new syndrome of acute lung injury, ranging from a mild, nonspecific chemical pneumonitis to full-blown ARDS with diffuse alveolar damage. The unifying characteristic of these products is the presence of fluoropolymers that are not present as

TABLE 101.8: Newly emerging occupational respiratory conditions and associated risk factors/exposures

Disease or Syndrome	*Emerging Exposure or Newly Recognized Risk Factor*
Bronchiolitis obliterans	Flavoring industry chemical exposure (diacetyl)
Bronchiolitis obliterans	Boat building (fiberglass coating materials)
Lymphocytic bronchiolitis	Flock fibers (nylon, polyethylene, polypropylene,rayon)
Pneumonitis, acute lung injury	Waterproofing materials (various consumer applications)
Alveolitis, pulmonary fibrosis	Flat panel display production (indium tin oxide)
Dendriform pulmonary ossification	Rare earth pneumoconiosis (cerium oxide)
Pulmonary fibrosis, pleural effusion	Heavy industrial exposure to polyacrylate nanoparticle aerosols
Anthracofibrosis	Mining, dusty trades (heavy mineral dust exposure)
Extrinsic allergic alveolitis	Animal feed industry (phytase enzymes)
Asthma	Point of sale computer terminal use (thermal paper)
Asthma	Biochemical synthesis (peptide couplers)
Asthma	Orthopedic casting (isocyanates)
Asthma	Nail salon work (methacrylates)
Silicosis	Sandblasting jeans (silica)
Respiratory bronchitis - interstitial lung disease	Hospitality work (secondhand smoke)
Idiopathic pulmonary fibrosis	Wood and metal working (wood, metal dusts)
Sarcoidosis	Building debris clean up (mixed dust)

propellants but as an ingredient that provides the key waterproofing characteristic of the application in question.

Exposure to indium tin oxide, a sintered metal alloy that is a key component used in the manufacturing of liquid crystal or plasma flat-panel display units (Table 101.1), has been linked to alveolitis and pulmonary fibrosis among production workers. Although, to date, this novel form of pneumoconiosis has been reported only from Japan, where the industry is concentrated, it is likely that additional cases are occurring wherever this alloy is heavily used in manufacturing or where exposure may occur through recycling.

Recording of detailed exposure histories together with medical surveillance in the workplace has allowed the recognition of new risk factors for established diseases (as in the case of newly recognized agents for occupational asthma such as animal feeds, commercial cleaning products, thermal paper, etc.) or new exposure situations for established cause of disease (such as isocyanates in health care, silica in sandblasting of denim jeans and asbestos in ship breaking).

In summary, an effective surveillance strategy at the workplace is critical to manage well known risks and recognize newly emerging risks. This will allow prevention of many conditions that were hitherto labeled as "idiopathic" for need of routine data on health and exposures at the workplace.

CONCLUSION

The preceding paragraphs provide an overview of the important environmental risk factors that contribute significantly to the prevalence and burden of respiratory disease. With an exception of high-level occupational exposures that may trigger outbreaks or episodic illness that may be relatively easily recognized through company level medical surveillance, the other population level risk factors in the outdoor and indoor environment contributing may not merit much attention in routine medical practice. Lack of recognition and awareness on the merging body of scientific evidence for exposures and related health impacts often poses significant challenges for public health, as professionals vested with the responsibility of intervention do not perceive the "risks." In developing countries with large populations such as India, there is a tremendous need for conduct of epidemiological studies that may generate the much needed "evidence for policy" at the local levels. Few, if any, longitudinal studies that examine multiple risk factors and their interactions in contributing to health impacts for the general population as well as development, progress and management of clinical conditions, are available in settings where exposures predominate.

Inclusion of the results of important recent scientific research related to the recognition and evaluation of environmental risk factors for respiratory disease in routine curriculum of medical and public health programs is necessary to build capacities to address these risks in the near term. As with most disease conditions, prevention is far more cost-effective than management but is particularly so with the risk factors in the "modifiable environment." It is hoped that information provided in this chapter has made a small but significant incremental step in that direction.

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Climate Change and Lung Disease—With Special Focus on Developing Countries

Kin Bong Hubert Lam, Jon G Ayres

CLIMATE CHANGE: AN INTRODUCTION

The Earth's climate is a system determined by complex interactions between solar radiation, atmosphere (temperature, precipitation, humidity, atmospheric pressure and wind), lithosphere (land masses and tectonic activity), hydrosphere (water bodies) and biosphere (living beings). Climate is thus highly dynamic, influenced by both internal components and external factors (known as "forcings") and evolves over time. As a result, it is often described by "statistical description in terms of the mean and variability" of its meteorological elements (primarily temperature, precipitation and wind) over a period of time.[1] Over the last decade or so, global temperatures have been rising and increasing concern has been expressed about the likely impact of this climate change on the Earth, in general and on health, in particular.

While by definition natural phenomena such as solar variations and volcanic eruptions can cause fluctuations in climate, there is an increasing body of evidence which has suggested that anthropogenic activity, since the industrial revolution, has been the key driver of climate change. An increasing worldwide population and economic development have resulted in greater demands on energy supply, transport, agriculture and industry, which ultimately have led to increased emissions of carbon dioxide (CO_2) from fossil fuel combustion and other greenhouse gases (GHG) including halogen-containing gases, methane (CH_4), nitrous oxide (N_2O) and tropospheric ozone. For instance, atmospheric CO_2 levels at Mauna Loa, Hawaii rose from 316 parts per million by volume (ppmv) in March 1958 to 389 ppmv in January 2010,[2] while historical data derived from ice cores suggest that preindustrial atmospheric CO_2 was probably in the range 275 to 284 ppmv.[3] At the same time, between 1906 and 2005 global surface temperatures have increased by about 0.74°C (±0.18°C).[1] Although this warming is not globally uniform, the trend is reconciled by observed changes in other components of the climate system, such that the increase in atmospheric concentration of GHG has been implicated as the predominant forcing of climate change and is otherwise unlikely to be fully explained by confounders.

Increase in the mean surface air temperature on a global scale is just one of the manifestations of climate change. Consistent with the overall warming trend, the number of extremely hot days and warm nights has been increasing since the 1950s,[4] and in recent years heat waves have been more common worldwide. Severe heat waves were recorded in Europe in 2003 and 2006, and a large part of Asia was affected in 2007; resulting in marked increases in mortality. Climate change also results in alterations in precipitation patterns. Compounded by oscillations in climate pattern such as El Niño, climate change is regarded as being responsible for more frequent and intensive floods and droughts, severely affecting the developing countries where water supply, irrigation and sewage infrastructure is not very well established.

Climate change is a challenge faced by all living beings and is not restricted to a single geographical region, posing serious threats to both developed (coincidently mostly situated in the temperate latitudes) and developing countries (often within the intertropical zone), although it is expected that the developing countries, particularly those who live in poverty, will be disproportionately more affected by climate change.

FUTURE PROJECTIONS OF CLIMATE CHANGE

It is generally agreed that global temperatures will continue to rise for decades to come, largely due to GHG produced by human activities. The Intergovernmental Panel on Climate Change (IPCC) forecasts an increase of 1.1°C to 6.4°C in the global mean surface air temperature over the 21st century.[5] However, the extent of effects on individual regions will vary by latitude, altitude and proximity to water bodies as well as by external factors such as the level of human activities, and development (e.g. deforestation, urbanization). For example, between 1961 and 2000, an increase in the number of warm spells over southern and western Africa was recorded,[6] while in eastern Africa decreasing trends in temperature were observed from weather stations close to the coast or to major inland lakes.[7] Similarly, different precipitation patterns exist in different regions, as a result it is difficult to assess or to project the exact impact of climate change in individual regions.

In certain regions, warmer temperatures with increased precipitation may bring short and medium-term benefits (e.g. in the agricultural industry). However, when taken as a whole, the damage caused by climate change is likely to outweigh the benefits and to increase over time.[8] Decreased rainfall in northern Africa and much of the south is projected,[9] leading to increased water stress and reduced agricultural production. Likewise, a decrease in precipitation in central Asia is expected, accompanied by an increase in the frequency of very dry spring, summer and autumn seasons. In contrast, it is likely that there will be an increased risk of flooding along the coasts of South and Southeast Asia due to the rise in sea level. In south and south-western Latin America, the retreat of glaciers in the Andes and reduced precipitation will probably reduce fresh water availability. In North America, increased frequency, intensity and duration of heat waves is projected and storms are likely to be more often in the coastal areas. Floods in maritime and inland areas are projected to occur more often in Europe. There will almost certainly be less number of cold days, but accompanied by prolonged episodes of hot weather. Climate models suggest there would be more heat waves and greater intensity of droughts in Australia. Climate change will also result in major changes in vegetation and hence ecosystems such as the likely replacement of Amazonian tropical rainforest by savannas.

IMPACT OF CLIMATE CHANGE ON HEALTH

Human health is determined by complex interactions between an individual and the environment in which the local climate plays an important role. Extreme temperatures on their own can cause morbidity (e.g. heat stroke and frostbite) and mortality. Climate-associated disturbances in ecosystems and environment can lead to changes in the spatial and seasonal distribution of disease vectors and allergens, which in turn cause an impact on the incidence and prevalence of communicable diseases and allergy. Indirectly, climate change, through the action of extreme events such as droughts and floods, can incur injury and fatality thereby causing implications in food production and settlement. The burden on cardiorespiratory and gastrointestinal morbidity due to deteriorating air and water quality is expected to increase. The extent of the effect of climate change on human health varies by region, by vulnerability of population groups and individuals, and by the ability of the society to adapt to the change.

CLIMATE CHANGE AND LUNG DISEASE

While the health impact of climate change is nonspecific, its effect on respiratory health warrants special attention, as the respiratory system is inevitably susceptible to changes in atmospheric parameters. Several critical components of climate change (Table 102.1) could influence lung diseases, notably asthma, rhinosinusitis, chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis and respiratory tract infections. The impact varies in extent and severity according to the susceptibility of populations and individuals; with areas of greater poverty with less-well-developed or limited access to medical services suffering more. This will include migrating populations and areas where population growth is greatest.

Extreme Temperature Events

The relationship between health and temperature follows a U-shaped curve, with excess impacts increasing with both colder and hotter temperatures. Heat waves and cold "snaps" are the prime examples of extreme temperature events. For heat waves, the impact is likely to be greater in temperate regions due to poorer preparation for hot weather in these areas. But the

TABLE 102.1: Climate change components which could influence lung disease

- Extreme temperature events
- Changes in air quality
- Precipitation patterns
- Allergen disposition
- Vector transmission

developing countries, despite the fact that some of them lie in tropical regions, could be as vulnerable because of inferior medical services. Populations with limited adaptive capacity, such as the elderly and patients with COPD or other chronic conditions are likely to be particularly susceptible.

Western Europe experienced a large scale heat wave in the summer of 2003, with maximum temperatures rising to over 40°C in many places. It was estimated that some 22,000 excess deaths resulted in England and Wales, France, Italy and Portugal during and immediately after the heat wave.[10] In France during the period from August 1st to 20th, respiratory mortality increased by 90% (95% CI 80% to 100%) overall. This effect increased with age, mortality increasing by 50% (30% to 70%) for those aged 45 to 74 years; and 110% (100% to 120%) for those aged 75 or older (Fig. 102.1).[11] Many parts of Asia suffered similarly. In Shanghai alone, it was estimated that mortality went up by 13% (95% CI 6 to 20%), with respiratory deaths increasing by 23% (95% CI 2 to 48%) during the heat wave compared to other summer days in the same year.(12)

But these adverse effects are not simply seen with overt heat waves, there being a general relationship between health outcomes and temperature. This was first quantified by Farr in the UK in the first part of the 19th century who showed the degree to which mortality increased for each degree in temperature fall in the winter months *(Macfarlane A. Daily mortality and environment in English conurbations. Air pollution, low temperature, and influenza in Greater London. Br J Prev Soc Med. 1977;31(1):54-61)*. More recently, data from New York City suggested that there is a 2.7% (95% CI 1.3% to 4.2%) increase in risk for respiratory admission on the same day for every 1°C above a calculated temperature threshold of 28.9°C.[13] Similar findings were reported in a study of 12 European cities, which estimated a 2.1% (95% CI 0.6% to 3.6%) increase in respiratory admissions in Mediterranean cities and 1.2% (0.1% to 2.2%) in the north-continental cities for a 1°C rise in maximum

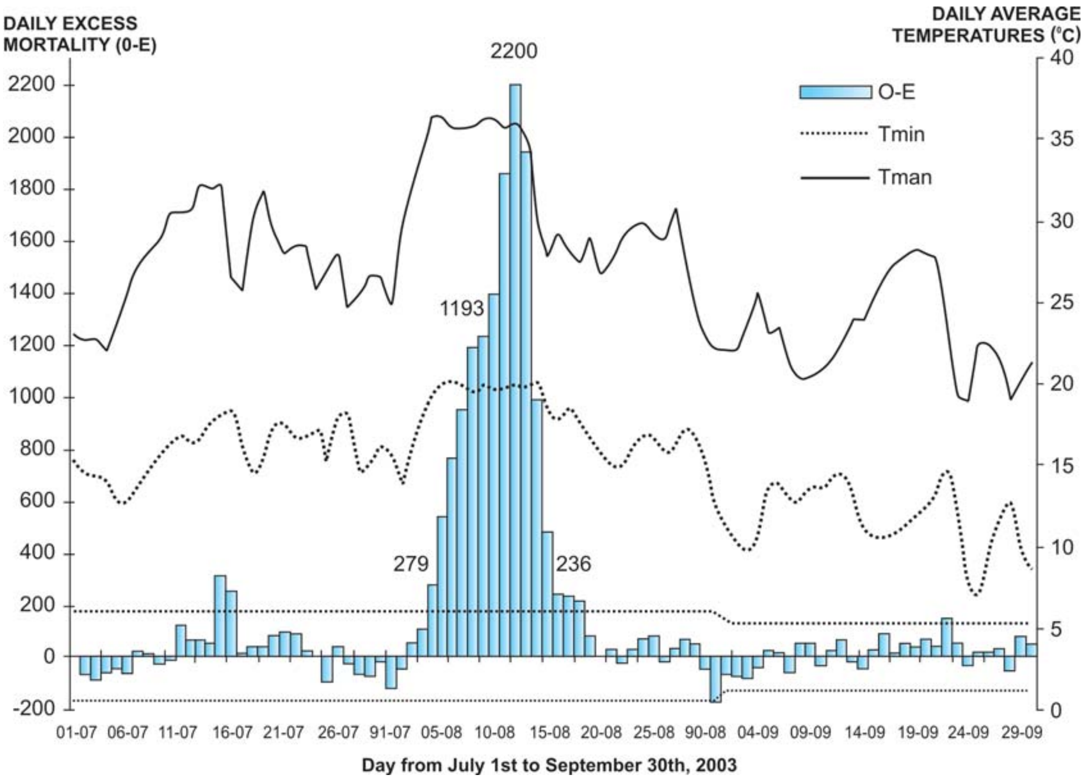

Fig. 102.1: Number of excess deaths and average daily maximum (Tmax) and minimum (Tmin) temperatures during the 2003 heat wave in France

The x axis shows the 92 days from July 1st to September 30th 2003. The histogram shows the numerical values of the daily excess mortality for August 4, 8, 12 and 16.

The dotted horizontal lines show the limits of the 95% fluctuation intervals of the daily number of deaths.

Adapted from Reference 11.

apparent temperature above the city-specific threshold,[14] with an effect on respiratory mortality appearing to be larger. A related meta-analysis based on mortality data from 15 cities indicated a 6.7% (2.4% to 11.3%) increase in respiratory mortality in the Mediterranean region and a 6.1% (2.5% to 11.1%) increase in the north.[15] In developing countries, particularly in rural areas, much of the hospitalizations and excess deaths during the heat wave period are probably due to heatstroke for which data and therefore predictions of respiratory deaths, are less reliable.

Air Pollution

Ground level air quality is highly dependent on weather conditions, which dictate the accumulation and dispersion of air pollutants. Human activities generate large quantities of pollutants, comprising mainly particulate matter (PM), sulphur dioxide (SO_2), nitrogen oxides (NO_x), carbon monoxide (CO), CO_2 and volatile organic compounds (VOCs). Depending on the country or area, the sources of these pollutants vary but the two main contributors are vehicle emissions and industrial emissions.

Ozone

The pollutant of maximum concern in the context of climate change is ozone because of its atmospheric chemistry. Under suitable weather conditions, NO_x, CO and VOCs will react with ultraviolet radiation to form ozone, a primary constituent of urban smog and a potent GHG in its own right. The rate of photochemical reactions in which ozone is formed is determined by temperature, solar radiation and atmospheric moisture with precursor emission levels.[16] Some of these factors are expected to be altered due to climate change and as current concentrations of tropospheric ozone are on the rise,[17,18] it is predicted that levels will continue to increase although wide regional differences are expected.[19]

In developed countries, exposure to high levels of ozone has been shown to be associated with an increase in respiratory morbidity and mortality (Table 102.2). At present, ozone is regarded as a non-threshold pollutant (i.e. at a population level effects from ozone occur linearly down towards zero) but if thresholds for some outcomes are identified this will have a major impact on calculations of health burden from any rise in ozone levels. There is some evidence to suggest that repeated exposure to ozone induces tolerance. However it is unclear to what extent this would be possible with a situation of gradually increasing levels day-on-day.

TABLE 102.2: Respiratory morbidity from exposure to high ozone levels

- Reduced lung function[20]
- Exacerbation of chronic respiratory diseases[21]
- Increased hospital admissions for pneumonia, COPD, asthma, allergic rhinitis and other respiratory diseases, and with premature mortality as well as with cardiovascular disease.[22-26]

Particulate Matter

PM may be influenced by climate change as its formation is in part determined by temperature and humidity while effects on industrialisation and population migration will also influence levels. The extent to which levels of PM will increase in global terms is uncertain, however, as events secondary to climate change such as reduction of emissions in some areas (albeit with increases in others), windblown dust as a result of deforestation and desertification and higher frequency of forest and bush fires could affect levels in varying and unpredictable ways.

Evidence for the health impacts of PM is stronger than that for ozone. Long-term exposure to PM has been associated with increased prevalence of symptoms and reduced lung function in asthmatic children,[27] and higher mortality in adults, including lung cancer deaths.[28-30] Similarly, short-term increase in ambient PM levels have been related to increase in cardiopulmonary hospital admissions and mortality.[31-33] In Malaysia and Brazil, increase in the number and extent of forest fires was associated with increased outpatient visits for respiratory disease.[34] PM generated in this way can affect air quality in areas thousands of kilometers away,[35] but accurate prediction of such effects is difficult.

Other Pollutants

While highway infrastructure is not well established in developing countries, but their urban air quality could be worse than the developed countries with high rate of car ownership, the reason being a combination of the use of low quality fuel (both in automobiles and power stations), poorly maintained vehicles and the lack of emission control legislation and enforcement. Coal-fired power stations are common in many developing countries. The use of coal with high sulphur content and the absence of flue-gas desulphurisation mechanisms lead to the emission of SO_2, which is a cause of acidification of soil and water. SO_2 has a marked bronchoconstrictor effect in asthmatics and this susceptibility was used as a driver in the UK to establish their Air

Quality Standard for this gas as a short term (15 minute) value.[36] SO_2 exposure has been associated with both respiratory,[37] and cardiac,[38] admissions although separating out the effect of this gas from PM (which are so often closely correlated in terms of air concentrations) is difficult and may have resulted in either over or under-estimation of the true effect sizes. Nevertheless, as temperature continues to rise with climate change, air conditioning will become even more widespread, especially in tropical regions, in turn boosting energy demand and producing more GHG (primarily CO_2) and SO_2, further impacting on the environment and the climate.

The burning of solid fuel, primarily biomass, in households is very common in rural parts of many developing countries and it has been estimated that over half the world's population (over three billion) is exposed indoors to smoke from burning of wood, animal dung, crop residues or coal. As a result of the use of these often low quality fuels and the use of simple open fires or low efficiency stoves, burning of biomass fuels often gives rise to large quantities of carbon with various additional components. These exposures are associated with increased risk of acute lower respiratory infections notably in children and also an increased risk of COPD and for coal in particular, lung cancer in the longer term. These emissions also contribute to global warming (from their gaseous rather than particulate components),[39] and changes in the use of biomass fuels associated with migrating populations associated with desertification may increase the spread and maybe the extent of the amount of fuel burnt in this way. In addition, as the impact of climate change intensifies, it is highly likely that the economies of developing countries will be affected (e.g. crop failure, population re-settlement because of extreme weather events). Without international support, the pace in the reduction of biomass emissions or the switchover to alternative fuel will be inevitably be slowed down or reprioritized.

SYNERGY BETWEEN AIR POLLUTION AND TEMPERATURE

Given temperature is the determinant of the formation of both ozone and PM, it is not surprising that climate change alone can enhance the adverse effects of these pollutants even when their levels remain stable. There is some evidence suggesting a synergistic effect between ozone/PM and temperature, particularly during the warm season,[40-43] for both respiratory and cardiovascular impacts. More recently, experimental work confirms that the redox activity of PM is amplified by ozone,[44] raising the possibility of a three-way interaction between PM, ozone and temperature.

Extreme Precipitation

Climate change is likely to cause increased variability in precipitation, with both more extreme episodes of rain and prolonged periods of drought. In either case, human lives and properties are as vulnerable. Floods threaten those populations whose habitation is in low-lying plains and coastal regions, which may result in both temporary displacement of the affected population and potentially longer term population relocation. The lack of clean water and food compounded with poor sanitation in crowded temporary settlements is one of the major causes of communicable diseases outbreaks. For example, diarrhoea and respiratory infection were the leading causes of morbidity and mortality in Bangladesh in 1988 during and after a major flood in the Irrawaddy delta.[45]

After floodwaters recede, the affected population is likely to move back to their homes, at varying times after the initial episode. If return is immediate the dwellings, while habitable, are likely to remain damp and run the risk of mould outgrowth. Living and working in damp housing is known to cause respiratory symptoms such as cough and wheeze,[46-48] and is also associated with an increased risk of developing asthma. This has been observed in both the developed and developing world.[49-51] It is not completely clear whether this association is simply due to damp or is related to allergic sensitization following mould exposure[52] or may represent the effects of other potential exposures, such as endotoxin,[53] and mycotoxins,[54] but living in damp housing is clearly associated with increased respiratory morbidity.

Droughts, on the other hand, do not directly impact on lung diseases except by reducing nutritional status and therefore increasing the risk of respiratory infection. In addition, desertification and the subsequent dust storms brought about by extended dry weather are likely to cause acute effects on the population with preexisting respiratory conditions as well as attacks of acute bronchitis even in those with previously healthy lungs.[55-57]

Effects on Allergens and Allergic Responses

Climate change, particularly increase in temperature and CO_2 levels, along with changes in humidity, is likely to have effect on the spatial distribution and life cycles of many species of flora, and hence the onset and length of their pollen seasons.[58-60] Plant species that were originally alien to a particular region may establish themselves because of changing climate and environment, thus introducing new allergens into the area and increasing rates of sensitization. [61] It is unclear whether allergic responses such as allergic rhinitis and asthma incidence and exacerbations would increase in absolute terms, but as ozone potentiates the effects of allergen exposure,[62] the likely increase in ozone levels should, regardless of whether new flora are present in any given area, result in more symptoms and attacks in sensitized individuals.

Changes in Respiratory Infections

The combination of higher temperatures and increased precipitation is likely to produce breeding conditions favoring greater incidences of a number of vector- and water-borne infectious diseases and prolonging their transmission season. In some cases this may increase the risk of acute respiratory infections in individuals compromised by such conditions although in general, the frequency of respiratory infections with climate change may decrease as such infections are more common during winter months.[63] Nevertheless, climate change can also affect population behavior, making it difficult to predict both the direction and magnitude of any change in infection incidence. For example, population dislocation due to extreme weather events could result in overcrowding and deterioration in hygiene and living conditions which may lead to an increase in tuberculosis, particularly in regions where the condition is prevalent.

Deforestation and other changes in the natural habitats brought about by climate change can have a major impact on wildlife, driving them to settle in closer proximity to the mankind, in turn leading to more frequent human contact and increased likelihood of zoonosis (infectious disease transmitted from animals to humans). Prime examples include the recent emergence of avian influenza virus (H5N1) and severe acute respiratory syndrome (SARS) coronavirus in East Asia, which are found in migratory birds,[64,65] and bats,[66,67] respectively. It is also possible that the seasonal and geographical distribution and transmission of pathogens could be altered by climate change. While there is no evidence showing the direct causal link, it has been reported that human adaption to climate change could also influence risks of infection. For instance, the use of open containers to store water during droughts has been associated with the outbreaks of Chikungunya fever, a mosquito-borne viral disease in Kenya.[68] First discovered in and thought to be limited to Africa, Chikungunya virus has recently emerged in Asian countries in the Indian Ocean,[69] as well as in the more distant Italy.[70] Although rising temperature in South Asia was suggested to be a contributory factor for enhanced transmission,[71] it is unclear whether the same holds true for its emergence in Europe.

CONCLUSION

While it is generally accepted that climate change is a mainstream public concern, the full extent of the scale and the effects of its direct and indirect consequences are not clear and can only be estimated by means of projections based on currently available evidence. The geographical and socioeconomic differences and disparities between countries add further levels of uncertainty. If there is one thing that is certain about climate change, it is that predicting health impacts is difficult and at times impossible. As the mean surface air temperature continues to rise, it is highly likely to be accompanied by more frequent and more intense extreme weather events, causing major disruptions to society and economic activities, and loss of life.

In terms of the impact on respiratory health, climate change is likely to increase the morbidity and mortality burden among those who have existing chronic conditions such as COPD. It also alters the patterns of seasonality, transmission and geographical distributions of infectious and allergic diseases. As strategies are being formulated to minimize, the health-related burden of climate change, it needs to be emphasized that its effects are not bounded by national frontiers and attempts at both mitigation and adaptation are needed through international and local collaboration. It should be regarded as mandatory to incorporate the specific needs of each individual population as there exists substantial regional variations, in terms of the scale of local climate change, population vulnerability and the ability to mitigate and adapt. Researchers, policy-makers and other stakeholders need to work more closely together to translate the research findings and develop appropriate action plans to ensure the sustainability of mankind in our approach to climate change.

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High Altitude Problems

Ajay Handa

INTRODUCTION

Ascent to altitude poses immense challenges on human body, including exposure to extremely low temperatures, low atmospheric pressures and hypoxia, which may lead to specific altitude related illnesses such as Acute Mountain Sickness (AMS), High Altitude Cerebral Edema (HACE) and High Altitude Pulmonary Edema (HAPE). These illnesses can be severe enough to compromise safety of travelers and if remain unrecognized may even prove to be fatal.

The occurrence of high altitude-related illnesses in those with pre-existing lung disease is of greater concern due to limited physiological reserve. However, there is scarcity of data regarding the risk of the development of altitude-related illnesses and the effect of high altitude on the underlying lung diseases. With changing lifestyle and increased spirit of adventure in the present era, more people with lung diseases are traveling to High Altitude Areas (HAA) for leisure and are therefore likely to develop these problems.[1]

Physical Changes with Altitude

The most significant change with altitude is decrease in barometric pressure with increasing altitude. This leads to lower inspired oxygen and thus lower alveolar oxygen partial pressure (P_AO_2) and arterial oxygen tension (P_aO_2) values. There is a reduction in air density and temperature with gain in altitude, this leads to greater insensible water losses through the respiratory tract. Air has less of house dust mite allergens with increasing altitude due to the low temperatures and reduced humidity. [2]

Pulmonary Adaptation to High Altitude

The various adaptive changes in the respiratory, cardiovascular and hematological systems, which allow the humans to survive in high altitude areas constitute "acclimatization". The main changes include compensatory increase in ventilation due to the decreased P_aO_2 called Hypoxic Ventilatory Response (HVR). There is an increased work of breathing and respiratory muscle oxygen consumption, thereby limiting exercise capacity at high altitude.[1]

Gas exchange in the alveolar capillaries is adversely affected by low P_AO_2 (reduced alveolar-capillary gradient) combined with a lower mixed venous oxygen levels, which delay alveolar-capillary equilibration.[3] These problems are aggravated during exercise due to increased cardiac output, shortened capillary transit time and greater venous oxygen desaturation leading to further arterial desaturation.[4]

Despite decrease in blood oxygen content, the delivery of oxygen to tissues is maintained by increased cardiac output and increased red cell mass (hypoxia induced erythropoietin secretion). Also, the hemoglobin-oxygen dissociation curve is shifted to right due to increased 2, 3 diphosphoglycerate production, which counteracts the hyperventilation induced respiratory alkalosis at high altitudes.[1]

The alveolar hypoxia triggers hypoxic pulmonary vasoconstriction (HPV) to maintain ventilation perfusion relationship and this causes a rise in pulmonary arterial pressure. This is important in the pathogenesis of HAPE and altitude related pulmonary hypertension.[5-7]

Most studies have shown a fall in vital capacity, an increase in TLC and residual volume at high altitudes.

The data regarding changes in the Forced Expiratory Volume in One Second (FEV_1) are conflicting. There is clear evidence that Peak Expiratory Flow (PEF) is increased and airways resistance is reduced due to the decreased air density at high altitudes.[8,9]

Specific Altitude-related Illnesses

Acute Mountain Sickness (AMS)

Acute Mountain Sickness syndrome affects 22 to 53% of travelers at altitudes between 1,850 and 4,240 m.[10] The diagnosis of AMS is essentially clinical based on the presence of headache plus one or more of the symptoms such as fatigue, anorexia, nausea, vomiting, giddiness and insomnia. The risk factors for AMS include the altitude reached and the rate of ascent. There are no specific physical examination findings or laboratory studies. AMS can be prevented by undertaking a slow ascent to high altitude areas. Acetazolamide and dexamethasone have been proven to be effective prophylactic agents.[11] Treatment requires cessation of ascent, symptomatic treatment with non-narcotic analgesics and acetazolamide in doses of 250 mg twice daily.

High Altitude Cerebral Edema (HACE)

HACE is a life-threatening condition characterized by the presence of ataxia, altered mental status (encephalopathy) or both in a patient with preceding symptoms of either AMS or HAPE. It is usually seen at altitudes above 4000 m. The main risk factor is rapid ascent to high elevations. Preventive measures are the same as that for AMS. Treatment requires immediate descent to lower elevations or recompression in portable hyperbaric chamber along with supplemental oxygen. Affected patients should also be treated with dexamethasone (loading dose of 8 mg followed by 4 mgq 6 hourly). If not recognized and treated immediately, HACE can even cause brain herniation and death.

High Altitude Pulmonary Edema (HAPE)

This is a noncardiogenic pulmonary edema that affects 0.2 to 15% of high altitude travelers.[12,13] It is usually seen at altitudes of above 3,000 m. HAPE occurs within two to five days of ascent and can either develop de novo or following symptoms of AMS or HACE. The main risk factors include the altitude, the rate of ascent, overexertion and cold-air exposure at high altitude. Individual susceptibility also plays a role, since susceptible individuals have been shown to have exaggerated pulmonary vascular responses to hypoxia and exercise at HAA.[5,6] The initial symptoms are vague and include decreased exercise performance and dry cough. With worsening disease, patients develop dyspnea on minimal activity and cough productive of pink frothy sputum. Physical examination reveals low-grade fever, resting tachycardia, tachypnea, cyanosis, and bilateral crackles. Prevention involves undertaking a slow ascent to high altitudes, avoiding overexertion and staged ascent to encourage acclimatization. Patients with a history of underlying respiratory diseases or pulmonary hypertension should be considered for prophylaxis with nifedipine 20 mg twice daily and/or inhaled salmeterol 125 μg twice daily.[14,15] This life-threatening disorder requires immediate descent to lower altitudes or recompression in a hyperbaric chamber with supplemental oxygen along with nifedipine 10 mg stat followed by nifedipine (sustained release preparation) 30 mg twice daily. Severe cases of HAPE can lead to severe hypoxemic respiratory failure and may require ventilatory support to correct severe hypoxemia and prevent fatal outcome.

Subacute Mountain Sickness (SAMS)

Subacute mountain sickness was described in Indian soldiers posted to elevations between 5800 and 6700 m for an average of 10 weeks.[16] The authors reported 21 cases of right heart failure that presented with dyspnea, cough and exercise-induced angina, had clinical evidence of pedal edema, polycythemia, cardiomegaly, pericardial effusion and ascites. It was postulated to occur due to an exaggerated hypoxic pulmonary vasoconstriction response leading to heart failure.[17] Treatment involved evacuation to lower altitudes, which usually leads to rapid resolution of the disorder.

Chronic Mountain Sickness (CMS)

This is a disorder, which usually develops in long-term residents with the stay of over one year at HAA. Monge et al[18] described a syndrome marked by the triad of polycythemia, hypoxemia and impaired mental function (headache, fatigue, impaired concentration and irritability). Clubbing and cyanosis may also be present. Treatment includes descent and stay at lower altitudes, periodic phlebotomy, diuretics and respiratory stimulants. Another form of CMS has pulmonary hypertension and right heart failure without polycythemia.[19] Treatment includes descent and stay at lower altitudes as the symptoms are known to recur on exposure to high altitudes.

Effects of High Altitude on Lung Diseases

Chronic Obstructive Pulmonary Disease (COPD)

There are numerous physiological derangements in patients with COPD, including impaired gas-exchange, reduced muscle strength and mild-to-moderate pulmonary hypertension. These patients are likely to have hypoxemia and worsened pulmonary hypertension at high altitude areas. Many studies have established that long-term residence at high altitudes is associated with increased mortality and a higher incidence of cor pulmonale in COPD patients.[20]

According to guidelines laid down by the American Thoracic Society, P_aO_2 should be maintained above 50 mm Hg during commercial flights.[21] The Aerospace Medical Association guidelines set this threshold at 55 mm Hg.[22] This target value is reasonable as P_aO_2 values in this range ensure arterial oxygen saturation above 85% and lie above the steep portion of the hemoglobin-oxygen dissociation curve. These cut off levels also serve as the guidelines for prescribing supplemental oxygen in-flight and during travel to high altitudes.[23] Most of these studies have included moderate-to-severe COPD patients without CO_2 retention, and therefore cannot be extrapolated to those with severe disease or with hypercapnia. The duration of exposure in these studies was shorter than what an individual would experience during a trip to high altitudes.

Another important issue in the COPD patient with severe bullous disease is whether the decrease in ambient pressure at high altitude predisposes to bulla expansion and pneumothorax? The available literature suggests that the physicians' concerns may be unwarranted. The bullae probably communicate with the airways to an extent greater than expected, allowing for pressure equalization to occur. The risks associated with scuba diving, where the pressure changes are greater are more than those with ascent to altitude, are much more.[1]

COPD patients with baseline FEV_1 less than 1.5 L should be assessed prior to high altitude travel to determine the need for supplemental oxygen. Prediction of the P_aO_2 at high altitude can be based on the regression equation provided by Dillard et al,[23] which is as follows:

$$P_aO_2 \text{ Altitude} = (0.5196 \times P_aO_2\text{SL}) + (11.856 \times FEV_1) - 1.76$$

Those with predicted P_aO_2 less than 50–55 mm Hg should travel to high altitude with supplemental oxygen. Patients should increase the flow rate of oxygen by 2 L/min when engaging in physical activity. Patients with preexisting pulmonary hypertension should be counseled against traveling to high altitude due to the high risk of developing HAPE or acute right heart failure. If the travel cannot be avoided, patient should travel with supplemental oxygen and should be started on nifedipine SR, 20 mg twice daily for duration of stay at altitude. Extreme caution should be taken with patients intending to travel to altitudes more than 3,048 m. Presently no data are available to guide recommendations above this elevation.[1]

Bronchial Asthma

There is reduced allergen load at high altitudes due to lower ambient temperature and humidity, therefore asthma exacerbations are inversely related to high altitude.[1] Hypoxia, hypocapnia and cold air can aggravate Bronchial Hyperresponsiveness (BHR) and worsen asthma control.[24] Protection of the nose and mouth from cold winds by using appropriate head gear helps to warm inspired air and must be used by all asthmatic subjects.[1]

The reduced air density at HAA should be beneficial for airflow limitation akin to effects of Heliox in asthma exacerbations, but these effects have not been studied systematically. The available data suggests that asthmatic subjects can travel to altitudes of up to 5000 m without any adverse effects for short-term trips. Patients with severe asthma should be advised against travel to HAA as they are likely to deteriorate and there is lack of medical facilities at most places. Patients must continue baseline medications and carry ample supply of rescue inhalers and oral prednisolone for any exacerbation. Peak expiratory flow must be measured and used for guiding self management plans.

Disorders with Pulmonary Hypertension

Several case reports suggest that those with pre-existing Pulmonary Arterial Hypertension (PAH) including those with altitude related PAH are at an increased risk for HAPE.[25] The severity of PAH in these reports have varied and it is not feasible to ascertain a threshold level for the risk. Patients with PAH may develop sudden rise in pulmonary artery pressure leading to acute right heart failure or progression to subacute mountain sickness on exposure to HAA.

Patients with PAH are advised to avoid travel to HAA. Those who cannot avoid the travel should be taught to recognize symptoms of HAPE and advised to use supplemental oxygen. Prophylaxis with nifedipine SR 20 mg BD for the entire duration of stay is also helpful. Phosphodiesterase inhibitor (sildenafil) and dexamethasone are other alternatives, which can be used for the prevention of HAPE.[26]

Pulmonary Thromboembolic Disorders

Those with past history of venous thromboembolism are at an increased risk for recurrence at HAA. Though there are no systematic studies, Anand et al[27] in a large retrospective study comprising of over 20,000 hospital admissions over 3 years period found 46 cases of vascular thrombosis (44 venous and 02 arterial) from HAA and 17 cases from low altitude areas. The calculated odds ratio of thromboembolic events at HAA was 30.5. The mean duration of stay of 10 months at HAA in patients who developed thromboembolic events cannot be extrapolated to shorter trips to high altitude areas. In the various case reports of thromboembolic events at high altitudes, a majority of subjects had the presence of pre-existing coagulopathy such as factor V Leiden mutation, protein C deficiency, hyperhomocysteinemia and use of oral contraceptive pills. From this it can be inferred that pre-existing prothrombotic state poses an increased risk for the development of thromboembolism at high altitudes.[1]

Patients with a history of venous thromboembolism who travel to high altitudes should continue their anticoagulation regimen and repeat coagulogram before and after their return from high altitudes. Women having underlying coagulopathy and using oral contraceptive pills should strongly consider discontinuing the use of oral contraceptives during their high-altitude exposure. Patients during their course of long flights or during other activities associated with a high degree of immobility, dehydration, or venous occlusion should be advised to maintain adequate hydration, regular movement and calf muscle exercises. An alternative strategy is to start low-dose aspirin during their stay at HAA.[1]

Interstitial Lung Disease

Of all the respiratory diseases, least data is available regarding the effects of high altitude on patients with ILD. There are reports of worsening dyspnea, resting hypoxemia and exercise-induced desaturation in patients with ILD.[28] In addition, most ILD patients have PAH and are at increased risk of developing HAPE.

Patients with ILD need assessment for need for supplemental oxygen based on the regression equation proposed by Christensen et al: [29]

$$P_aO_2 \text{ Altitude} = 50.74 + (0.396 \times P_aO_2SL) + (0.0336 \times TLC)$$

The patients with P_aO_2 levels between 50 and 55 mm Hg should receive supplemental oxygen during their travel to high altitudes. Patients with ILD and PAH are required to start nifedipine prophylaxis against HAPE. [1]

Pneumothorax

Those with pneumothorax and those following thoracic surgery are advised to wait for two weeks after resolution to undertake travel to HAA. Travel to HAA of patients with persistent pneumothorax or bronchopleural fistula with an *in situ* chest tube or Heimlich valve is considered safe. It is recommended to screen patients at high risk for secondary spontaneous pneumothorax for the presence of occult pneumothorax with CT scan prior to high altitude travel.[1]

Ventilatory Disorders

There is some data to suggest that obese individuals are at a risk of developing altitude induced pulmonary hypertension. Patients with obesity hypoventilation syndrome and obstructive sleep apnea are at increased risk for developing AMS, heart failure and HAPE. These patients should be advised to avoid travel to HAA. If the travel cannot be avoided, supplemental oxygen and acetazolamide in the dose of 125 mg or 250 mg BD are required. Patients with pulmonary hypertension should also start nifedipine SR 20 mg BD for prophylaxis against HAPE. Those patients on domiciliary CPAP therapy are advised to travel to high altitudes with CPAP unit and make necessary adjustments in set pressure for machines lacking pressure compensation.[1]

CONCLUSION

The pathophysiology of high altitude-related illnesses has been well documented in healthy individuals, but little is known about the risks of high altitude travel in patients with pre-existing lung diseases. The deranged physiological functions in patient with lung disease are aggravated at high altitude, lead to worsening of hypoxemia and of respiratory failure and predispose to the occurrence of HAPE. The presence of lung disease does not always preclude travel to high altitude. The travel may be safely carried out provided a thorough evaluation is done and adequate prophylaxis has been started to prevent ARI or worsening of the underlying lung disease.

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Aviation and Space Travel

Ajay Handa

AIR TRAVEL

Air travel has become the preferred mode of travel in most instances due to convenience and saving of time. Worldwide, over one billion passengers travel by air each year. The vast majority of people who travel by air are healthy individuals, but approximately 5 to 10% of passengers have underlying diseases, such as the respiratory ailments, including Chronic Obstructive Pulmonary Disease (COPD).[1] The prevalence of respiratory diseases is increasing worldwide and most such patients do prefer to travel by air to minimize discomfort. Many patients consult their physicians prior to planning air travel for fitness and prescription of supplemental oxygen during flight. Patients who have suffered from an acute medical ailment in the period preceding the air travel, or those with previous cardiopulmonary disease are particularly concerned. The knowledge of aviation physiology and medicine is important for pulmonary physicians to handle patients with chronic respiratory diseases.[2]

Respiratory Problems During Air Travel

The fall in partial pressure of oxygen with high altitude can cause hypobaric hypoxia during air travel. Commercial aircrafts fly at the height of 10,000–13,000 meters Above Sea Level (ASL), pressurization in the cabin is maintained to keep the level at about 2438 meters ASL. For technical reasons, the cabin altitude cannot be maintained at lower than 2438 meters. Breathing at this altitude (15% oxygen) causes the PaO_2 to fall to 53–64 mm Hg (SpO_2 85 to 91%). This mild hypoxemia does not produce any symptom, is well tolerated in healthy subjects, but it may cause significant hypoxemia and precipitate respiratory failure in patients with chronic lung disease.[3] Such patients need thorough preflight evaluation and recommendation to use supplemental in-flight oxygen.

Another physical effect of ascent to high altitudes is the expansion of gases due to decrease in ambient pressure (Boyle's law). The expansion of gas trapped in close cavities, such as the middle ear and the intestine can cause discomfort. The gas within a lung bulla will expand by 30% at 2450 m ASL, cause rupture and recurrence of complication of pneumothorax, pneumomediastinum and air embolism.[4] Patients of COPD with emphysematous bullae at increased risk for pneumothorax and respiratory failure during air travel are advised to avoid air travel. Due to the risk of the development of respiratory distress, untreated pneumothorax is the only absolute contraindication for travel by air.[1]

The analysis of in-flight emergencies from various studies has shown that respiratory problems account for 10% of all medical emergencies. This is the third leading cause of in-flight medical emergencies after cardiac and neurologic emergencies. Exacerbations of asthma and of COPD are the most common respiratory problems, which are encountered during air travel.[1]

Preflight Assessment

The aim of preflight assessment is to identify those individuals who are likely to develop significant hypoxemia onboard the flight. Patients on Long-term

Oxygen Therapy (LTOT) and those with cardiorespiratory illnesses constitute important categories. Patients with severe COPD, bronchial asthma, restrictive lung diseases, past venous thromboembolism, recent pneumothorax and pulmonary tuberculosis are at high risk of deterioration during air travel and must be subjected to preflight screening.[5] Patients with recent cerebrovascular accidents and congestive heart failure may also worsen on air travel and need to be assessed accordingly. In cardiac patients travel on commercial airlines is fairly safe after two weeks of myocardial infarction without the requirement of supplemental oxygen.

Preflight assessment should include detailed medial screening and counseling. The three methods usually adopted for preflight evaluation for oxygen supplementation include 50 meters walk test, use of prediction equations and the hypoxic challenge test.[1]

Airline medical authorities traditionally use the 50-meter walk test for screening passengers. Those who are able to walk 50 meters are considered “fit to fly”. The test provides a crude assessment of cardiorespiratory status and requires supervision. Failure to complete the distance or the development of moderate-to-severe respiratory distress should alert the physician to referral for assessment for in-flight oxygen by respiratory physician.

Nomograms and prediction equations for PaO_2 at altitude using blood gas parameters and spirometry at ground level have been developed through studies in COPD patients exposed to hypoxia (Table 104.1).[6] In clinical practice, such equations are most frequently applied to predict fitness and requirement of on board oxygen. Predicted PaO_2 value of less than 50 mm Hg constitute an indication for supplemental in-flight oxygen.[1]

There are no guidelines as to which of the above equation is to be used. Some authors use regression equation for calculating predicted PaO_2 at a particular altitude. If the calculated value is in the range of 50±3 mm Hg, hypoxic challenge test is advised for definitive recommendations.

The hypoxic challenge test remains the gold standard for preflight assessment regarding oxygen supplementation.[1,7] The subject is exposed to 15% oxygen in nitrogen using nonrebreathing facemask or body plethysmograph. Continuous monitoring with pulse oximetry and electrocardiography is done to prevent severe desaturation and to detect cardiac arrhythmias. Arterial blood gas analysis is done before and after the hypoxic exposure. The mean predicted altitude PaO_2 derived from regression equations compares well with actual PaO_2 obtained during the hypoxic challenge tests. Considering the limited availability of facilities for hypoxic challenge testing for a large numbers of patients with respiratory diseases and COPD who travel by air, the British Thoracic Society Guidelines[1] recommend that oxygen saturation measured by pulse oximetry can be used to initially screen groups of passengers. Those with SpO_2 of less than 92% are advised in-flight oxygen and those with SpO_2 between 92 to 95% are prescribed hypoxic challenge test (Table 104. 2).

Those passengers who have additional risk factors, such as hypercapnia, FEV_1 less than 50%, presence of predicted diseases such as lung cancer, restrictive lung diseases, comorbid cardiovascular or neurological diseases and those who are within six weeks of discharge from hospital for acute exacerbation, shall require hypoxic challenge testing.

The patients subjected to hypoxia challenge are categorized based on the measured PaO_2 after 15 min at FIO_2 15% and advised accordingly based on PaO_2 (Table 104.3).

TABLE 104.1: Equations for calculating predicted PaO_2 at 2450 m

1. PaO_2 altitude = 0.84 + 0.68 (PaO_2 ground)
2. PaO_2 altitude = 0.295 (PaO_2 Sea level) + 0.086 (FEV_1 % predicted) + 23.211
3. PaO_2 altitude = 0.245 (PaO_2 Sea level)+ 0.171 (FEV_1/FVC % predicted) + 21.028

TABLE 104. 2: BTS recommendations for initial screening

Pulse oximetry	*Recommendation*
SpO_2 > 95%	Oxygen not required
SpO_2 92% to 95% without risk factors	Oxygen not required
SpO_2 92%–95% with risk factors	Hypoxic challenge test
SpO_2< 92%	In-flight oxygen

TABLE 104.3: BTS recommendations after hypoxic challenge test

Blood gas report	*Recommendation*
PaO_2 >55 mm Hg	Oxygen not required
PaO_2 50–55 mm Hg	Borderline, advised 50 m walk test
PaO_2 <50 mm Hg	In-flight oxygen (2 l/min)

Prescribing In-flight Oxygen

Any patient with PaO_2 of less than 70 mm Hg ASL at rest will require supplemental oxygen during air travel.[8] Most commercial airlines provide in-flight oxygen on advance request and physician's prescription. The expenses are required to be borne by the travelers.

The oxygen is usually provided from cylinders during travel. The rate of flow and duration should be specified to assess the adequacy of oxygen during the journey. The flow rate of oxygen of 2 l/min is suitable for most passengers. Those on LTOT are advised to increase the flow rate by 2 l/min above the usual flow rate.[9]

Most airlines provide oxygen through simple face masks, passengers are advised to carry their nasal prongs to prevent rebreathing. The oxygen and cabin air inside the aircraft are devoid of moisture, which may cause drying of tracheobronchial mucosa and precipitation of bronchospasm. The airlines should be informed for the need of humidified oxygen for patients with asthma and COPD. In addition, such patients must be advised to carry their medications in their hand baggage for use in emergency situations.[10]

Airlines do not provide oxygen during waiting period and stopovers. Some airports restrict oxygen use because of the risk of explosion. Oxygen-dependant patients must make additional arrangements for use during the waiting periods at the airports. Patients cannot use their own cylinders or concentrators, but may be able to take these items with them as baggage for use at their destination. It is also important for these patients to carry their medical documents and extra-drug supplies during travel (Table 104.4).

Conclusions

For most passengers, air travel is safe and comfortable. Patients with cardiorespiratory diseases are at risk of significant hypoxemia during air travel. Most of these individuals complete the journey uneventfully with supplemental oxygen. All the present recommendations are based on the results of effects of simulated hypoxia on patients with lung diseases. More investigations are required on the effects of air travel on passengers with lung diseases.

TABLE 104.4: Guidelines for oxygen-dependent patients prior to air travel[11]

- Obtain medical certificate of fitness to fly
- Carry prescription of in-flight oxygen requirement
- Inform the airlines while booking tickets and 48-72 hours before date of journey
- Inform airlines need for oxygen before boarding and during stopovers
- Preferably take nonstop flight to destination
- Carry extra tubing and personal nasal cannula
- Carry extra copies of prescriptions and medical certificate
- Carry emergency supply of medications in hand baggage

SPACE TRAVEL

The effects of gravity and of its absence on respiratory physiology have intrigued scientists since time immemorial. The condition of zero gravity or weightlessness (microgravity) for assessing its effects on human body can be achieved by two methods. These are parabolic flight in aircrafts and space flight. The parabolic flights in commercial jet aircrafts are associated with the small periods of microgravity with thr periods of hypergravity (increased gravitational forces) during these maneuvers. Parabolic flight is more easily available and less expensive compared to space flight. It has the disadvantage of creating motion sickness on passengers during this "roller coaster" flight. The US, Russian and the European Union countries have regular parabolic flights for their research work.

Flights in spacecrafts are infrequent and extremely expensive. Space flights have sustained periods of microgravity from one week to up to a year. Most research work on space medicine has been done on board Russian space station, Mir and International Space Station (ISS) led by the USA. These space stations offer convenient environments for studying the effects of space on human physiology. The number of subjects is often limited to four, the crew serve as subjects and operators or both. Evaluation includes preflight and postflight testing of various parameters and their comparisons with data under microgravity.[12]

Microgravity and Weightlessness

There are some ground-based experiments, which mimic weightlessness such as the six degrees Head-Down Tilt (HDT) and Thermoneutral Water Immersion (TWI). These have been useful to study the cardiovascular and musculoskeletal responses. The significant effect of gravity on the lungs and pulmonary vasculature cannot be removed by these experiments. Furthermore, HDT and TWI caused larger reductions in resting lung volumes than microgravity, which cannot be ignored.[13]

To understand the effect of microgravity and weightlessness in space on the respiratory system, we can take a cue from the common knowledge that even though there are no structural differences between the upper and lower parts of the human lungs, gravitational forces lead to marked functional differences between these areas. The alveoli at the top of the lung are more expanded compared to those at the bottom of the lung, because of the weight of the lungs on the lower parts. On the other hand, the alveolar ventilation is higher at the bottom of the lungs as compared to that at the apex. Gravity also influences the intrapleural pressure, parenchymal stress and pulmonary blood flow, which may result in regional differences in lung function.[14,15] There is a great disparity in the pulmonary blood flow between the top and the bottom of the lung, with greater flows at the bases in comparison to that at the apices. This is due to the effect of hydrostatic forces on the low-pressure pulmonary circulation. As a result of the profound effects of gravity on alveolar ventilation and pulmonary perfusion, ventilation perfusion ratio $\dot{V}/\dot{Q}$ is higher at the apices than at the lung bases and there are regional differences in gas exchange in the lungs.[16]

The influence of gravity on the lung on earth and by increasing the gravitational effect has been studied. Most of the changes in lung function are attributable to gravity. The conclusions of these studies cannot be extrapolated to zero gravity conditions. A large number of studies on the respiratory functions in the absence of gravity have been performed in the last decade and a half. The results of some of these studies are summarized here in the succeeding paragraphs (Table 104.5).

Effects on Lung Volume and Spirometry

The first study on lung volumes during space travel, done in 1970s showed that Vital Capacity (VC) was reduced by 5 to 10%.[17] The subsequent studies have shown that VC reduction by 5 to 6% for the first-two days, which normalizes by the day four, onwards. This was explained by the early in-flight increase in intrathoracic blood volume, which subsequently reduces to normal, as the plasma volume reduces during the sustained space flight.[18] As the effect of gravity was removed, the Functional Residual Capacity (FRC) reduced by 5 to 10% due to cranial shift of diaphragm and outward movement of the ribcage.[19] Residual Volume (RV) remains unchanged with microgravity.[20]

Peak Expiratory Flow (PEF) remained unaffected in most studies.[21] During the initial space flight, there was a reduction in the PEF due to the lack of a firm platform to push against during the forced expiration, there was subsequent recovery attributable to better performance after adaptation to microgravity. There was no change in Forced Expiratory Flow (FEF) in the effort independent portion at lower volumes (i.e. FEF 25 to 75%), which suggested that behavior of the central and peripheral airways as well as the respiratory muscles was unaffected in space.[21]

TABLE 104.5: Summary results of studies on effects during space travel on pulmonary function

Effects	*First findings*	*Afterwards*
1. Lung volumes and flows		
• VC	Reduced	Normalized
• FRC	Reduced	Normalized
• RC	Unchanged	
• PEF	Unchanged	
• $FEV_{25\text{-}75\%}$	Unchanged	
2. Pulmonary diffusion		
• DLCO	Increased	Increased
3. Gas exchange		
• Tidal volume	Reduced	
• Respiratory rate	Increased	
• Minute ventilation	Marginal decrease	
• Physiological dead space	Reduced	
• Oxygen consumption	Unchanged	
• CO_2 production	Unchanged	
4. Cardiac output	Increased	–
• Heart rate	Increased	–
• Stroke volume	Unchanged	–
5. Response to exercise		
• Cardiac	Reduced	–
• Ventilatory	Unchanged	–
6. Ventilatory control		
• Hypoxic drive	Reduced	–
• CO_2 drive	Unchanged	–
7. Sleep		
• Sleep efficiency	Poor	Poor
• Sleep apnea syndrome	Reduction in events and snoring	

Effects on Diffusion Capacity and Pulmonary Perfusion

There was substantial increase in diffusion capacity by 28% over the baseline and it remained elevated over the course of nine-day flight, due to an increase in pulmonary capillary blood volume and membrane diffusing capacity.[22] These phenomena were attributed to transition of the lung from its zone 1, 2, 3 $\dot{V}/\dot{Q}$ configurations on ground level to zone two or zone three in entirety in space causing a more uniform capillary filling.[22]

Effects on Gas Exchange and Ventilation Perfusion Relationship

The tidal volume was reduced and breathing frequency increased, thus the minute ventilation was reduced only marginally.[23] Moreover, the physiological dead space reduced, thus the effective alveolar ventilation remained the same. In spite of these ventilatory changes, studies have shown that oxygen consumption and carbon dioxide production remained unchanged in space.[23] The peak oxygen consumption however reduced by 22% on return to ground and gradually recovered over the next six to nine days to the preflight levels, postulated to be due to circulatory blood volume changes.

Effect on Cardiac Output and Exercise

Cardiac output increased after two weeks in space as a result of increased heart rate with constant stroke volume.[24] The ventilatory response to exercise remained unchanged in microgravity, but the cardiac response to exercise was less in short duration space flights when compared to ground level changes. No data is available for long duration space flights.[25]

Ventilatory Control and Sleep in Space

There was substantial reduction in the ventilatory response to hypoxia with halving of hypoxic drive, whereas the response to carbon dioxide remained unchanged. This change in the hypoxic response was possibly due to an increase in blood pressure at the level of the carotid bodies due to zero gravity. The systemic blood pressure remained unchanged, but the blood pressure at the carotid bodies was higher due to the abolition of hydrostatic pressure difference normally present on ground.[26]

There was poor sleep efficiency during space flights, these were related to poor ventilatory control and altered circadian rhythm.[27] The subjects with obstructive sleep apnea syndrome had improvement in sleep quality with reduction in events and snoring. The cause of sleep deficiency in space is not related to respiratory system changes.[27]

CONCLUSION

It can therefore be concluded from the comprehensive data on changes in respiratory physiology in space that the effects are generally benign and unlikely to limit the activities of astronauts in space.

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Diving Medicine

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Whether due to occupational requirements or recreational choices, exposures to extreme environments impose some significant health risks. One unique environmental exposure is water diving to various depths for recreational, commercial and military purposes. While free-water diving has been practiced for centuries, it was the introduction of the Self-contained Underwater Breathing Apparatus (SCUBA) by Cousteau and Gaston in 1942 that triggered a dramatic increase in diving and its popularity as a recreational sport. Currently more than 10 million individuals participate in diving for recreation, competition or occupation. Diving requires physical and emotional stamina that may be limited by medical conditions that would increase the risks of this environmental exposure. Pulmonologists and other medical specialists are called upon to assess an individual's health status either prior to dive training, or after a dive and decompression exposure to evaluate and treat associated complications. This chapter on diving medicine will generally cover the types of diving, physiological aspects, medical conditions resulting from diving, and the management of diving related injuries/ illnesses. With advances in technology and knowledge of diving, human beings are able to dive to greater depths relatively safely.

HISTORICAL BACKGROUND

One of the first instances of man overcoming the limitations of simple breath hold swimming was recorded in 332 BC, when Alexander the Great descended to the seabed in a glass barrel during the siege of Tyre. Since then, diving equipment has evolved from simple diving bells that allow a diver to breathe trapped air with to modern day sophisticated rebreathing apparatus. The development of caissons for building bridges and technology for surface-supplied breathing mixtures significantly increased the time an individual could remain under pressure. With such advances came a greater understanding of the unique and complicated aspects of diving physiology and its inherent risks. In the beginning we knew little about the physiological changes that occur during diving and decompression. In the 17th and early 18th century, technological improvements included replenishing the air in diving bells to increase time at depth. In the 19th century, compressed air delivered from the surface using helmets was commonly used and the 20th century brought independent breathing systems that freed the diver from the surface and spurred on today's popularity. Also in the 19th and 20th centuries, an understanding of decompression sickness began to emerge. Descriptions of decompression sickness were first detailed the written observations of Haley (1716) and Triger (1845) and since than numerous descriptions of this syndrome are available.[1]

DIVING PHYSICS AND PHYSIOLOGY

Diving is an underwater strenuous activity where environmental conditions have an impact on the organs and functions of the body. At normal surface exposure, humans are exposed to an ambient pressure of 750 mm Hg [100 kPa = 1 bar = 1 standard atmosphere (atm)]. Underwater, pressure increases with depth at a rate of 1 atm increase for every 10 meters descent. Recreational divers go to depths as deep as 40 meters, while commercial and military divers (occupational divers) may explore depths greater than 500 meters in the open ocean. In a hyperbaric chamber, descent to a pressure equivalent to a depth of 700 meters has been recorded.[2]

To be able to move the bellows of the lung, internal pressure must be equilibrated with the ambient pressure. Achieving this balance through the use of compressed gas exposes the diver to two basic laws of gas physics as described by Boyle and Henry. Boyle's law states that the volume of a gas is inversely proportional to the pressure applied to it when temperature is constant. That is to say, for every 10 meters of depth, pressure increases by 1 atm and air volume decreases by 50%. A corollary of this is the reversal that occurs during ascent to the surface. Organs and cavities that hold gas are therefore more greatly affected by compression and decompression. According to the gas laws and pressure-volume relationships, gas compresses within body organs, such as lungs, sinuses, middle ear, and intestine during descent, and similarly that same gas expands during ascent. Hence, this single phenomena explains something as relatively harmless as an "ear squeeze", as well as catastrophic pulmonary injury that can result in an air-gas embolism or pneumothorax.[3-5]

According to Henry's law, at constant temperature, the amount of gas dissolved in a liquid is directly proportional to the partial pressure of that gas. The increased pressure of a diver's breathing gas causes that gas to dissolve in body fluids and tissue in proportion to the pressure increase. While oxygen is metabolized, physiologically inert gases, such as nitrogen remain in solution. As pressure decreases during ascent, the dissolved gas can come out of solution, forming bubbles, and resulting in decompression sickness. A gradual decrease in pressure can allow the inert gas to slowly come out of solution and be exhaled, thus minimizing decompression sickness.[3-9] So called "diving tables" were painstakingly calculated to estimate the amount of gas dissolved in tissue beds (based on time and depth) during the compression phase of diving to determine the ascent rate for the safe elimination of excess gas during decompression. These dive tables are reliably used in military and recreational diving.[8]

In addition to the laws of gas physics, immersion in water itself has multiple effects. Though outside the scope of this review, water immersion can shift intravascular blood to the thorax and increase peripheral vasoconstriction. The increased energy transfer of water when compared to air can not be overstated and also explains why water immersion increases the risk of thermoregulatory concerns.[9,10]

TYPES OF DIVING

Apnea diving, otherwise known as breath-hold diving, is the oldest type of diving. Female apnea divers in Japan and Korea can boast a long history of collecting pearls from shellfish and harvesting seafood. In the recent years, apnea diving has become a competitive sport, the goal to achieve the maximum dive depth and longest dive duration. Breath-hold duration depends on the diver's ability to withstand hypercapnia and hypoxia. Breath-hold divers train to minimize metabolic rate, increase lung capacity and develop psychological tolerance to overcome the sensation of asphyxia. Though apnea divers generally stay underwater for less than five minutes, world record breath-hold times in excess of 11 minutes and depths up to 200 meters illustrate remarkable limits of tolerance. One overt risk in breath-hold diving is that increases in the partial pressure of oxygen can mask the decrease in oxygen content, until one nears the surface. The marked decrease in oxygen partial pressure certainly translates into a high risk of black-outs and drowning.[11-15] One method to increase Total Lung Capacity (TLC) and the TLC/Residual Volume (RV) ratio practiced by some breath-hold divers is known as buccal pumping or "lung packing". Following a full inhalation to TLC, further air intake is achieved by keeping the glottis open and forcing more air into lungs; this may increase capacity to an additional 39%.[16]

Commercial Diving

Commercial divers are exposed to a broad-spectrum of diving variables, such as depth, temperatures, salinity and contamination. These exposures coupled with the responsibility of their livelihood, puts them at increased risk for physiologic and psychologic stresses. Commercial divers are skilled in diving, as well as their underwater work requirements. They must master the safe operation of a wide array of industrial equipment, such as welding machinery. In addition, they must achieve and maintain a higher standard of physical and mental strength, endurance, dexterity, flexibility, adaptability and situational awareness. It is well known that physiologic stresses adversely impact performance and safety. In the case of commercial divers these include thermal stress, environmental stress, workload stress, oxygen stress, inert gas stress and decompression stress. Some stresses can be mitigated, for example with diving helmets and/or protective suits. Dive helmets of course provide head protection, but also reduce the breathing effort and minimize respiratory dead space.

Fig. 105.1: Commercial diving

Conventional helmets use an oronasal mask to reduce the reinhalation of carbon dioxide. Protective suits prevent direct skin contact with the surrounding water, providing both thermal and hazardous waste protection[17-19] (Fig. 105.1).

Two major types of commercial applications are surface-based diving and saturation diving. In surface-based diving, the diver is situated at work depth for a fixed length of time and ascends following the standard decompression tables. This dictates, and thereby limits their productivity. Saturation diving is so named because the diver's tissues are fully saturated with gas. Once saturated, a diver can remain under that pressure without incurring further obligations for decompression. Generally in saturation diving, a team of divers descends to working depth in a decompression chamber where they remain under pressure for an extended time working in shifts and spending their "leisure" time remaining at that pressure. When the job is completed they undergo one single decompression within the same chamber.[17,18]

Recreational Diving

Fig. 105.2: Scuba diving

Diving as a recreational sport has gained popularity over the last few decades with the development of SCUBA (Fig. 105.2). Many organizations have emerged to provide safety training for SCUBA diving. There are three major types of recreational diving. The most common is the "open-circuit SCUBA" using compressed air; it is technically simple, easily to learn and inexpensive. In open-circuit diving, air is inhaled through regulators from a high pressure tank and exhaled into the environment. In general, open-circuit diving is for depths of less than 40 msw time restrained by the limited supply of gas in the tank. The second type of recreational diving is "technical SCUBA" where divers use more complex equipment and breathing gas mixtures and dive to greater depths than open-circuit SCUBA. Technical diving requires more sophisticated equipment and extensive training. The third type of recreational diving is the "semi-closed" and "closed SCUBA" where exhaled gas is recycled through a chemical chamber that removes carbon dioxide. While this feature enables longer dive durations, the consequences of any malfunction that would accumulate carbon dioxide could lead to significant adverse effects.[20-23]

Diving certification agencies, such as Diver Alert Network (DAN) and Diving Emergency Services (DES) are established to support recreational diving with safety a primary concern. Many countries have instituted safety and training requirements for recreational diving.

DIVING-RELATED INJURIES/ILLNESSES

As the depth and duration of diving have increased over the years, so too has the number of divers participating for sport and recreation. Fortunately, this has motivated research into understanding the pathophysiology and treatment of diving-related injuries. In general, these are classified into four types of adverse events:

1. Decompression Sickness (DCS)
2. Barotrauma affecting cranial sinuses, ear, and pulmonary (and resulting in arterial gas embolism)
3. Toxicity of increased partial pressure of gases, nitrogen narcosis
4. Pulmonary edema

Other complications associated with scuba diving that are not included in this discussion are hypothermia, trauma, drowning and marine envenomations.[24-29]

DECOMPRESSION SICKNESS

Pathophysiology of Decompression Sickness

Bubble formation from dissolved inert gas in blood and tissues is considered central to the pathophysiology of decompression sickness. As ambient pressure decreases, the ability of tissue to dissolve inert gas is exceeded, a state known as super-saturation. If this excess gas is not exhaled, this inherently unstable state may lead to bubble formation in the vascular system (most commonly) or within tissue beds. The vast majority of bubbles in the vascular system are detected in the venous/right heart and pulmonary artery. In most divers, venous bubbles can be detected within the minutes of surfacing; they are generally trapped in the lungs from where they are safely eliminated. However, bubbles may bypass this filter mechanism in the presence of right-to-left shunts, such as seen in Patent Foramen Ovale (PFO). Additionally, large bubble loads may overwhelm the filtering capacity of the lung capillary bed and become "arterialized." These bubbles damage the endothelial cells and luminal surfactant layer, especially in the lungs and the cerebral vessels. Bubbles can interact with blood components leading to platelet aggregation, affect leukocytes, increase cytokines release, impact the coagulation pathway, and activate complements. Bubble damage to the pulmonary vasculature can result in the release of leukotrienes, blood-lung barrier injury, elevated pulmonary artery pressure, decreased cardiac output, pulmonary edema and hypoxemia. In severe cases, these changes may lead to cardiac failure, respiratory arrest and death (known as the "chokes").[30-32]

Bubble detection by Doppler ultrasonic techniques has become a valuable research tool. Yet, the fact that bubbles can be demonstrated in divers after surfacing contradicts the low incidence of DCS. Clearly, much remains to be learned.[31]

Clinical Presentation of DCS

Decompression disorders were originally referred to as Caisson's disease, compressed air illness or tunnel disease. Other terms, such as diver's palsy, "chokes", and "staggers" pointed toward the multiple system involvement. The commonly recognized term "bends" described limb pain, calling attention to Caisson workers walking "bent" over from pain. Matthews used the term decompression sickness in 1939. In the mid-to-late 20th century, the further classification of DCS was established. The current classification was first described by Elliott and Kindwall.[31]

DCS is a systemic disease with generally focal manifestations. Various strategies have attempted to classify DCS syndromes. In reality, there is not often a clear distinction between mild and severe DCS and there is considerable clinical overlap with Arterial Gas Embolism (AGE). In general, DCS presentation is somewhat delayed compared to AGE. A few common accepted classifications are outlined below.

One method to classify DCS severity uses the terms Type I and Type II. Type I DCS is milder with divers reporting joint pains, pruritis and skin rash. Type II DCS is a more severe manifestation that may result in cardiopulmonary compromise, neurologic injury and death. Neurologic injury from DCS likely results from gas bubbles obstructing regional blood flow with clinical symptoms, such as blurred vision, paresthesias, paraparesis, convulsions and death. Golding (1960) reviewed 685 cases of DCS and classified them as Type I for simple clinical manifestations and Type II for serious manifestations. In his review, the majority of DCS was considered Type I. With advanced diagnostics and diving technology, the differentiation between the two types is not always clear and they may coexist.[33]

Multiple databases are maintained in the commercial, military and recreational diving communities. The collection of data for recreational divers remains a challenge as it is likely that not all DCS is reported or recognized. One large recreational database is maintained by DAN. In addition to extensive educational resources, DAN publishes an annual compilation of diving-related injuries. More recent reports of manifestation frequency differ from earlier reports, especially in sport divers. DCS is a multisystem disease with diverse manifestations that differ with the type of diving. For example, while military divers report limb pain as most common, sport divers most frequently report neurologic symptoms, nearly 50% being altered sensation.[31]

Cutaneous Manifestations

Diving may produce skin itching, thought to be secondary to bubbles within the hair follicle. While this may be uncomfortable, it is not considered to be DCS. Cutaneous marmorata, a skin manifestation is a symptom of DCS characterized by purplish discoloration, which results from transcutaneous bubble migration causing vasospasm, release of inflammatory mediators and complement. Though considered mild, cutaneous manifestations may predict the development of more severe DCS. Also considered are the rarely observed lymphatic forms of DCS. Localized swelling from lymphedema is thought to result from a bubble obstruction of lymphatics; this condition resolves without further therapy.[5,22,34-36]

Constitutional Symptoms

Constitutional symptoms, such as fatigue, malaise, anorexia, poorly characterized muscle pains and headache are commonly reported. It is unclear if these are the result of decompression, thermal regulation, dehydration or environmental changes. This aspect of diving has not been thoroughly studied, but the proinflammatory effects of bubbles may also have an impact. In such cases, complaints must be clinically evaluated and a detailed neurologic exam performed to exclude focality.[5,22, 34-36]

Neurologic Manifestations

The data from DAN in the 1990s show the most common manifestations as neurologic, ranging from 40 to 77%. The predominant neurologic symptoms are paresthesias (tingling/numbness). These symptoms generally occur shortly after ascent and the loss of consciousness was frequently noted. Another CNS manifestation soon after is numbness and weakness in the legs that progresses overtime. There may also be pain, bladder dysfunction and rarely bowel dysfunction. Most commonly involved are the thoracolumbar and the cervical cord. The majority of cases report sensory changes without objective changes. Theories to explain the mechanism of spinal cord involvement include arterial bubble embolism, agglutination of blood elements, venous infarction hypothesis, activation of complement hypothesis, and autochthonous bubble hypothesis.[5,22,34-37]

Musculoskeletal Manifestations

Pain in the extremities was reported as the second most significant symptom following neurological symptoms. In the 1998 DAN data, pain in the arm was 3–5 times more common than pain in the legs. However, divers that decompress from saturation or near saturation tend to manifest leg pain more frequently. The character of the pain is often a deep ache close to a joint, but without joint swelling or inflammation.[22,25,34]

While no single mechanism for joint symptoms is proposed, autochthonous bubble formation is most likely. Gas formation in a joint and bone marrow cavity results in pain. Another hypothesis suggests the possibility of referred pain from an injury to central and peripheral nerves, but animal studies did not support this.[38]

Risk Factors for Bubble Formation and DCS

Even though many factors that might either predispose a diver to bubble formation or predispose tissues to bubble injury, true correlations are lacking. It is difficult to resolve the fact that the vast majority of dives are associated with intravascular bubble activity, yet the incidence of DCS is only 1:10,000 dives. There is significant intersubject variability in the incidence of bubble formation despite similar diving depths and duration. Some diver-specific risk factors that have been suggested include the percentage of body fat, as nitrogen is more soluble in lipids than aqueous tissues, advancing age with possible less physiological reserve, history of previous DCS, dehydration prior to the dive, female gender, poor physical fitness, and PFO. Some nondiver-related risk factors for DCS are the duration and depth of the dive, the ascent rate, repetitive dives, exercise under pressure, exposure to cold, and exercise after decompression.[32,33]

One factor that may increase DCS risk is the right-to-left shunt. All intracardiac right-to-left shunts increase the risk of paradoxical air emboli. Venous bubbles may cross Patent Foramen Ovale (PFO) (or other right-to-left shunts). Normally the direction of flow across the PFO is from left-to-right. When there is pulmonary hypertension with DCS, or large amount of bubbles, a reversal of flow can occur, putting bubbles in the arterial circulation. This reversal can cause significant disease in humans.[39-41] Moon and associates reported 61% of those with PFO who developed DCS had neurologic manifestations.[29] Wilmhurst and associates showed 52% of 100 divers with neurologic DCS had medium-to-large shunts compared to 12.2% of 123 divers without DCS. Even in asymptomatic humans, 20 to 34% are reported to have PFO. Hagen and associates reported 31% of divers who never had DCS had PFO.[42] Though, it appears that there is an association between PFO and DCS risk, the significance is unclear and controversial.[42-44] The current practice is not to screen every diver for PFO with a bubble-contrast echocardiogram; however screening for PFO after a DCS appears reasonable and may better inform the diver and the practitioner.[42]

Since cabin pressure in commercial planes is not maintained at one ATM, it stands to reason that flying after diving would have significant interactions. Air travel within 12 hours following a single dive or within 48 hours following multiple dives may increase a diver's DCS risk in flight. Divers should avoid flying during this high-risk period. Furthermore, when seeking medical attention for a postdive event, divers must be thorough in reporting to a physician who may not make the historical connection and recognize DCS manifestations.[45]

Certain coexisting medical conditions increase the risk for DCS. While pregnancy is not an absolute contraindication for diving, pregnant women should be advised against diving as fetus may suffer from DCS.[45-48]

Patients with intra-atrial shunts, ventricular arrhythmias, or congenital QT syndromes are at high risk for DCS. The British Thoracic Society has established guidelines for the respiratory evaluation of divers that provide key points essential for clinical assessment before diving[5] (Tables 105.1 to 105.3).

TABLE 105.1: The diving environment

- Diving is an arduous underwater activity in which environmental conditions affect bodily structure and function.
- For every 10 meters descent in sea water, ambient pressure increases by 100 kPa, equivalent to 1 atmosphere (1 bar). The volume of a given mass of gas changes inversely in proportion to pressure. The gas in bodily cavities, such as the lungs, sinuses, middle ear and intestine is therefore subject to compression during descent and expansion during ascent. This may lead to tissue damage.
- Partial pressure of gases increases in direct proportion to the increase in ambient pressure. Greater quantities of inert gas, mainly nitrogen, therefore dissolve in tissues at depth and come out of solution on ascent.
- The density of inhaled gas increases with pressure, restricting breathing.
- Immersion displaces blood from the periphery into the thorax, reducing lung volume.
- Work of breathing increases due to a combination of increased gas density, increased hydrostatic pressure, and altered respiratory mechanics.
- Underwater breathing apparatus adds dead space and increases resistance to breathing.
- During diving, carbon dioxide retention may result from the above listed effects on the body.

TABLE 105.2: Summary of key points and recommendations: Potential risks of diving

- *General risks:* Panic, hypothermia, physical trauma and drowning.
- *Equipment/technique problems:* Hypoxia, hyperoxia, or poisoning by inappropriate gas mixtures or contaminant gases may result from equipment malfunction or poor dive planning. A malfunctioning respiratory regulator may result in aspiration.
- *Barotrauma:* It is caused by compression or expansion of gas-filled spaces during descent or ascent, respectively. Compression of the lungs during descent may lead to alveolar exudation and hemorrhage. Expansion of the lungs during ascent may cause lung rupture leading to pneumothorax, pneumomediastinum and arterial gas embolism.
- *Decompression illness:* It may occur when gas, which has dissolved in tissues while at depth, comes out of solution as bubbles. Clinical manifestations vary, the most severe being cardiorespiratory and neurological.
- *Loss of buoyancy control:* It is a cause of many accidents, usually when it leads to rapid uncontrolled ascent. It is also essential to consider comorbidities, such as diabetes and epilepsy, which may influence capability for diving, but are outside the scope of this document.

The physician should bear the following general concepts in mind when assessing respiratory fitness to dive:

- The subject may be required to swim in strong currents.
- The subject may be required to rescue a companion (dive buddy) in the event of an emergency.
- The diving environment is associated with a risk of lung rupture.
- The gas breathed by the diver may be very cold.
- Buoyancy control is essential and requires training, experience, and use of appropriate equipment. The following recommendations are therefore made.

BAROTRAUMA

Pulmonary Barotrauma (PBT)

Recalling that gas volume inversely decreases with pressure (and expands with decreasing pressure), it follows that gas containing organs are subject to marked changes in volume. If gas in these spaces is unable to escape, then these organs are at the risk of injury, so called barotraumas.[30,34]

Pulmonary barotrauma is the most life-threatening form of barotrauma and is the second leading cause of diving-related deaths.[27-29,34] The expansion of gas within the lung during ascent can rupture alveoli resulting in air in the interstitium that travels along the perivascular sheaths.[48-50] This would create entry to the mediastinum (mediastinal emphysema), pleural space (pneumothorax), and subcutaneous space (subcutaneous emphysema), or into circulatory system resulting in an

TABLE 105.3: Summary of key points and recommendations: Assessment of respiratory fitness to dive

- In the history, particular attention should be paid to current respiratory symptoms, previous history of lung disease, including childhood history, previous trauma to the chest, and previous episodes of pneumothorax.
- Respiratory system examination should be performed.
- Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and peak expiratory flow rate (PEF) should be measured. FEV_1 and PEF should normally be greater than 80% of predicted and the FEV_1/FVC ratio greater than 70%.
- Routine chest radiography is not considered necessary in asymptomatic subjects with no significant respiratory history and normal examination findings. However, all professional divers, including recreational divers, who plan to work as instructors are recommended by the health and safety executive to undergo prior chest radiography.
- Chest radiography is appropriate if there is a previous history of any significant respiratory illness—for example, pleurisy, pneumonia, recurrent respiratory infections, sarcoidosis, chest surgery or trauma, pneumothorax—and in those with current respiratory symptoms and/or abnormal examination findings.
- Routine measurement of the expiratory flow-volume loop, exercise testing, or bronchial provocation testing are not considered necessary although these tests may be useful in specific cases.
- Thoracic CT scanning, which has greater sensitivity than standard chest radiography to detect lung structural abnormality, may be useful in specific cases.

AGE.[51,52] Since, pressure and volume changes are near instantaneous, it stands to reason that the clinical presentation for PBT is rapid and may occur while decompressing or soon after surfacing. The most common symptoms with PBT are cough, chest pain and hemoptysis.[51,52] Often the chest pain is noted laterally, but generalized or substernal pain has been also reported. When AGE occurs with PBT, the associated radiographic changes may include alveolar or interstitial opacities, pneumomediastinum, subcutaneous air, intravascular air, pneumothorax, pleural effusion, and retroperitoneal air.[48-52] While no strong evidence supports definite risk factors for developing PBT, some data support that smaller lung volume, less compliance, breath holding, coughing and airway obstruction may put divers at higher risk for PBT.[53-58]

Of the PBT syndromes, mediastinal and subcutaneous air are the most frequent. On auscultation pericardial crunch, known as Hamman's sign synchronous with the heart beat may be heard. A careful chest radiograph examination is required to recognize mediastinal air. If subcutaneous emphysema of the neck area is noted, it is an extension of pneumomediastinum. Though pneumomediastinum is a marker of PBT, and is the most-frequent radiographic finding in AGE, in isolation it generally follows a benign course and may require simple observation.[59,60] Pneumothorax is rare, but potentially devastating, as any trapped air will continue to expand with decreased ambient pressure. Symptoms of pneumothorax may include dyspnea, chest pain, tachypnea, tachycardia, hypotension or cyanosis. On physical examination, distended neck veins, tracheal deviation, hyperresonance to percussion, unilateral decrease in breath sounds are seen; in 20 to 25% of cases, there is associated subcutaneous emphysema. Divers with tension pneumothorax should get a large bore needle insertion into the second intercostal space, immediately followed by tube thoracostomy.[59,60] Divers with airflow obstruction (active asthma, chronic obstructive lung disease), bullae, or cystic lung disease are at high risk for pneumothorax during diving and are advised not to dive.[5,53-58]

Arterial Gas Embolism

In some of the earliest reports, AGE was referred to as submarine lung or compressed air illness in submarine escape trainees (SET). In 1932, Behnke recognized AGE as an air embolism resulting from pulmonary injury.[61] The remarkable clinical presentation of AGE is seen immediately upon or within the first few minutes of surfacing from the dive.[62] Loss of consciousness was noted in 81% of the cases; when coma was the presenting feature, it was seen within 30 seconds of surfacing. In nearly one-third of AGE, chest pain, irregular breathing or apnea and vomiting were noted. Weakness or paralysis, hemoptysis, sensory loss, cardiac arrest, confusion, headache, vision change were noted in 15 to 25% of cases. Less than 10% of the cases reported symptoms of dizziness, dysarthria, ear pain, nausea, dyspnea, ataxia, abdominal pain, diffuse joint pain, and retro-orbital pain were reported.[42]

The presentation of AGE in recreational divers is similar to that of SET, but the clinical course is different because recreational divers are usually not close to a recompression facility; loss of consciousness, stupor or confusion are frequent. Other symptoms often include seizures, vertigo, visual disturbances and sensory changes.[63] Many of the sport diving symptoms often resolve before treatment is initiated. A 2–12 hours treatment delay postembolization has not been associated with an increase in residual neurologic changes.[64] In sport divers AGE is frequently attributed to breath-holding when a diver runs out of air or with buoyancy challenges during ascent. Sport divers may present a combination of clinical features from AGE and DCS. A severe form of spinal cord DCS referred to as "biphasic decompression sickness" may occur; initial presentation being coma and hemiparesis, which improve with breathing oxygen prior to recompression treatment. This initial phase is then followed by a second phase during the recompression treatment with spinal cord manifestations, such as the bladder and bowel dysfunction or paraparesis. Divers with biphasic illness generally do poorly with further hyperbaric treatment. Injured divers may also manifest clinical features of near drowning, such as hypoxia, hypotension and acidosis. These findings further complicate the clinical course of AGE.[62-68]

There is limited human data of AGE as it is rare and in all cases should be treated with rapid recompression therapy. However, animal studies demonstrate air from barotrauma entering the arterial system via the pulmonary vasculature (resulting in focal ischemia), systemic and cerebral vascular systems. Systemic hypertension is noted and this may be secondary to a reflex mechanism.[66] An increase in cerebral blood volume may occur with a rise in intracranial pressure and compromise autoregulation of cerebral perfusion. These changes lead to further increase in cerebral blood volume. EEG changes and evoked potential changes are noted after AGE.[49] Interruption of normal cerebral blood flow and glucose metabolism increases lactic acid production, a major contributor to cerebral infarction. Sudden death in AGE is most likely from ventricular arrhythmias and hypotension from either arterial embolization to the cerebral circulation or the coronary arteries.[68-70] AGE is primarily a clinical diagnosis and should always be treated expeditiously.

Audiovestibular/Sinus and Dental Barotrauma

Since, a closed gas-filled cavity is necessary for barotraumas, it stands to reason that the most frequently involved organs include the ear, nose and throat system. Ear barotraumas during descent occur when middle ear pressure does not equilibrate with the ambient pressure due to Eustachian tube obstruction; this leads to the exudation of fluid, bleed or rupture of the tympanic membrane.[34,71-73] Symptoms of inner ear barotrauma include a sensation of pressure, pain or hearing loss that may resolve. Tympanic membrane rupture during diving may lead to nausea, vertigo and disorientation. Divers are trained to prevent ear barotraumas by using maneuvers to keep the Eustachian tubes open. Treatment of ear injury includes decongestants, analgesics and, if infection occurs, antibiotics.[34,71,72] While middle ear injury is common, inner ear injury is rare, but may lead to persistent vestibular deficits.[73] Treatment of inner ear includes injury bed rest and head elevation, may require tympanotomy and (if necessary) patching of the round window.[55]

Like ear barotrauma, sinus barotrauma may occur during descent or ascent. Descending injuries include mucosal swelling and inflammation causing sinus ostial blockage leading to headache, epistaxis and pain. Topical and systemic decongestants are effective treatments. In extreme cases, ascension injury may result in sinus rupture and pneumocephalus.[34,74,75] Dental barotraumas may occur in infected tooth areas, or around fillings resulting in pain or breakage.[76]

NITROGEN NARCOSIS

The impairment of intellectual and neuromuscular performance and behavioral changes may occur from an increased partial pressure of nitrogen in the nervous system. This syndrome is known as nitrogen narcosis and is often seen at depths of 100 feet or greater. Hallucinations and loss of consciousness have been reported from nitrogen narcosis at depths beyond 300 feet. Risk factors for nitrogen narcosis include hypercapnia, fatigue, hypothermia and alcohol consumption. A compromised mental status at depth is particularly dangerous as judgment errors may quickly result in drowning.[4,77]

PULMONARY EDEMA

Pulmonary edema in scuba divers is rare, but has been reported. Though the etiology of pulmonary edema in divers is not clear, it is known that water immersion significantly increases intrathoracic fluid. This volume increase may combine with heavy exercise, hydration and peripheral vasoconstriction to cause failure of the pulmonary capillary bed. This condition may be associated with cough, hemoptysis and dyspnea. Findings of pulmonary edema are noted on physical examination and radiography (Fig. 105.3). Generally, this syndrome resolves with supportive care in a short period of time.[78-82]

TREATMENT OF DECOMPRESSION DISORDERS

There has been remarkable effort put forth to prevent and treat decompression illness resulting in the decreases of diving accidents and increases in effective treatments.

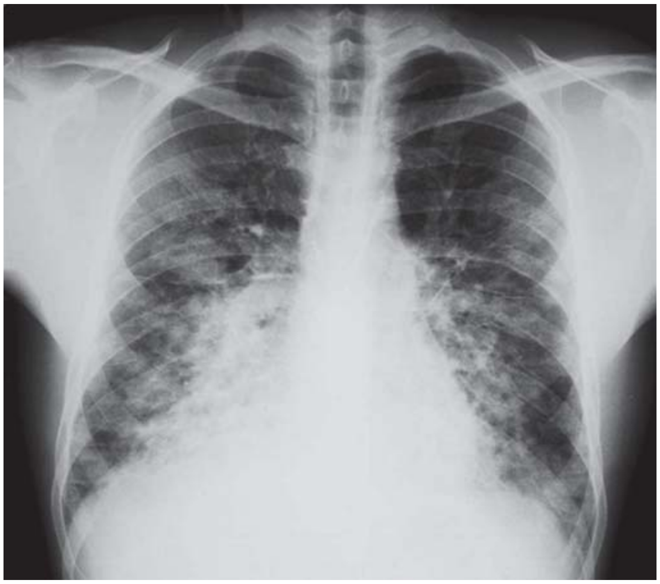

Fig. 105.3: Immersion pulmonary edema

In the last five to six decades, major advances have been made in training, technology and preventive education along with the development of standardized treatment tables. Prior to these recent advancements, DCS treatment since the mid-nineteenth century consisted of recompression with air. Today's improved treatment modalities have significantly improved the clinical outcome.

A thorough history and physical examination is critical to any decision on DCS treatment. The history should include detailed information on the clinical symptoms, the onset and progression (or regression) of symptoms, depth and duration of diving exposure, presence or absence of barotraumas and any underlying illness prior to diving. Symptoms of neurological DCS manifest within the first 10 minutes of surfacing in more than 50% of the cases; more than 90% within the first three hours.[83] Pain manifestation of DCS may have a much longer onset, up to 6 hours or more, particularly after saturation dives. Symptoms occurring prior to decompression (at depth) are often due to barotraumas, gas contamination or other extraneous injury. The differential diagnosis of DCS includes other causes, such as myocardial infarction, environmental toxins, or other neurologic diseases not recognized prior to the dive. Psychiatric illnesses and factitious disorders should also be kept in mind.[84,85]

If divers experience only pain on surfacing, it is usually not accompanied by any physical findings, such as joint swelling or redness. Skin manifestations may include a macular or pruritic rash. Skin changes that involve deeper layers with lymphedema are referred to as cutaneous marmorata. Despite advances in imaging techniques for CNS, the most reliable tool for treatment and follow-up in DCS is the clinical assessment. Abnormalities of gait, especially when assessed with a tandem gait test, denote an early specific feature; however, they are often out of proportion to motor and sensory changes. Sensory changes, if present, are patchy and have a nondermatomal distribution. Multiple levels of neurologic manifestations affecting cerebrum, brain stem, spinal cord, and peripheral nerves may be seen.[86-88] Dyspnea, tachycardia and hypotension indicate the critical nature of DCS and are often due barotraumas and AGE.

In general, imaging studies are not useful in the initial evaluation of DCS. However, chest radiograph can identify pulmonary barotraumas, such as the mediastinal air, subcutaneous emphysema or pneumothorax. Divers are at risk for drowning, aspiration and pulmonary edema, which may be evident by radiograph. Diffuse capillary leak from gas embolism may present with Acute Respiratory Distress Syndrome (ARDS)/pulmonary edema changes on chest radiograph.[86,89]

Neuropsychological, electrophysiological testing (such as the electrophysiology [EEG]) and somatosensory evoked potential have not been clinically useful in the assessment and the management of neurological DCS, especially in the pretreatment phase, and would likely serve only to delay therapy.

Initial Stabilization

Initial stabilization of airway patency, breathing and circulation should be addressed in all divers who manifest with DCS. Initiating treatment with supplemental oxygen, fluid replacement and chest tube drainage if pneumothorax is noted, are initial stabilization considerations. In suspected AGE, head-down position is recommended to minimize the risk of cerebral embolization without increasing the risk of cerebral edema. Oxygen supplementation is preferred via face mask to provide 100% FiO_2 en route to recompression therapy. In the case of air medical evacuations, the lowest safe altitude should be maintained so as not to contribute more to the decompression stress. Recompression treatment is recommended for all divers with neurologic, cardiopulmonary and some joint manifestations of DCS as it seems to provide some beneficial prognostic advantage. Given the overall safety of recompression therapy, a general low threshold for its implementation is routine and in some circumstances, may add diagnostic utility.[22,26-29,34]

Recompression

The management of DCS involves returning the diver to pressure and the use of Hyperbaric Oxygen (HBO); so called recompression therapy. The return to pressure "crushes" the existing bubbles and the HBO enhances the washout of inert gas and enhances oxygen delivery to tissue beds. Several treatment strategies, known as treatment tables, are used, but the most common is the United States Navy's treatment table 6 (TT6). The Navy TT6 uses HBO at 2.8 ATA with short periods of air to minimize oxygen toxicity.[22,26-29,34]

Early hyperbaric therapy is recommended, however there is no time limit beyond which the recompression has been determined to be not efficacious. This is important because recreational divers may have limited access to recompression therapy. Treating diving-related injuries requires clinical expertise and certified personnel for the safe operation of a hyperbaric chamber (Figs 105.4 and 105.5). Hence, it is recommended (and in some cases regulated) that personnel with experience and expertise initiate and treat DCS.

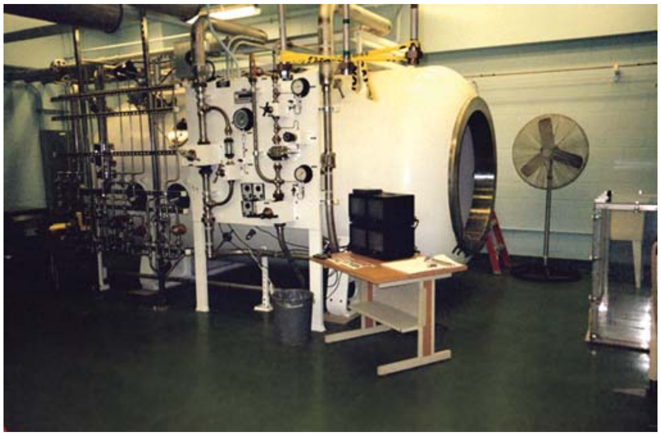

Fig. 105.4: Hyperbaric chamber-outside

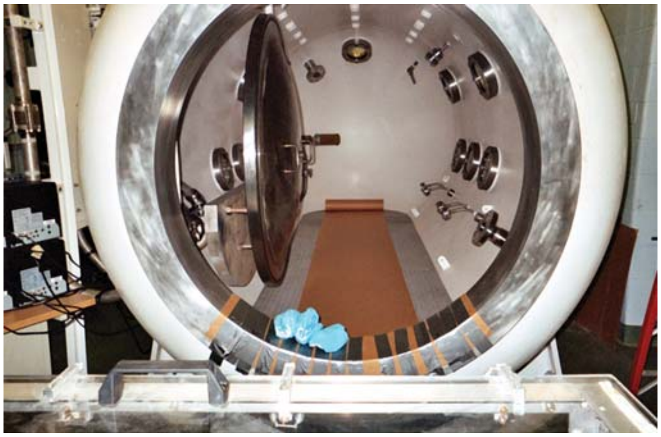

Fig. 105.5: Hyperbaric chamber-inside

If the resolution of DCS symptoms is incomplete after a single hyperbaric treatment, further hyperbaric treatments may be used once or twice daily until there is resolution of symptoms, or no further improvement is observed. Most require one to two treatments. Rarely with severe neurologic DCS, up to 20 treatments have been completed. Adjunctive measures to hyperbaric treatment for DCS include intravenous fluid administration; use of corticosteroids and indomethacin are of limited value. There is reasonably strong evidence to support the use of lidocaine as it appears to preserve blood flow to the brain, reduce cerebral edema and infarct size, and reduce intracranial pressure.[88-92]

Return to Diving after Diving Injury

Pulmonary barotrauma is an uncommon event and generally, chest radiographs and CT scans have not been useful in predicting barotrauma risk. Similarly, spirometric and compliance evaluations have not been uniformly helpful in assessing barotrauma risk. However, physicians consider a prior diving-related barotrauma as a high risk for recurrence and many recommend CT scans of the chest to look for parenchymal and pleural abnormalities.

Return to diving depends on the residual neurologic damage and dysbaric osteonecrosis. A minimum one month delay after a DCS event is recommended before the next dive. In non-recreational divers with DCS, those that were successfully treated with a diving treatment table 5 can return to diving after 7 days; those that required a Treatment table 6 should return only after 4 weeks and after a dive clearance by a physician trained in diving medicine.[93,94]

LONG-TERM EFFECTS OF DIVING

Divers are exposed to acute changes, but may also have long-term effects from diving.[95] This chapter previously described some factors that might put a diver for acute adverse events. Table 105.4 summarises the key points and recommendations of diving with specific respiratory conditions. Some environmental factors encountered during diving, as well as the impact of DCS and AGE, have the potential for long-term effects on different organ systems (Table 105.5).

Effects on Lung

Ambient pressure, duration and breathing gas mixture may have a direct impact on lung function. Other factors

TABLE 105.4: Summary of key points and recommendations: Specific respiratory conditions

- Lung bullae or cysts increase the risk of barotrauma and are contraindications to diving.
- Previous spontaneous pneumothorax is a contraindication unless treated by bilateral surgical pleurectomy and associated with normal lung function and thoracic CT scan performed after surgery.
- Previous traumatic pneumothorax may not be a contraindication if healed and associated with normal lung function, including flow-volume loop and thoracic CT scan.
- Subjects with asthma should be advised not to dive if they have wheeze precipitated by exercise, cold, or emotion.
- Subjects with asthma may be permitted to dive if, with or without regular inhaled anti-inflammatory agents (step 2 of the BTS guidelines 4), they:
- Subjects are free of asthma symptoms;
- Subjects have normal spirometry (FEV_1 >80% predicted and FEV_1/VC ratio >70% predicted); and
- Subjects have a negative exercise test (<15% fall in FEV_1 after exercise).
- Subjects with asthma should monitor their asthma with regular twice daily peak flow measurement and should refrain from diving if they have:
- Active asthma—that is, symptoms requiring relief medication in the 48 hours preceding the dive;
- Reduced PEF (more than 10% fall from best values); increased peak flow variability (more than 20% diurnal variation).
- COPD carries a theoretical increased risk of barotrauma and reduced exercise tolerance. Subjects will probably be advised against diving on the basis of reduced pulmonary function (FEV_1 <80% predicted).
- Sarcoidosis has been associated with pulmonary barotrauma. Diving is contraindicated in subjects who have active sarcoidosis. Those in whom sarcoidosis has resolved should have normal chest radiography and pulmonary function testing before being advised that they may proceed with diving.
- Tuberculosis is a potentially transmissible disease that may cause residual impairment of lung structure and function. A subject with active tuberculosis should not dive. After curative treatment they may dive if lung function and chest radiograph are normal.
- Cystic fibrosis is often associated with abnormal pulmonary function and the increased risk of pneumothorax. Diving is contraindicated in those patients who have pulmonary involvement.
- Fibrotic lung disease reduces lung compliance and impairs gas transfer. Diving is therefore contraindicated in subjects who have fibrotic lung disease.

TABLE 105.5: Long-term effects of diving on the lung

- Divers tend to have large lung volumes with proportionately greater increases in vital capacity than in FEV_1. This may be attributable in part to the effects of repeatedly breathing dense gas through increased resistances.
- Divers may have reduced expiratory flow rates at low lung volumes, possibly reflecting small airway disease.
- Vital capacity of divers may decline with age at an increased rate.
- Saturation diving causes a fall in carbon monoxide transfer, which once the dive is completed, gradually returns to predive values.

that may indirectly affect lung function include DCS, gas bubbles in pulmonary vasculature, breathing effort, respiratory heat/cold, dehydration and contaminated water exposure. Clearly, individual diver's Vital Capacities (VC) is important. Divers have been reported to have vital capacities larger than predicted.[96,97] Generally, there was an initial increase in VC until the age of 30, at which point it declined. It was found that the Forced Expiratory Volume in one second (FEV_1) the most frequently used index for assessing and quantifying airflow limitation, did not increase proportionately resulting in a lower than predicted FEV_1/FVC ratio. An international consensus conference concluded that there is evidence to suggest changes in bone, lung, and central nervous system in some divers who had not experienced a diving accident or exposure to environmental hazards.[95]

Dysbaric Osteonecrosis

Grützmacher in 1941 first reported osteonecrosis in a diver even though it had previously been observed in tunnel and caisson workers.[98] Dysbaric Osteonecrosis (DON) is often seen in the humeral head as against femoral head in other nontraumatic osteonecrosis. Osteonecrosis develops when decompression after hyperbaric exposure produces gas bubbles in fatty bone marrow expanding the adipocytes. This can lead to local and disseminated intravascular coagulation and intraosseous thrombosis along with platelet aggregation, lipid emboli, and the release of vasoactive substances. DON is most common in native diving fishermen who perform routine, repetitive diving for livelihood over many years.[99,100] Shinoda and associates detected DON in all 23 divers who underwent Magnetic Resonance Imaging (MRI) exam of shoulders, hips and knees. They also demonstrated a correlation between the diving depth and DON severity in the humerus.[101] DON is reported rarely in recreational scuba divers.[102] Risk factors for DON are obesity and alcohol abuse, cigarette smoking, fatty liver, hyperlipidemia, and impaired fibrinolysis.[103] Alcohol-induced osteonecrosis has been reported in nondivers.[104]

CNS

Diving-related events, such as DCS and AGE result in acute injury, but may also have adverse long-term outcomes to the spinal cord and brain. There are also concerns regarding possible CNS effects in divers who never experience DCS or AGE. Many studies have used psychometric testing, MRI and other imaging modalities to assess CNS function in divers who never suffered AGE or DCS. In general, no significant or progressive disability has been noted. However, in those who have suffered DCS with spinal cord injury, nearly 10% have sustained permanent gait changes and were unable to return to work. Also, those who had significant cerebral DCS were found to have permanent impairment, such as poor concentration, memory deficits and headaches that were correlated with imaging abnormalities. Saturation and commercial divers examined have not shown any sustained brain function impairment.[104,105]

Morbidity and Mortality in Scuba Diving

DAN publishes an annual report of diving-related accidents, injuries and mortalities. However, a true incidence based on these numbers is difficult to ascertain. The common morbidities result from running out of air underwater, rapid ascent and drowning. DAN reports that 6 to 14% of fatalities were of cardiovascular origin, and 5 to 14% from air embolism. A medical screening is required prior to scuba training, but the physical standards, which are required, vary among countries. Scuba training emphasizes safety: Proper use of equipment, controlled ascents, decompression stops, adequate air supply checks, etc.

SUMMARY

Over its long history, diving has been used primarily for the commercial and military operations. However, over the last few decades, the popularity of diving as a recreational activity has grown steadily. The technical aspects of diving have evolved over the years to allow the deeper diving of longer duration in challenging locations. Diving requires specialized training and is associated with multiple risks. Physical fitness is an essential requirement for training and many training centers also require medical clearance for diving certification.

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“No financial or other potential conflicts of interest exist for the above authors. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government. I/We certify that all individuals who quality as authors have been listed; each has participated in the analysis of data, the writing of the document, and the approval of the submission of this version; that the document represents valid work; that if we used information derived from another source, we obtained all necessary approvals to use it and made appropriate acknowledgements in the document; and that each takes public responsibility for it. Nothing in the presentation implies any Federal/DOD/DON endorsement”.

APPENDIX: SIGN LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS

Levels of Evidence

Ia: Evidence obtained from meta-analysis of randomized controlled trial.
Ib: Evidence obtained from at least one randomized controlled trial.
IIa: Evidence obtained from at least one well designed controlled study without randomization.
IIb: Evidence obtained from at least one other type of well designed experimental study.
III: Evidence obtained from well designed nonexperimental descriptive studies, such as comparative studies, correlation studies and case-control studies.
IV: Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of Recommendations

A (Levels Ia, Ib): At least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Levels IIa, IIb and III): Requires well conducted clinical studies, but no randomized controlled trial on the topic of recommendation.

C (Level IV): Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

BTS guidelines on respiratory aspects of fitness for diving www.thoraxjnl.com.

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Section

13

OCCUPATIONAL DISORDERS

PS Shankar

106

Lung Diseases in Coal Workers

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INTRODUCTION

Coal is not a pure mineral. It is formed by the accumulation of vegetable matter covered by sedimentary rock (thereby sealing it from air) and subjected to pressure and temperature over the ages. This causes the physical and chemical properties of the matter to change. The matter dries, becomes warmer and loses oxygen content, all the while increasing the relative carbon content.[1]

The first step in this conversion of vegetable matter to coal is the formation of peat, a moist spongy material. This transformation of organic deposit can occur in a stagnant water bed relatively quickly (at a rate of approximately one foot per 100 years). An approximately 100-foot accumulation of peat compresses to form a one foot wide coal seam. In the simplest terms, coal is comprised of moisture (which lessens with time), pure coal (carbon) and mineral matter.[2]

The process of conversion (coalification) from organic matter follows a transformation of wood to peat to lignite to bituminous coal to anthracite coal (Table 106.1).[3] The terms “brown coal” and “black coal” refer to the coals of low and high rank, respectively. Rank describes the extent of change from vegetation to mineral-free coal.

The composition of coal mine dust varies with the coal seam. Most of the dust is composed of carbon, although in some seams it may only approximate 60% of the dust, with more than 50 different elements and their oxides.[4] Dusts of high rank typically have more silica than the dusts of lesser rank because the anthracite seams often have roofs and floors of quartz, which contaminate the coal during mining. Although the amount of coal mined yearly continues to increase, coal continues to decline in its importance as a world energy source, while petroleum and natural gas are increasingly used as substitutes. In addition, a byproduct of burning coal is carbon dioxide, a greenhouse gas and a major source of concern with respect to changes of the global climate.

In the US, electric power generation accounts for the utilization of more than 80% of the coal produced each

TABLE 106.1*: Coal characteristics

Coal rank	*% volatile matter*	*% carbon*	*% ash*	*% moisture*	*BTU**/pound*
Peat (dried)	70	25	5	10	8,000–12,000
Lignite	41	36	9	14	5,500–7,000
Bituminous	32	55	10	3	12,000–14,000
Anthracite	5	87	5	3	> 13,000

*adapted from Haught OL. Coal and coal mining in West Virginia. Published by the West Virginia geological and economic survey, Morgantown, WV. 1955. pp. 1-32 (reference 3).

**One BTU (British thermal unit) is equivalent to the amount of heat necessary to raise the temperature of one pound of water from approximately 4º to 5º F.

year. In India, like in the US, coal production yields approximately half of the country's energy needs.[5] The country's industrial heritage has been built upon indigenous coal. Commercial primary energy consumption in India has grown by about 700% in the last four decades, and in the face of a rising population and expanding economy, this is likely to continue. With the relatively limited amount of petroleum and natural gas, the restrictions placed on the development of hydroelectric projects and the political disagreements associated with nuclear power, coal will remain in the forefront of India's energy structure. India's proven hard coal reserves are estimated to be 92 billion tons (with three or four more times this amount likely). These deposits are recognized to be dispersed over 27 major coalfields, mainly in the eastern and south central parts of the country. Lignite, or soft coal, reserves approximate 36 billion tons, the great majority located in the southern state of Tamil Nadu.[6]

Epidemiologic Features of Coal-Induced Lung Disease

The current system of classifying the radiological severity of pneumoconiosis began with the work of Davies and Mann.[7,8] These investigators postulated that the number of small opacities visualized on the chest radiograph reflects the severity of pneumoconiosis and introduced the concept of the "major" categories of simple pneumoconiosis (based on the profusion and extent of opacities). Liddell is later credited as the first to divide each major category into three subcategories.[9] These notions were incorporated into the International Labour Organization (ILO) 1958 classification of the radiographs of pneumoconioses, in which a continuum of the profusion of opacities is separated into four distinct categories—from 0 to 3.[10] The next steps were to relate these standardized abnormalities on the chest radiograph to spirometric and demographic data.

The International Union Against Cancer (UICC) Working Group on Asbestos and Cancer in 1964 recognized the need to improve comparability and build on this classification.[11] Further changes of this scheme form the basis of what is the basically the current ILO system, initially introduced as the 1970 UICC/Cincinnati classification.[12] These included the division of pleural changes into "calcified" and "noncalcified", as well as changes in the manner that small opacities were described. A 12-point scale reflecting a series of "shades of gray" within a major category was added. In addition, the lung was separated into three zones for more descriptive imaging, rather than characterized as a single entity, and small opacities separated into "rounded" and "irregular" shapes, and then further separated small opacities into different sizes ('p', 'q', 'r' and 's', 't', 'u'). Copies of "standardized" radiographs were made available from several investigators. The 1968 ILO classification system was a modification to incorporate asbestos-related diseases based in part on the UICC/Cincinnati classification system.

The 1980 ILO classification system made several more refinements. These included a set of 22 standard chest radiographs (available to all interested parties), which were examples of the size, shape and profusion categories of opacities. An estimate of film quality became a part of the protocol and the description of the pleura was more detailed.[13] In 2000, the ILO gave the scheme it's most recent "face lift." Standard films illustrating "u" shape shadows and pleural abnormalities were changed. Film quality was now judged on a scale from unimpeachable (+) to unusable ("u"). If not "+", then written comments are needed. Obliteration of the costophrenic angle was necessary for "diffuse pleural thickening." New symbols for chest radiological findings were also included.[14,15,16] Although the chest radiograph is the foundation for the diagnosis of Coal Workers' Pneumoconiosis (CWP), it may be insensitive at low profusion of macules and nodules.[17,18] In this setting, High Resolution Computed Tomography (HRCT) scanning may be more informative.

CLINICAL FEATURES OF COAL DUST EXPOSURE

Coal inhalation can result in industrial bronchitis and CWP, presenting as either simple pneumoconiosis or as complicated CWP or Progressive Massive Fibrosis (PMF).

Industrial bronchitis is a common diagnosis among workers exposed to dusts, including coal dust.[19] It manifests as a productive cough, which persists for at least three months per year for at least two years (chronic bronchitis) associated with workplace dust exposure. In a defining autopsy study, coal dust exposure resulted in an increase in the maximal gland: wall ratio (independent of smoking), but no relationship between mucous gland size and the amount of lung dust or presence or absence of pneumoconiosis was found.[20] These data suggest that mucous gland enlargement is related to the inhalation of larger (non-respirable) dust particles, which present a chronic burden to the mucociliary escalator and act as irritants to the airway, whereas pneumoconiosis is related to respirable dust exposure with the internalizing of these particles into the lung interstitium.

Early reports showed that the prevalence of bronchitis in coal miners varied by smoking history, age and job.[21] In all reports, smoking miners had bronchitis more frequently than nonsmokers, and when studied, showed bronchitis to increase with age (a surrogate for years of dust exposure in the workplace). Marine identified 543 lifetime nonsmokers among 14,888 British coal miners (3.6%) studied between 1953 and 1967 who were less than 65 years of age, worked at the coal face in most instances, did not have PMF, and who had participated in three surveys over 10 years.[22] Of these, 17% had bronchitis at the third survey. In a second report of coal miners, 16% had bronchitis.[23]

Coal workers' pneumoconiosis results from the inhalation and deposition of coal mine dust, and the lung's reaction to its presence. Three criteria are necessary for this diagnosis.[24] They include:

1. A chest radiograph consistent with the features of CWP;
2. A work history (typically underground coal mining) sufficient in exposure and latency to result in pneumoconiosis; and
3. The absence of other illnesses which may mimic CWP.

Therefore, the diagnosis of CWP can be made with confidence without histologic confirmation. Clinical features, such as dyspnea, cough and sputum production are important in addressing the degree of a miner's impairment, but are not a part of the diagnostic criteria. The radiographic appearance of CWP cannot be differentiated from silicosis, and coal miners may develop disease from exposure to both dusts.

Coal workers' pneumoconiosis is categorized as simple pneumoconiosis or PMF. The radiograph in simple pneumoconiosis shows small opacities, ranging in size from pinhead to 1 cm in diameter. Rounded nodules predominate and tend to appear first in the upper zones and then the middle and lower zones as the number of opacities increase. With prolonged excessive exposure, these small opacities may coalesce and form larger opacities, typically in the upper zone, recognized as PMF lesions and characterized by one or more large opacities greater than 1 cm in diameter. Associated distortion of lung architecture typically includes the deviation of the trachea and major airways to the side of the most prominent area of coalescence, loss of upper zone lung volume, elevation of the hila, and basilar emphysema (typically of a panacinar type), attributable to traction placed on the lower lung zones by the elevation of the hila. Importantly, CWP can progress after the cessation of coal mine dust exposure.[25]

In a population comparing miners without CWP to those with CWP, respiratory symptoms and physical signs were no more prevalent in those with simple CWP.[26] The not infrequent presence of a chronic cough and sputum production, even in the presence of CWP, is reasonably attributable to "industrial bronchitis." Alternatively, these same clinical features in a smoking miner may be partially attributable to bronchitis caused by the inflammatory stimulus of cigarette smoke. Finger clubbing is not a feature of CWP, and if noted, should prompt further investigations. Yet, when PMF is recognized on the chest radiograph, the worker frequently describes dyspnea, cough and sputum production, although it is recognized that the degree of impairment and presence or absence of symptoms does not correlate well with the extent of chest radiographic abnormalities.

The effect of pneumoconiosis on the heart has been described by several investigators. Lapp performed cardiac catheterization during rest and exercise in miners with CWP, some with airways obstruction.[27] Those with underlying obstructive lung disease or PMF had increased pulmonary artery pressures. In those without these two illnesses, increased pressures occurred in the presence of pinpoint (p) opacities on their radiograph. This type of opacity is associated with diminished diffusion and a decreased vascular bed.[28] A later autopsy study of British coal miners addressed the relationship between coal dust exposure and Right Ventricular Hypertrophy (RVH) comparing those with simple CWP or no pneumoconiosis to those with PMF. The prevalence of RVH was the same in those with simple CWP as in those without pneumoconiosis (approximately 15%) and was related to the extent of airways obstruction. Right ventricle enlargement did not occur unless the miner was a smoker with severe airflow obstruction or PMF.[29]

Typically, CWP is a slowly progressive illness, with radiographic features progressing over a period of many years. The appearance of a cavity in a PMF lesion or an aggressive rate of radiographic progression should prompt the examination of the sputum for mycobacterial infection. The chest radiograph in simple CWP correlates with the amount of dust in the lung at autopsy.[30] This is not true of the complicated form of the disease, suggesting that inadequately defined host factors play a role in the development of this lesion. Hypotheses which might explain the differences in tissue response to coal dust in those who remain with simple CWP and those who progress to PMF include:

1. Inhalation of significant amounts of silica in addition to coal in mine dust;

2. Infection with an atypical mycobacterial organism; and
3. Development of specific immunologic factors, which are responsible for progression.

Yet, none of these explanations appear to satisfactorily explain the development of PMF. First, PMF has been reported in carbon electrode workers. This suggests that silica exposure is not necessary for PMF to occur.[31] Treatment of miners with simple CWP in Wales with antituberculous drugs did not prevent PMF.[32] Autoantibodies reactive to lung tissue antigens have been demonstrated in the sera of miners suggesting a role in the tissue response.

A special case of nodular lung reaction occurs in dust-exposed individuals who either have rheumatoid arthritis or who develop rheumatoid arthritis within the subsequent 5 to 10 years.[33,34] This leads to discussion regarding the potential role of immunological factors in mineral dust pneumoconioses. The nodules of Caplan's syndrome vary in diameter from 0.5 to 5 cm and are usually multiple, bilateral and situated peripherally. Grossly, the lesions resemble a giant silicotic nodule. Microscopically, the amount of dust in the lesion is small, there is a necrotic area in the center, and there is a surrounding cellular zone infiltrated with lymphocytes and plasma cells. In many nodules there is a peripheral zone of active inflammation with neutrophils and a few macrophages. This observation was further enhanced when similar radiographic appearances in miners without arthritis, but in whom circulating rheumatoid factor was demonstrated. An increased incidence of circulating positive rheumatoid factor among miners with PMF has also been reported. In a group of 60 consecutive cases of scleroderma, Rodnan described 26 cases with a history of employment as a coal miner or employment in an occupation where silica exposure was encountered.[35] Although, the course of scleroderma did not vary in the two groups, it appears that chronic fibrogenic dust exposure may be a risk factor for the development of scleroderma.

The clinician may be presented with the diagnostic dilemma of attempting to distinguish a primary or metastatic neoplasm from an unusual presentation of PMF. When large opacities of PMF occur bilaterally on a background of simple CWP, one can be reasonably confident that the lesions are less likely to represent neoplastic disease. When there is a sparse background of simple CWP or none, or there are crops of nodules (as in Caplan's syndrome), the differentiation from neoplasm may indeed be difficult.[36] Among underground miners (Fig. 106.1), those working at the face and are exposed to higher concentrations of coal mine dust had a higher prevalence of CWP than surface workers (Fig. 106.2) or those whose jobs caused them to enter the face area intermittently.[37]

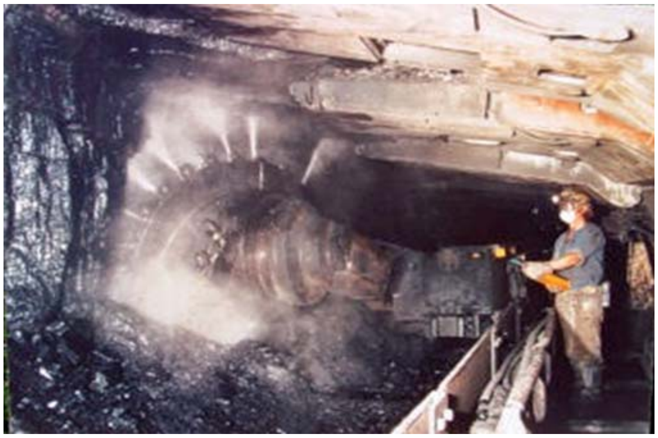

Fig. 106.1: Shows the aggressive aspect of underground mining and how productive this process is. The cutting head is cooled and generated dust limited by the spray. The miner is protected by roof cave-ins by standing under the overhead supports

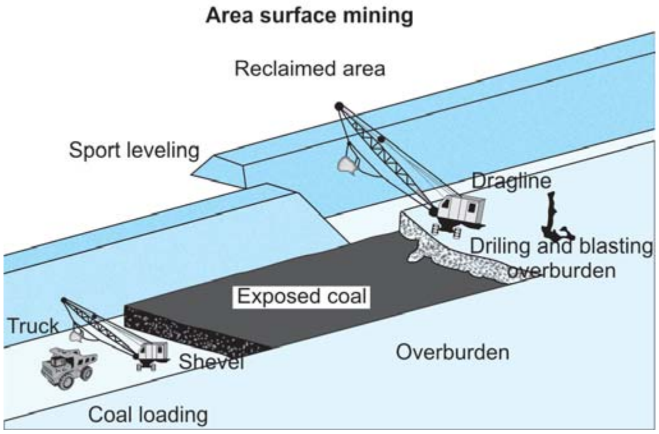

Fig. 106.2: Surface mining mines coal located near the surface. This process requires removing the overburden (earth and rock covering the coal seam) with heavy earth-moving equipment, such as draglines, power shovels, excavators and loaders. Once exposed, miners drill, place explosives charges and fracture the coal. This allows for the systematic removal of coal using trucks or conveyors and the transport to a coal preparation plant

PATHOLOGY OF CWP

As the normal dust clearance mechanisms of the lung are overwhelmed, dust deposition increases. With the

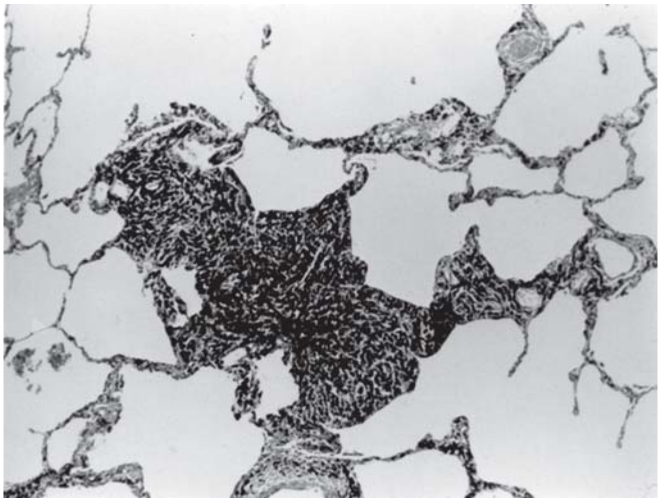

Fig. 106.3: This is a photomicrograph of a coal macule. There is coal dust, reticulin fibers, and coal dust-laden macrophages, with minimal fibrosis. The periphery of the nodule shows air space enlargement

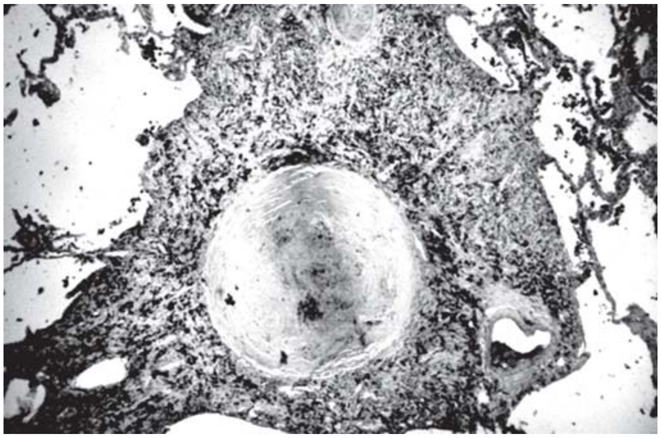

Fig. 106.4: This figure shows a photomicrograph of a lung biopsy from a roof bolter with the histologic evidence of both a coal macule and a silicotic nodule. This reflects the accumulation of coal and silica dusts exposure, which have occurred over his working lifetime. On the periphery, there is coal dust with coal-laden macrophages. Centrally, there are the whorls of fibrosis characteristic of a silicotic nodule. The cellularity is most prominent in the periphery of the lesion

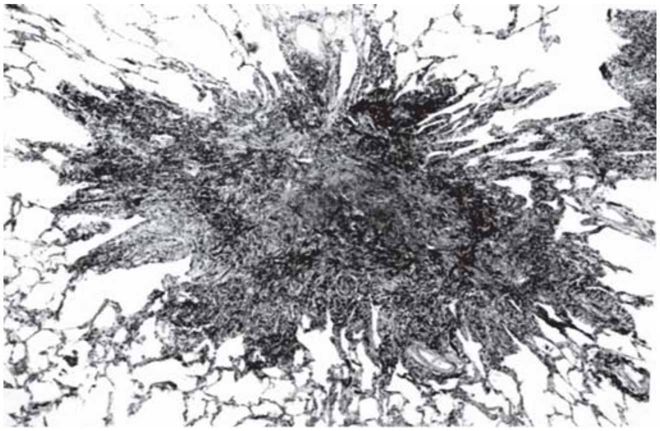

Fig. 106.5: The figure shows a coal nodule surrounding a respiratory bronchiole. As the macule enlarges, smooth muscle atrophies, and the bronchiole enlarges. Of interest in this photomicrograph are the enlarged air spaces surrounding the macule, a feature described as focal emphysema

initiation and progression of fibrosis, the lung lesions increase in size and number. A focal collection of coal dust in pigment-laden macrophages around dilated respiratory bronchioles, which tapers off towards the alveolar duct, is initially apparent.[38] This is the coal macule, the characteristic lesion of CWP (Figs 106. 3 and 106.4).[39,40] A fine network of reticulin within this collection of cells may be visible early on. Focal emphysema is a specific entity that is an integral part of the simple lesion of simple CWP (Fig. 106.5). It is characterized by the enlargement of the air spaces immediately adjacent to the dust macule.[41]

What impact this has on lung function has been the subject of considerable discussion. In nonsmoking, nonobstructed miners, Morgan[42] showed an increase in the Residual Volume (RV) in miners. In miners without CWP, the RV was 105% of a group of nonminers. This increased to 108% and 114% of controls in miners with category 1 or category 2 and 3 simple CWP. Morgan considered that this may be attributable to focal emphysema. He also considered this hyperinflation to be the result of coal macules narrowing the airways with the alteration of the peripheral flow rates by and increasing resistance. On gross examination of the lung, larger collections of dust are described as coal nodules, classified as micronodular, if they are 7 mm in diameter or less and macronodular, if they are larger than this. These are palpable whereas coal macules are not.

Progressive massive fibrosis is diagnosed when one or more nodules attain a size of 2 cm or greater in diameter, typically on a background of simple CWP[43] (Fig. 106.6). The 2 cm diameter is an arbitrary choice of a minimal diameter that has allowed better correlation with clinical and radiographic measurements. In other reports, nodules exceeding 1 cm are included as PMF. Gross examination of the lung in PMF reveals a solid, heavily pigmented lung, which is rubbery-to-hard in texture. These features are most common in the posterior portions of the upper lobes or the superior segments of the lower lobes. These lesions tend to occur asymmetrically, occasionally showing first in one lung and then the other, leading to a suspicion of malignancy. When these

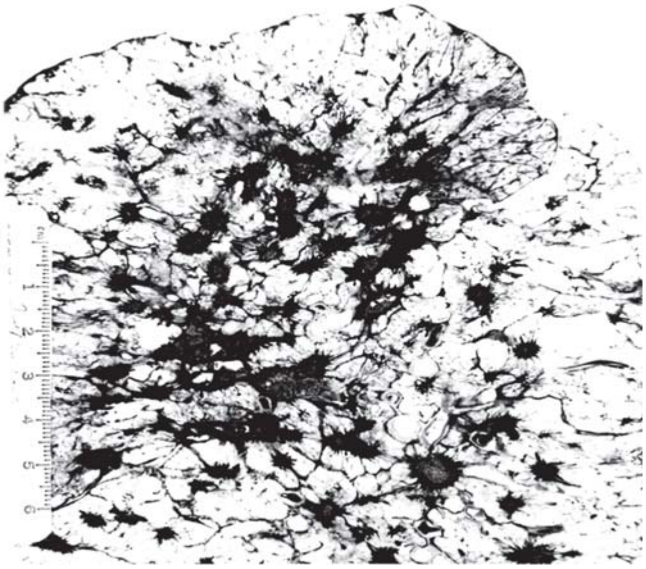

Fig. 106.6: This is a Gough section of the lung. Simple coal workers' pneumoconiosis (category 1) is percent on a background of diffuse emphysema. The black deposits are the coal macules. The degree of emphysema is widespread and does not appear associated with the coal macules

lesions are ashed, they appear to be composed of varying amounts of coal, silica, calcium and other substances. About ¼ of the proteinaceous material in the center of these lesions is collagen.[44] These lesions may also cavitate and the worker may expectorate an ink-like fluid (a clinical sign described as melanoptysis), or when these cavitary lesions are cut, they may drain ink-like fluid. Airways and vessels adjacent to the lesions are distorted and destroyed within the lesions.

Excessive silica exposures in surface coal mine drillers can also result in PMF lesions and result in "cor pulmonale" and respiratory failure (Figs 106.7A to 106.9).

How CWP Develops: Cellular and Immunologic Factors

Coal workers' pneumoconiosis is the result of coal dust-induced cell damage with the activation of the fibrotic process. Lapp provided a well-outlined approach to addressing how coal dust causes lung damage.[45] The potential mechanisms include:

1. Direct cytotoxicity of coal dust;
2. The release of oxidants, enzymes, and cell membrane constituents from Alveolar Macrophages (AMs) in association with cell death due to coal dust exposure; and

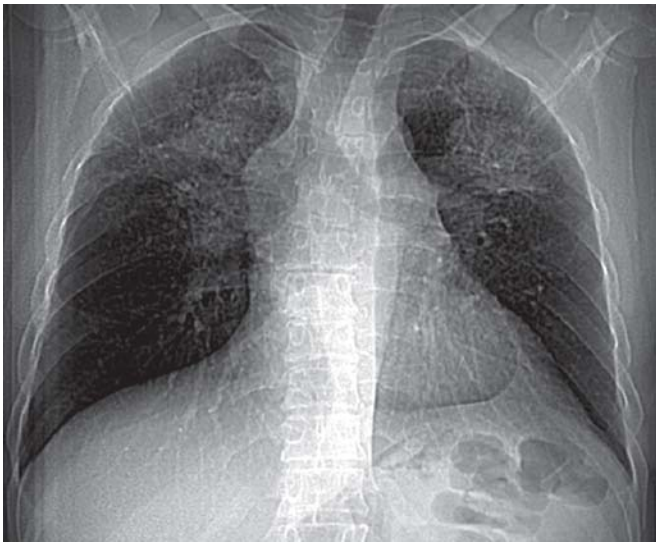

Fig. 106.7A: The figure shows multiple small rounded densities bilaterally, predominantly located in the upper lung zones. Mass-like densities are also present in the upper zones, and the overall appearance is typical for PMF

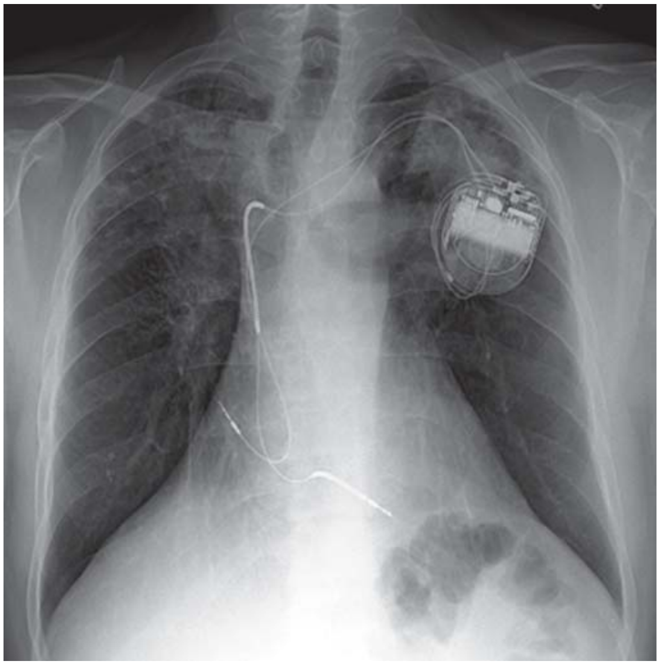

Fig. 106.7B: The picture is taken six years later, it shows progression of PMF over time. In the time between figures 106.8A and 106.8B, a pacemaker-defibrillator with intracardiac 2 leads had been inserted

3. Stimulation of cytokine release from AMs to recruit effector cells (other macrophages or neutrophils) and stimulate fibroblast proliferation and collagen synthesis in the area of coal dust deposition.

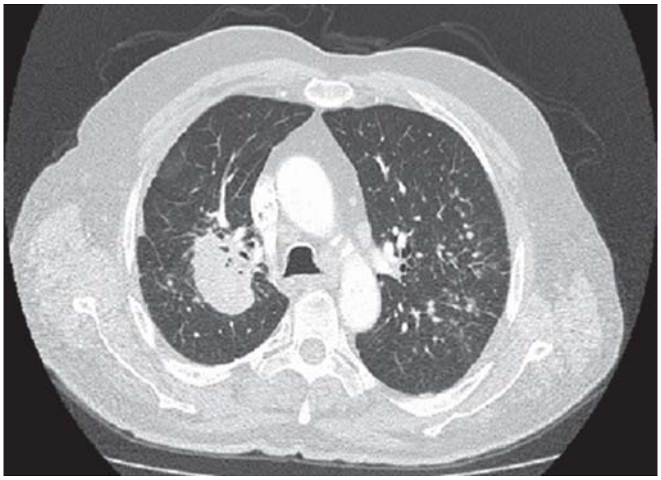

Fig. 106.8A: Chest CT scan in a surface coal mine drillers, which shows bilateral upper lobe fibrosis, more prominent on the right compared to the left, and a RUL mass

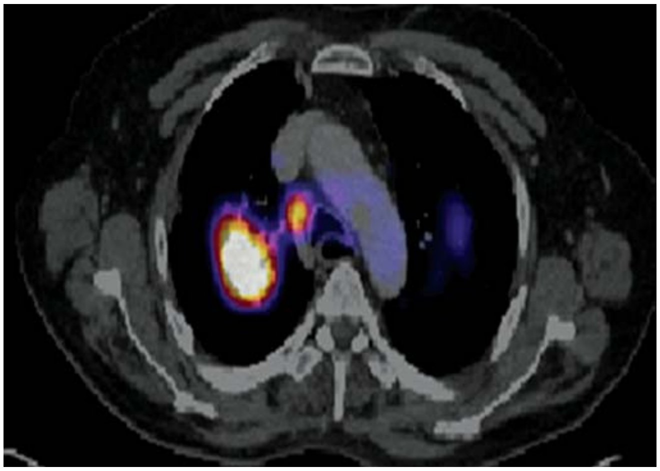

Fig. 106.8B: A PET scan taken near the time of figure 106.8A shows asymmetric PMF lesions (right more than left) as well as right peritracheal adenopathy

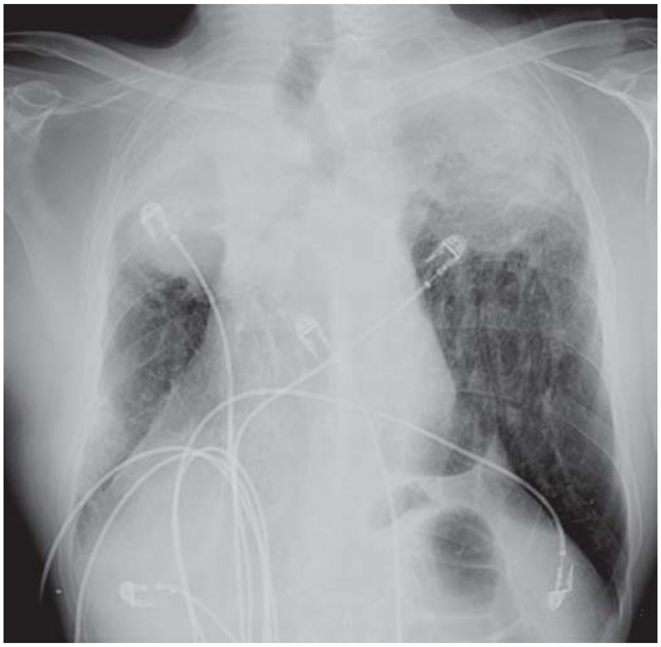

Fig. 106.9: A radiograph shows large opacities in both upper zones with associated calcification and fibrosis consistent with the diagnosis of PMF

Coal dust is much less fibrogenic than silica. As an example, a mixture of 10% silica and 90% coal is far more cytotoxic to macrophages than pure coal dust.[46] However, both dusts, when cleaved, show surface radicals by electron spin resonance spectroscopy. The free radicals generated by crushing anthracite coal are more numerous than those generated from crushing bituminous coal leading to speculation regarding free radical release from different coal ranks and the suggestion that exposure to anthracite coal increases the risk for the development and progression of disease.[47]

Long-term coal dust exposure in animals increases the number of alveolar cells recovered by lavage.[48] In addition, an elevation in the number of blood monocytes and an increased rate of mitosis has been recognized in cells from animals undergoing chronic coal dust inhalation.[49] This suggests that there was recruitment of cells into the lung from the alveolar capillaries and the interstitium of the lung. Recruited "young" AMs appear to be more active in phagocytosis than older AMs. This may imply a more effective clearance of particles.[50]

Exposure of AMs to particles can result in the release of proteolytic enzymes, reactive oxygen species [i.e. hydrogen peroxide (H_2O_2), hydroxyl radical (OH) and superoxide anion (O_2^-)], and leukotrienes via breakdown of arachidonic acid in the cell membrane. Again, silica is a much stronger stimulus to the release of these agents than coal dust.[51] Excessive release of these reactive oxygen species has the potential to overwhelm the naturally protective antioxidant system within the lung and begin the process of inflammation and fibrosis.

Activated macrophages secrete a wide variety of mediators, which can attract neutrophils into the affected area and then stimulate them to release reactive oxygen species and enzymes. Similarly, the macrophage-derived inflammatory factors can act as chemotactic agents for neutrophils (e.g. tumor necrosis factor, interleukin 8 and leukotrienes), and increase neutrophil adherence and reactive enzyme release (platelet-derived growth factor and platelet-activating factor). The presence of these factors escalates the inflammatory process. Finally, secretions of many of the above factors by activated AMs are likely to enhance fibroblast growth and/or stimulate the production of collagen.

Development of Bronchoalveolar Lavage (BAL) as a means for sampling lung cells and fluid has provided an opportunity to study the lung's response to the inhalation of various dusts. Studies of the mechanisms of inflammation and fibrosis using BAL-derived material have opened the possibility for studying at least some of the mechanisms in the pulmonary reactions in CWP.

It has been suggested that constitutional differences may help to explain the variation in response to inhaled dusts, especially the attack rates and progression of CWP. One study looked at the prevalence of histocompatibility antigens in coal miners.[52] So far it has not been possible to confirm any definite association between these factors and CWP.

MANAGEMENT OF CWP

There is no proven therapy for CWP. The primary prevention of lung disease in miners must include continuing efforts at reducing coal mine dust exposure. Management is best directed at prevention, early recognition and treatment of complications. The major challenges to the physician are the recognition and management of airflow obstruction, respiratory infection, hypoxemia, respiratory failure, cor pulmonale, arrhythmias and pneumothorax.

Workers presenting with respiratory symptoms should have careful evaluation. The initial history and examination should be supplemented by chest radiograph, spirometry with bronchodilators, diffusing capacity, electrocardiogram, and resting arterial blood gas measurement as indicated. A thorough initial data base allows accurate assessment of the worker's respiratory health and serves a starting point for observing the response to therapy or progression of disease.

Smoking cessation is important regardless of symptoms of respiratory disease, chest radiograph abnormalities or pulmonary function status. Physician encouragement to stop smoking should be supplemented by support from smoking cessation groups, use of nicotine substitutes and behavior modification techniques.

Symptomatic reversible airflow obstruction should be treated with inhaled bronchodilator therapy as indicated. Patients with severe obstruction and inadequate improvement from the usual measures should be considered for a trial of glucocorticoid therapy.

Hypoxemia can be a serious complication in those with PMF. It is typically present first during exercise, but can occur with rest and during sleep. Chronic hypoxemia can lead to the complications of polycythemia, pulmonary hypertension, cor pulmonale and cerebral dysfunction. Therapy with low-flow oxygen is indicated when the arterial oxygen tension is less than 55 mm Hg or when clinical evidence of cor pulmonale is present.

Miners should receive appropriate immunization with influenza and pneumococcal vaccines. Bacterial and viral episodes of bronchitis or pneumonia should be promptly recognized and appropriately treated. Similarly, miners with concomitant exposure to silica dust (most often roof bolters, drillers and motormen) deserve special attention with regard to mycobacterial infection. Symptoms of weight loss, fever, sweat, change in sputum production or malaise should be promptly investigated with a chest radiograph and examination of the sputum through stain and culture for Acid- Fast Bacillus (AFB). Occasionally the sputum may be negative and the infecting mycobacterial organisms can only be obtained by fiberoptic bronchoscopy with brushings and washings. Active tuberculosis in this population can be usually successfully treated with the usual drug regimens.[53,54] In coal miners with a significant history of concurrent silica exposure, the treatment for tuberculosis may need to be more aggressive, and long-term follow-up is indicated in the view of the reports of recurrent pulmonary tuberculosis in patients with PMF after the completion of apparently adequate therapy.[55]

Pneumothorax can be particularly troublesome in miners with pneumoconiosis. Those with bullous disease in the presence of advanced complicated pneumoconiosis are at the greatest risk. Typically, once the lung collapses, it is difficult to expand, a feature attributable to the decreased compliance associated with interstitial lung disease. Therapy with one or several chest tubes is often therapeutic; however, recurrent pneumothorax that cannot be expanded is recognized and may require an open procedure and pleurodesis.

Respiratory failure may complicate advanced PMF as it does in other chronic respiratory diseases. Ventilatory support measures are indicated when the failure is precipitated by a treatable complication. The application of ventilatory support measures should be discussed with the patient before the need arises. In general, miners with advanced pneumoconiosis are poor candidates for long-term mechanical ventilatory therapy.

Over-all, improved mining methods and lower dust levels appear to be reducing exposures and the new cases of both simple and complicated pneumoconiosis in the

US Medical surveillance programs, using chest radiographs, allow the early recognition of workers with simple pneumoconiosis. Yet, recent work in a series of US coal mines has reminded all that the hazards remain.[56,57] Workers with simple pneumoconiosis should be encouraged to transfer from jobs with high-dust exposure to jobs with low-dust exposure.[58] It is our opinion that any worker with simple CWP should be encouraged to leave dust exposure. Those with category 2 or great pneumoconiosis are at clear risk for progression even in the absence of additional coal dust exposure.

SUMMARY

Coal workers' pneumoconiosis is a disease distinct and separate from silicosis. Although, the coal particle is not nearly as fibrogenic as the silica particle, excessive exposures over a period of time overwhelms effective clearance mechanisms and initiates chronic interstitial lung disease. Simple CWP is clearly related to the amount of dust deposited within the lungs. PMF most often, but not always, occurs on a background of simple CWP and is the result of dust deposition plus other inadequately defined host factors. Immunological and local cellular factors may contribute to the development of this form of the disease.

Progressive massive fibrosis is clearly associated with alterations in the ventilatory, mechanical and vascular function of the lungs. These abnormalities in PMF contribute to the premature morbidity and mortality of this disease. Similarly, there is no therapy for CWP. Prevention remains the cornerstone of eliminating this occupational lung disease. The education of workers and employers regarding the hazards of coal dust exposure and measurement and effective control of dust exposure remains the sole means of eliminating this disease.

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Silicosis

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INTRODUCTION

Exposure to potentially harmful substances may occur at work in certain occupations. Silicosis is the most prevalent chronic occupational lung disease. It is an irreversible and chronic fibrotic disease of the lungs caused by inhalation, retention and pulmonary reaction to large amounts of silica dust, usually in the form of alpha quartz. The condition is an extensively studied occupational disease and it remains among the most serious potentially fatal occupational diseases.[1]

Silica and Silicosis

Silica is a chemical compound, silicon dioxide (SiO_2). Silicon is distributed widely in nature and it contributes to about 28% of the earth's crust. Silicon is highly reactive and does not remain in the state of an element. It combines either with oxygen to form free silica (SiO_2, silicon dioxide) or with oxygen and other cations, such as magnesium, aluminum or iron to form silicates. Examples of silicates include mica, soap-stone, talc, tremolite and cement. Silica and silicates form the bulk of most kinds of rocks, clays and sands. Silica exists in two distinct forms as crystalline and amorphous. "Crystalline" refers to silicon and oxygen atoms oriented and related to each other in a fixed pattern. In amorphous form, silicon and oxygen atoms are distributed in a random fashion.[2]

The term silicosis is applied for the lung disorders caused by inhalation of the free silica. The inhaled silicon dioxide is usually in crystalline form, most often as quartz. Crystalline silica produces different polymorphs at different temperatures and pressure. Alpha quartz (simply referred to as quartz) is stable over most temperatures and pressures found on the earth's surface. It forms the most common polymorph found in the earth's crust. *Cristobalite* and tridymite are other crystalline forms of silica; they are stable at high temperatures and low pressures. Beta quartz is stable at high temperatures.[2] Free silica refers to quartz, cristobalite and tridymite. Since silica is colorless and nonirritant, its exposure in large amounts remains unrecognized. It does not produce any immediate effect in most instances. Chronic exposure leads to a progressive fibrosing disease, which may also predispose to the development of tuberculosis.[3] In high-pressure environment at different temperatures as found in different industrial processes, such as ceramic manufacturing and foundry process, quartz may be heated to high temperatures at high pressures.

The examples of amorphous forms of silica include opal, diatomaceous earth, silica-rich fiberglass, mineral wools and silica glass. Generally they are harmless to humans except the fiberglass.[4]

Occupational Exposure

Silicosis is encountered in mining and quarrying of hard rock, anthracite coal and metals. The sand stone industry, sand blasting, stone quarrying and dressing, granite industry, grinding of metals, sand blasting, iron and steel foundries, brick yards, silica milling, flint crushing, glass making, ceramic manufacturing and manufacturing abrasive soaps are some of the occupations related to silica exposure. There is exposure to silica particles of respirable size with an aerodynamic diameter of 0.5 to

5 microns. In India it has been observed that there is a high risk of silicosis in slate pencil and agate grinding industry.[5,6]

About three million workers who are at high potential risk of silica exposure, are employed in occupations, such as mining and quarries; manufacture of nonmetallic products, such as refractory products, structural clay, glass mica; and manufacture of basic metals and alloys, such as iron and steel, copper, ferro-alloys, aluminum, etc.[7] The development and progression of silicosis frequently occurs after exposure to silica has stopped.

Problem of Silicosis in India

There are several populations in India at high risk of developing silicosis. The workers in gold, mica and coal mines, and those employed in ceramic and pottery industry, agate and slate pencil industry, brick workers and stone cutters are particularly at risk.[8]

Silica sand is an inexpensive and useful component of a variety of manufacturing processes. Rock cutting and rock carving to build temples, sculpturing stone containing granite, mining and metallurgy have been in existence in India since a very long period of time. However, the cases of silicosis were first described by Caplan and Burden only in 1940s in the underground workers of the Kolar Gold fields, Karnataka (then Mysore State).[9] The condition was benign since the free silica dust in Kolar Gold fields did not possess fibrogenic property.[10] Several reports on the occurrence of silicosis became available thereafter.[11-15] Radiographic evidence of silicosis was reported in 28 of 42 stonecutters and 3 of 24 stone breakers.[16] Reports of silicosis in industrial workers soon followed.[17,18]

The epidemiologic studies carried out in India have shown marked variation in the prevalence of silicosis.[5,6,9,14-27] The prevalence rate has varied from 3.5% in ordnance factories to 54.6% in the slate pencil industry. The variation is due to the fact of variability of concentration of silica in work environment of different occupations, duration of exposure and the physical properties of the silica (Table 107.1).

The Indian National Institute of Occupational Health (NIOH) has undertaken environmental and medical surveys in several industries and found the prevalence of silicosis to be very high in most instances.[28] The prevalence of silicosis was attributed to a high concentration of total and respirable dust and the great percentage of free silica in the dust, the free silica levels of between 55% to 60% of total dust were reported at some of the industrial sites; up to half of the workers were reported to suffer from silicosis.[28] The average duration of exposure before the development of silicosis, in most of these surveys, was approximately 10 to 12 years or less. The human cost was great, with approximately 55% of slate pencil industry workers having silicosis nearly 18% developing progressive massive fibrosis and 22% dying within 16 months of diagnosis.[29]

TABLE 107.1: Prevalence of silicosis in India

Industry (ref. no)	*Prevalence (%)*
Iron and steel workers[14]	2.5
Ordnance factory[15]	3.5
Mica mines and mica processing[16]	5.2
Glass bangle workers[17]	7.3
Gold mines[9]	8.8
Emery polishers[18]	0.7
Quartz crushing[19]	12.0
Quartz mill stone grinding	14.0
Ceramic and potteries[20]	15.1
Brick makers[21]	16.7
Stone cutters[22]	20.0
Stone grinding[23]	27.8
Lead and zinc mines[23]	30.4
Mica miners[25]	34.1
Stone cutters[26]	35.2
Agate workers[6]	38.0
Slate pencil workers[5]	54.6

Environmental Pneumoconiosis: An interesting form of nonoccupational pneumoconiosis is reported in some parts of India, mostly from the high altitude villages in Central Ladakh and Kaza in the Himalayas. Silicosis was common in the older inhabitants of villages exposed to frequent dust storms containing free silica.[30] Silica exposure was unrelated to any specific occupation. This condition appears to be similar to that described in residents of the Sahara and the sub-Saharan desert. [31]

Other Asian Countries (Table 107.2)

There are occasional published reports of silicosis from developing countries in Asia (e.g. Nepal, Pakistan, Bangladesh and Sri Lanka) where the environmental and working conditions in factories are similar to those found in India.[32] The problem of silicosis in China and Hong Kong, which accounts for an important health concern, has been extensively investigated.[33-37] The problem remains significant in Japan among workers involved in occupations, such as ceramic industry, tunnel construction and whetstone cutting.[38-40] Silicosis is now recognized more frequently in industrial workforce in

TABLE 107.2: Occurrence of silicosis in different populations at risk from Asian countries

	Population	*No. studied*	*Silicosis (%)*
1. Thailand			
• Yingratanasuk[42]	Stone carvers	97	2
• Aungkasuvapala[41]	Workers in Factories	33	9
2. Vietnam			
• Chien[46]	Brick refractory	158	10
3. China			
• Hong Kong (Law)[35]	Pneumoconiosis outpatient clinic	1056	61.4
• Guangizhou (Jiang)[36]	Agate Mill	32	46.9
• China (Chen et al)[37]	Tin miners	3010	33.7

South Eastern countries, such as Thailand, Singapore and Vietnam.[41-46] A survey among workers in 33 factories in Thailand revealed radiologic silicosis in 61 (9%) workers, while 13 (1.9%) workers had pulmonary tuberculosis.[41] Thirty-one of the thirty-three factories had measurements of either total dust or respirable dust exceeding the threshold limit values. The prevalence of silicosis was 10% in Vietnam among refractory brick workers.[46] This was almost linearly related to the duration of work.[45]

Pathogenesis

Crystalline silica particles are inhaled while the respirable-sized particles are deposited in the distal airways and alveoli. Alveolar macrophages ingest the silica particles, migrate into the interstitium, enter the lymphatics and are transported to the regional lymph nodes.

The interaction of silica and the pulmonary alveolar macrophages is a crucial event in the development of silicosis. Macrophage injury or death will release intercellular proteolytic enzymes that are likely to take part in the lung injury. There is also the release of cytokines, which attract other inflammatory cells such as neutrophils and T-lymphocytes.[47] The injured macrophages and the other inflammatory cells release superoxide anions and hydroxyl radicals and they cause injury to the lung tissue.[48] Silica-activated macrophages and lymphocytes also release many inflammatory mediators, such as interleukin-1 and tumor-necrosis factor that contribute to the production of fibrosis. Silica has great fibrogenic potential and the dying macrophages liberate fibroblast stimulating factor, which causes excessive production and release of collagen by fibroblasts.

Forms of Silicosis

Silicosis has a long latency period and three different patterns of silicosis have been recognized, i.e. chronic, accelerated or acute forms primarily based on the degree and duration of exposure and onset of symptoms.[2] The presentations of the disease reflect the variable intensity of exposure, rate of silica deposition in the lungs, retention of total amount of crystalline silica, latency periods and natural histories.[49]

1. *Chronic (or Classic) Silicosis*: The physiology of chronic silicosis involves chronic inflammation due to the accumulation of a variety of inflammatory mediators and fibrogenic elements. The rate of progression of the disease depends upon the rate and amount of silica deposition and retention in the lungs. The condition can be simple or complicated.

   The simple chronic silicosis develops following exposure to low-to-moderate concentration of free silica overr 20 years or more. Initially, there is collection of silica-laden macrophages in the loose reticulin fibers in the peribronchial, perivascular, paraseptal and subpleural areas. Later, there is formation of silicotic nodules in which the central area gets organized with a concentric whorl-like arrangement of collagen. The lesions may have variable degrees of calcification. The nodules are seen in the pulmonary parenchyma typically in the upper lobes, and the hilar and peribronchial lymph nodes. A few birefringent silica particles may be demonstrated in the center of silicotic nodules under polarized light. They represent inhaled silicate particles mixed with silicon dioxide. The inflammation continues in the periphery of the nodule, which gets enlarged by including adjacent pulmonary structures. Such a stage is referred to as Progressive Massive Fibrosis (PMF).[50]

These nodules are referred to as histologic tornadoes; with a "quiet" center of hyaline and collagen fibers concentrically arranged around the center.[51] In the periphery, there is a collection of inflammatory cells such as macrophages and lymphocytes. Later it becomes the seat of a fibrotic reaction.

In complicated silicosis, the nodules coalesce to form large masses of hyalinized tissue. The masses may have a variable diameter of 2 cm or more. The blood vessels and bronchioles are obliterated. The amount of silica or inflammatory cells is negligible. They are found in the apices of the lung, and tend to be bilaterally symmetrical in distribution. There can be central necrosis and cavitation. These patients exhibit an increased susceptibility to infection with *Mycobacterium tuberculosis,* as a result of which the lesion may get cavitated.

2. *Accelerated Silicosis*: The condition is encountered in persons who are exposed to heavy amounts of silica, often over a period of 5 to 10 years. Accelerated silicosis occurs over a relatively shorter time course when compared with chronic silicosis. The rate of progression is more rapid. The condition progresses even after removal of the person from the continued silica exposure. Pathologically, there is filling of alveolar spaces with eosinophilic granular material. The collagen vascular diseases, such as systemic sclerosis, systemic lupus erythematosus and rheumatoid arthritis, are sometimes associated with this type of silicosis.
3. *Acute Silicosis:* Acute silicosis is rare, but often fatal. It is likely to occur in workers as a consequence of intense exposure to very high concentrations of silica over a period varying from several months up to about five years. Cases have been encountered in sandblasters, in silica flour manufacturing and rock drilling. The mechanism of injury is different from that seen in chronic silicosis. There is a stronger inflammatory response due to the presence of freshly fractured silica exhibiting abundant cleaved particle surfaces. Lungs exhibit consolidation without silicotic nodules. The lungs involved by acute silicosis show presence of hypertrophic type II pneumonocytes lining the alveoli. They are responsible for the production of an excess amount of proteinaceous material and surfactant protein. The alveolar spaces are filled with eosinophilic proteinaceous material. This is referred to as silicoproteinosis. There is diffuse alveolar damage and desquamative pneumonitis.

Clinical Features

The most common presentation of silicosis is in the form of uncomplicated chronic silicosis. Chronic silicosis develops only after decades of repeated exposures to high concentrations of silica dust. Generally, it is asymptomatic even when the radiographic appearance suggests fairly advanced silicosis. Dyspnea on exertion is considered to be the most frequent and directly related symptom of silicosis.[1] There can be cough and sputum production from nonspecific bronchitis or from cigarette smoking. Chest pain and hemoptysis indicate the likely complication of tuberculosis. Acute silicosis presents with dyspnea, fatigue, weight loss, fever and pleuritic pain. Rarely, bilateral pneumothorax is also reported.[52]

In addition to the development of pneumoconiosis in silica-exposed workers, there are several reports on increased respiratory symptoms and impaired lung function in industrial workers, miners, stone cutters and others in the absence of a definitive radiological diagnosis of silicosis.[53-55] This nonspecific symptomatology is attributed to chronic dust exposure. Stunting of lung growth is reported on long term exposure to respirable dust in childhood and early adult life.[53]

Diagnosis

Clinical and radiological features that distinguish silicosis from other fibrotic disease include the following:

i. Occupational exposure to a substantial amount of silica,
ii. Silicotic nodule, and/or
iii. Involvement of hilar lymph nodes.

Radiologically, there is a close resemblance between silicosis and miliary tuberculosis. However the size of nodules seen in tuberculosis, are less than those seen in silicosis. The radiographs of patients with silicosis usually exhibit an increased translucency as against general loss of translucency in tuberculosis.[1]

The symptoms in a patient with simple nodular silicosis are markedly less in comparison to the patients with miliary tuberculosis. Furthermore, the incidence of miliary tuberculosis in adults is less common and exhibits toxic manifestations. The distinction between PMF and post-primary tuberculosis may pose difficulties sometimes. The conglomerate shadows of PMF do not show cavitation. The PMF often exhibits large fibrotic masses with an upward displacement of the mediastinal and hilar structures from volume loss. The lower lung zones may remain hyperinflated and emphysematous. The onset of cavitation should prompt a search for an active mycobacterial disease. Associated features, such as

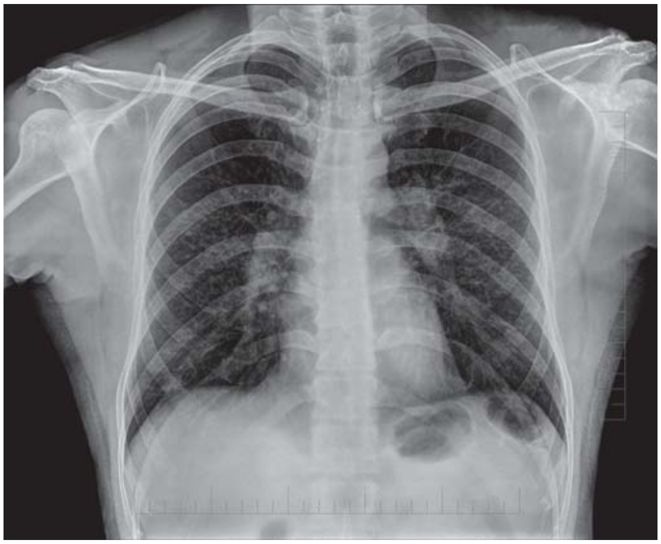

Fig. 107.1: Chest radiograph of a patient of silicosis demonstrating hilar lymphadenopathy and small nodular infiltrates

pleural effusion, localized increase in size of opacities and distortion of intrathoracic structures due to fibrosis are noted in tuberculosis.

Acute silicosis produces a homogeneous ground glass appearance on chest radiograph. It has to be distinguished from pulmonary edema, alveolar hemorrhage, pulmonary alveolar proteinosis, pneumonia and bronchoalveolar cell carcinoma.

Radiographic Patterns

The diagnosis of silicosis is established by a history of occupational exposure, and chest radiograph with typical nodules. Exclusion of other diseases and very rarely, histologic examination of lung tissues may be necessary.

Chest radiography is vital for the diagnosis of silicosis (Fig. 107.1). There is a clear relationship between total dust exposure and severity of radiographic changes. In the initial stages, there is reticulation of the lung fields due to thickening of the perivascular and intercommunicating lymphatics. The diagnosis of silicosis is possible only after the appearance of nodules.

The classic radiographic features of simple silicosis are rounded opacities ranging in size from 1 to 10 mm and occurring predominantly in the upper lung zones. They can be categorized using the International Labour Organization (ILO) International classification of radiographs of pneumoconiosis on the basis of size, shape and profusion category.[56]

The small rounded opacities are grouped into three diameter ranges designated as "p" (up to 1.5 mm), "q" (1.5 to 3.0 mm) and "y" (1.0 to 10 mm). As the disease progresses, the opacities are also seen in the mid- and lower-lung zones. The nodules are of homogeneous density and usually bilaterally symmetrical.

In addition to the size and shape of the nodules, the abundance (profusion of nodules within the parenchyma) of the lung is also important. By comparison with standard films provided by the ILO, the profusion of nodules in the patient's films can be categorized in order of increasing severity as category 1, category 2 or category 3.

Hilar lymphadenopathy is also seen sometimes in advanced nodular parenchymal shadows. There can be "egg shell" calcification of the lymph nodes, and it is strongly suggestive of silicosis. However the egg shell calcification is not specific and it may be seen with sarcoidosis, radiation-treated Hodgkin's disease, blastomycosis, scleroderma, amyloidosis or histoplasmosis.[57]

On continued dust exposure, the nodule increase in size and number ultimately covering most parts of the lungs. They may unite and form conglomerate shadows, which are described as PMF. The ILO classifies these large opacities as A, B and C based on size or on total cross sectional area relative to the size of right upper zone (or on both). With coalescence of the nodules, the upper lobes become fibrotic and contract making the conglomerate nodules to migrate towards the hilar areas. The hilar structures are pulled upward, leaving areas of compensatory emphysema at their margins and in the lung bases. With these alterations the small rounded opacities that were evident previously on the radiograph become less visible or may at times disappear. Pleural abnormalities are not commonly encountered, but they may be sometimes seen in the lesions.

Acute silicosis may present with radiographic alveolar filling pattern leading to a ground glass appearance, and association with conglomerate silicotic nodules is rarely seen. Pulmonary tuberculosis in the patient with silicosis may be associated with pleural effusion, localized increase in the size of opacities and cavitation.

Pulmonary Functions

Pulmonary function tests help in the evaluation of persons with suspected silicosis. There are no specific patterns of ventilatory impairment in silicosis. There can be significant airflow limitation. Both Peak Expiratory Flow (PEF) and Forced Vital Capacity (FVC) are reported to reduce in chronically exposed individuals.[53-55] Tobacco smoking in the presence of other dust exposure further aggravates the presence of airway obstruction. In patients with PMF, restrictive ventilatory impairment is seen in association with arterial hypoxemia. The pulmonary function changes occur earlier and are more marked in acute and accelerated silicosis. They make a rapid progress compared to chronic form of the disease.

Other Investigations

Bronchoalveolar Lavage (BAL) study is rarely indicated. It may be undertaken when exposure history and clinical presentations are atypical. The BAL fluid of workers exposed to quartz dust will demonstrate an increased number of cells, protein and quartz in the macrophages. The amount of mineral dust in BAL fluid cells is related to the intensity of exposure and duration of employment.

Lung biopsy (open or thoracoscopic) is rarely needed to establish the diagnosis. It may be indicated in some clinical settings when complications are present. This is particularly important when lung malignancy is suspected as a complication (Fig. 107.1).

The demonstration of tubercle bacilli in the sputum of patients suffering from silicotuberculosis is difficult in many instances. The walling in of the tubercle foci by the silicotic fibrosis prevents the elimination of tubercle bacilli in the sputum.

Complications (Table 107.3)

In the presence of worsening of respiratory symptoms and rapidly changing or progressive lesions on chest radiographs, mycobacterial infection (*Mycobacterium tuberculosis* or atypical mycobacteria) should be suspected and investigated. Tuberculosis can either complicate silicosis or pose a problem in the differential diagnosis. There is an increased susceptibility to pulmonary tuberculosis and rarely to fungal infection. It is thought that macrophage dysfunction caused by the presence of silica appears to be the cause of increased susceptibility to tuberculosis and other infections.

TABLE 107.3: Important complications seen in patients with silicosis

1. Pulmonary hypertension and chronic cor pulmonale
2. Chronic respiratory failure
3. Respiratory infections
4. Silicotuberculosis
5. Silicomycosis
6. Autoimmune disorders
7. Necrotizing nodules–Caplan Syndrome
8. Scar carcinoma
9. Acute/Accelerated silicosis–Alveolar proteinosis
10. Massive pulmonary fibrosis

TABLE 107.4: Characteristics of tuberculosis in silicotics

- Frequent occurrence
- Increased risk
- Severe and persistence respiratory symptoms
- Rapid progression to fibrosis
- Poor response to antituberculosis therapy
- Necessity of longer duration of therapy

Patients with PMF are prone to mycobacterial infections and spontaneous pneumothorax. Tuberculosis has been reported in 18.6% of mica workers and 60% of workers in the pottery and ceramic industries.[26,29] The prevalence of tuberculosis has varied from 1.9% to 3.6% in brick makers, metal workers and coal miners with silicosis. According to NIOH reports, tuberculosis was present in 4.8% of coal miners and 48% of stone cutters.[19] Silicotuberculosis has been identified as an important comorbidity in several other Asian populations.[41,43,58] Even in the developed countries, such as Japan, silica exposure had a significant association with tuberculosis.[45,39]

Reports appearing in the past few decades continue to identify a clinically important rate of tuberculosis in silicotics. Tuberculosis exhibits the same specific characteristics in persons with silicosis (Table 107.4).

Free silica impairs macrophage function, thereby increasing the chances of mycobacterial infection.[59,60] Important predisposing factors relate to social circumstances and to living and working conditions. Tobacco smoking is an important predisposing factor. Most of these workers live in crowded and unsanitary conditions, while their jobs are in dusty environments and silica exposures are not controlled. The chances of spread of infection are higher in such surroundings. Many reports of silicotuberculosis cited earlier do not necessarily attribute the presence of tuberculosis to underlying silicosis. However, when the conditions are present together, there is an increased morbidity and mortality, with clear evidence of rapid silicosis progression. Studies from Singapore have reported the occurrence of tuberculosis as a significant factor associated with the development of progressive massive fibrosis and a strong predictor of mortality in patients with silicosis.[61,62] Occasionally silicosis is complicated by fungal invasion (Fig. 107. 2). Aspergillosis complicating a cavitary silicotic nodule is also reported.[63]

There is an increased incidence of autoimmunity and diseases, such as rheumatoid arthritis in patients with silicosis. These patients exhibit positive latex fixation tests, antinuclear antibodies and increased levels of

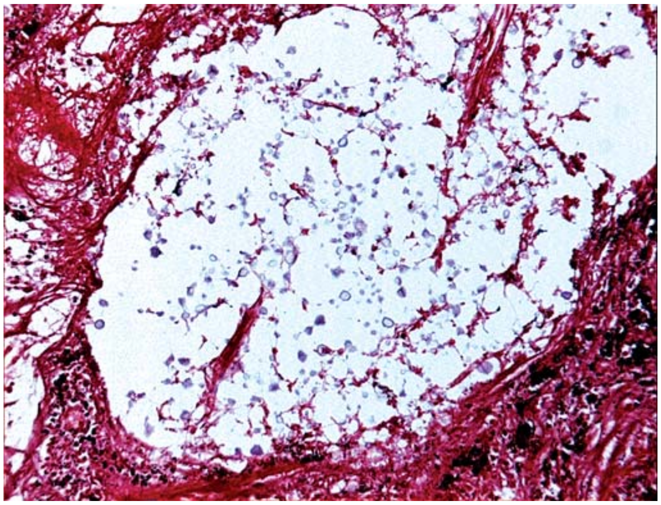

Fig. 107.2: Post-mortem lung histology-Photomicrograph showing silico-mycosis. Clusters of Cryptococci and fibro-collagenous material with extensive blackish pigment, which revealed needle shaped silica particles under polarized light examination (Courtesy: Dr Ashim Das, Department of Pathology, PGIMER, Chandigarh)

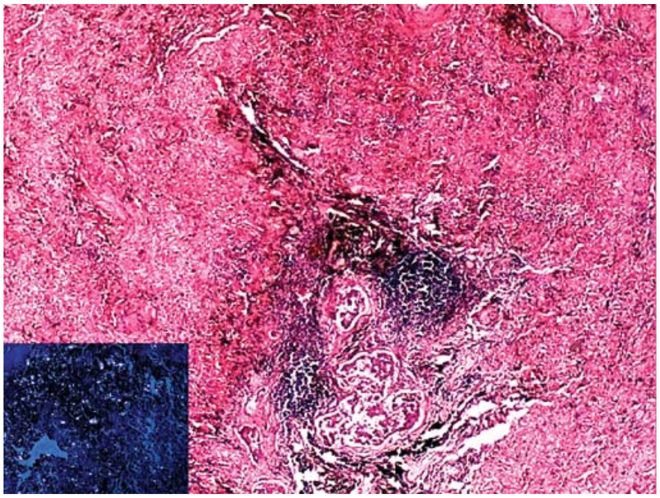

Fig. 107.3: Postmortem lung histology-Photomicrograph showing pigment deposition, fibrotic nodular formation and adenocarcinoma (Courtesy: Dr Ashim Das, Department of Pathology, PGIMER, Chandigarh)

immunoglobulins. Necrotizing rheumatoid nodule in silicosis is a characteristic clinical picture, which is known as Caplan Syndrome. Chronic silicosis gradually leads to development of pulmonary hypertension, chronic cor pulmonale and chronic respiratory failure. The onset of these complications is rapid in case of massive fibrosis.

There is an increased relationship between quartz exposure, silicosis and development of bronchogenic carcinoma. Furthermore, there is an increased mortality from lung cancer among workers exposed to silica dust.[64-66] This cancer is mostly an adenocarcinoma, which commonly occurs over a silicotic scar in the lung (Fig. 107.3). Tobacco smoking acts as an added risk factor for carcinogenesis.

Prognosis

Patients with conglomerate fibrosis progress to cor pulmonale and respiratory failure. The clinical course of patients with acute silicosis is inexorably downwards with the development of pulmonary fibrosis, followed by restrictive lung disease and ultimately respiratory failure resulting in death. Silicosis especially when "acute" may be complicated by secondary alveolar proteinosis with marked respiratory distress and failure.

Treatment

There is no specific treatment for silicosis and the therapy is directed largely at the complications of the disease. Corticosteroids and aluminum citrate have been used with varying success in silicosis.[67-69] Corticosteroids have limited efficacy in the treatment of silicosis.[68,69] Inhaled aluminum citrate powder coats silica particles retained within the lung, thereby reducing the solubility of those particles. It has been proved to be unsuccessful.[21] The polymers such as Polyvinyl Pyridine N-Oxide (PVPNO) and polybetaine though showed protective effects in experimental animals, were not found suitable for human disease. Tetrandrine though found to diminish fibrosis and collagen synthesis in silica-exposed animals has not found to be effective in humans and has shown to be teratogenic.

Following the diagnosis of silicosis, it is advisable to avoid further exposure to silica-containing dusts. The individual should be promptly removed from such surroundings. In advanced disease or if it has developed following a short exposure, further exposure to dust has to be avoided. The comorbid conditions, such as chronic obstructive pulmonary disease should be identified and managed.[70-72] Severe airflow obstruction and cor pulmonale are treated with bronchodilators, diuretics and oxygen. Tobacco smoking, if present must be stopped.

Treatment of tuberculosis in these workers poses tremendous problems. Results of standard chemotherapeutic protocols for tuberculosis in the presence of silicosis are less effective than therapy for tuberculosis alone.[73] A partial explanation for the poor response has been attributed to impaired macrophage function and poor penetration of the drugs into the fibrotic nodules.[58-60] Short course chemotherapy with two months of streptomycin, isoniazid, rifampicin and pyrazinamide followed by seven months of daily isoniazid and rifampicin was effective, with only a 5% failure rate in 16 previously treated silicotics and 56 anthrasilicotic patients with mycobacterial positivity.[73] Clinical comparison was made between two antituberculosis treatment regimens, comprising of four primary drugs administered thrice weekly for six and eight months in 240 Chinese silicotics. Although the six-month regimen was inadequate, since 22% of 41 patients relapsed bacteriologically during the first 3 years, the 8-month regimen was substantially found to be more effective.[73]

It is generally recommended that patients with tuberculosis should receive at least four antimycobacterial drugs, such as isoniazid, rifampicin and pyrazinamide for two months followed by two antituberculosis drugs (isoniazid and rifampicin) for a total of nine months or longer. The exact duration of therapy remains debatable.

Acute silicosis with respiratory failure needs aggressive treatment that includes whole-lung lavage in an attempt to improve gas exchange and to remove alveolar debris. However the benefit has yet not been established.[74] Though a short-term controlled trial of systemic corticosteroids improved lung function in patients with silicosis, majority of studies have not shown any benefit.

Prevention

Prevention remains the main goal of silicosis. It comprises of medical screening and surveillance and dust control measures.

Medical Surveillance: Workers exposed to silica dust should undergo periodic medical examination to screen for adverse health effects and dust measurements in work environment.[75] The medical examination comprises of preemployment and periodic examinations including chest radiographs, sputum examination for tubercle bacilli and spirometry. The preemployment medical examination provides the base-line data for each individual. The periodic medical examination helps in early detection of silicosis and silicotuberculosis. Health education is important to get active cooperation of the workers at risk.

Dust Control Measures: Silicosis does not develop without exposure to dust. The dust levels in the work place correlate well with the incidence and severity of the disease. Hence elimination or suppression of dust at the work place forms the essence in the control of silicosis. The work process should be isolated and enclosed. Adequate ventilation should be provided. Personal protection is important.

Exposure to dust can be reduced by the use of improved ventilation and local exhaust, use of substitution innocuous substances that are less hazardous than silica, isolation and enclosure of the sources of dust, use of wet abrasive techniques, humidification of work environment and personal protection. Masks are advocated only when other dust control measures have failed. The dust masks are of little value when the dust concentrations are high as the dust particles will clog the pores in the filter.[1] Further, masks are less suited for hot and humid climate.

In summary, silicosis is an old disease, which remains a major occupational health hazard in India and is responsible for high, morbidity and mortality in industrial workers. Workers exposed to high concentrations of free crystalline silica in unprotected settings are at great risk for developing pulmonary fibrosis. The disease is progressive and irreversible. All measures should be undertaken to avoid and control dust exposure. The lack of therapy emphasizes the importance of primary prevention in our approach to the problem.

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Berylliosis

PS Shankar

INTRODUCTION

Beryllium (Be), a light metal exhibiting thermal and electrical conductivity and tensile strength, is found in the Earth's crust. Beryllium-containing minerals are processed to beryllium metal, beryllium alloys and beryllium oxide for use in the aircraft industry, nuclear reactors, electronics industries and manufacture of heat-resistant ceramics and fluorescent lamp industries. Mining, industrial processing, smelting and fabrication of beryllium or its alloys result in the emission of beryllium to the atmosphere, surface waters and soil.[1] There is little recognition of berylliosis in India, but for an occasional report.[2] Beryllium exposure is associated with both acute and chronic manifestations.[3,4] The recent evidence in fact suggests that both the acute and the chronic forms of berylliosis represent a continuum of disease involving hypersensitivity.[5]

Acute Beryllium Disease

Beryllium enters the lungs by inhalation route. Massive exposure induces a generalized acute inflammatory reaction in the respiratory tract and alveoli resulting in tracheobronchitis and chemical pneumonitis [Acute Beryllium Disease (ABD)]. It appears to be due to an irritative phenomenon from direct toxicity.[3] Improved industrial hygiene standards have reduced its incidence.

Chronic Beryllium Disease

Exposure to low concentrations of beryllium over a long period of time may cause a chronic form of disease [Chronic Beryllium Disease (CBD), berylliosis]. The condition has a delayed onset with granulomatous response and pursues a chronic course. Long-term exposure is responsible for a mixed pattern of lung function impairment, pulmonary fibrosis, cavitary lung lesions, pneumothorax and respiratory infections.[4,6]

Ingested beryllium is poorly absorbed from the gastrointestinal tract. It gets accumulated in the skeleton and gets eliminated very slowly through the kidney.[7] Beryllium is a potent chemical sensitizer. Direct contact of soluble beryllium compounds with skin or mucosa causes allergic contact dermatitis and ulcers in susceptible persons. Occupational exposure to beryllium can also result in an increased incidence of lung cancer.[8]

PATHOGENESIS

Chronic beryllium disease is primarily an inflammatory lung disease due to an inhalational exposure to both soluble and insoluble forms of beryllium. Beryllium is one of the most toxic elements. It occurs as an industrial hazard. Unusually, it can also develop in nonindustrial workers who reside near beryllium-plants exposing themselves to airborne emission from the plant. It is characterized by the formation of granulomas with varying degree of interstitial fibrosis, due to a delayed cell-mediated immune response to beryllium particles in the lung.[9] It may develop in a fraction of exposed workers (1.5%) especially those who are genetically predisposed.[10] Alleles of the major histocompatibility gene, Human Leukocyte Antigen-DP (HLA-DP) are associated with genetic susceptibility to CBD.[4,11]

CBD is caused only by inhalation of beryllium in a low dosage over a long period of time (10 or more years).[11,12] Inhaled beryllium gets deposited in the periphery of the lung. The minute beryllium ion functions like a haptene that binds with normal lung protein to form an antigen. This antigen is presented to helper T-cells, which form sensitized T-cells. These cells proliferate in response to beryllium in a dose-dependent manner. There is an increased secretion of lymphokines leading to formation of clusters of macrophages. It produces non-caseating granulomas in the pulmonary interstitium along with diffuse interstitial inflammation and fibrosis. Hilar lymphadenopathy may be present. Thus the condition will have many of the characteristics of sarcoidosis. Unlike sarcoidosis, the antigen is known in CBD.

CLINICAL AND RADIOLOGICAL FEATURES

Berylliosis can present as an allergic immune response (beryllium sensitization, acute toxic pneumonitis – like reaction, or CBD)[11] (Table 108. 1). The manifestations of chronic berylliosis develop very gradually with progressively increasing dyspnea, weakness, fatigue, loss of weight, arthralgia and cough with mucoid sputum. On physical examination, there may be evidence of clubbing and bibasilar crackles at lung bases. Systemic examination may show skin rashes, hepatomegaly and lymphadenopathy. Radiogram of the chest shows diffuse round and reticular nodules, which later progress to diffuse linear fibrosis throughout the lung fields or remain confined to the upper lobes.[13] The hilar nodes are enlarged. It must be noted that hilar adenopathy does not occur in the absence of lung changes. High Resolution Computed Tomography (HRCT) findings significantly improve the diagnostic accuracy.[14] In both stages there is development of extensive interstitial pulmonary fibrosis and pulmonary hypertension. Both the clinical and the radiological picture at this stage may show features of chronic cor pulmonale and cardiac and respiratory failure.

TABLE 108.1: Clinical features of different types of beryllium exposure

Type of Berylliosis	*Clinical Features*
1. Beryllium hypersensitivity	– Usually asymptomatic–sometimes skin rashes, nasal and constitutional symptoms – Positive beryllium lymphocyte transformation test – Progression to berylliosis
2. Acute beryllium disease	– Irritative, chemical phenomenon – Acute tracheobronchitis – Chemical pneumonitis
3. Chronic beryllium disease (Berylliosis)	– Develops gradually over years – Progressively increasing dyspnea, cough, weakness, fatigue, and weight loss – Systemic manifestations – Pulmonary fibrosis, chronic cor pulmonale

DIAGNOSIS

Diagnosis is generally suspected on the basis of history of exposure, clinical manifestations and radiography. Pulmonary functions show a restrictive pattern and reduction in the diffusion capacity. Occasionally there is hyperuricemia and hypercalcemia. On bronchoscopic examination, there is an increase in number of CD4+T cells in BAL fluid.[15] Presence of non-caseating granuloma on transbronchial lung biopsy specimens greatly support the diagnosis. Blood or BAL lymphocyte transformation test is generally positive.[15] Patients with chronic berylliosis exhibit cutaneous delayed hypersensitivity to a patch test with 1% to 2% beryllium nitrate or sulfate. As there is a danger of flaring-up of the underlying lung lesions following the test, it is not widely used.

A blood test to detect beryllium-specific cell proliferative responses in the blood of beryllium-exposed workers referred to as Beryllium Lymphocyte Proliferation Test (BelPT) is used as a biomarker of beryllium-health effect. It consists of in vitro culture of lymphocytes obtained from peripheral blood and then exposure to soluble beryllium sulfate to stimulate lymphocyte proliferation.[16] Occurrence of beryllium-specific proliferation implies Beryllium Sensitization (BeS). The test is being increasingly used in workplace screening and surveillance efforts to detect beryllium sensitization and CBD. Those exhibiting abnormal blood BelPT results require clinical evaluation with bronchoalveolar lavage and transbronchial lung biopsy to confirm diagnosis of CBD. The response is more prominent in the lung cells in comparison to the blood cells.

Beryllium sensitization precedes CBD. However, the natural history and rate of progression from sensitization to disease are not completely understood. In a longitudinal cohort study of a group of individuals detected as having BeS without any evidence of CBD, 31% individuals progressed to CBD over a period of 3.8 years, as evidenced by granulomatosis and/ or mononuclear cell infiltrates in the lung tissue.[17]

TREATMENT

The most important step in the management involves the cessation of beryllium exposure. This is not only important for symptomatic treatment of beryllium hypersensitivity and acute toxicity, but also for prevention of CBD.[18] Corticosteroids constitute the mainstay of treatment for CBD.[19,20] Presently no randomized trials are available to assess the therapeutic efficacy of corticosteroids. However, long term steroid therapy is helpful in suppressing granulomatous lesions and in stopping the evolution of fibrosis.[19] Treatment is generally monitored by using pulmonary function tests and HRCT of the chest.[20] The treatment is of little help after the development of pulmonary fibrosis, but does help in the management of cardiac and respiratory failure.

In experimental studies, some chelating agents have been shown to reduce beryllium concentration in the liver, kidney and lungs of rats.[21] Their clinical use is not yet known. Diminution in the ambient levels of beryllium shows an improvement in the pulmonary status of the workers.

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Hard Metal Lung Diseases

Dilip Maydeo, Nikhil Sarangdhar

INTRODUCTION

There are a number of metals that are associated with the development of a variety of lung diseases such as diffuse parenchymal lung disease. The list of such metals continues to expand, and includes aluminum, cadmium, cobalt, copper, iron and others. They can induce a wide range of abnormalities, including lung fibrosis, reactive airway disease, chemical pneumonitis, granulomatous interstitial pneumonitis and cancer.[1,2] Metal fume fever is an acute, short-lived response mediated by the release of specific cytokines, typically in response to zinc oxides. Airway diseases, such as asthma occur in response to the inhalation of antigenic metals such as chromium, nickel or cobalt. Hard metal is generally produced by compacting powdered tungsten carbide (WC), cobalt (Co), and some other agents into a polycrystalline material, a process known as sintering, hence the term "sintered carbides" (or cemented carbides) is also sometimes used.

Incidence

The incidence of granulomatous lung disease in workers exposed to the hard metals is unknown. Only rare case reports have described the disease in affected workers. Although the problem is well recognized in clinical practice in India, the published literature is rather scarce.[3, 4] Due to the relative paucity of reports on these other metals, disease incidence can be inferred to be low. Several factors may contribute to the lower rates, such as the lower exposure to the respirable and ultrafine particulates, particle deposition and clearance in the upper airway that protect the lower airways from exposure.[5]

ETIOLOGY AND PATHOGENESIS

Metals that cause parenchymal lung disease do so by inducing formation of granulomas in the lung. Varying degrees of fibrosis are found with aluminum, cobalt, copper and rare earth exposure. Histologically, the pathologic lesion is composed of a cluster of immune effector cells, predominantly lymphocytes, macrophages, epithelioid cells, multinucleated giant cells, mast cells and fibroblasts.[6] Different metals may induce different types of immune responses (Table 109.1). Unlike in berylliosis, the recognition of both immunopathogenesis and genetic susceptibility are inadequate.[1,2]

Whereas typical protein and polysaccharide antigens are processed and degraded following antigen presentation, metals are unique in that the antigenic metal is frequently retained in the lung and may be detected in the center of the surrounding granuloma. It is possible that retention of the antigen contributes to the formation of a non-caseating granuloma, as well as to the eventual progression to fibrosis.[7] Other metals can trigger a

TABLE 109.1: Types of immune response in metal induced lung disease

1. **Antigen-specific cell mediated immunity:** Titanium, Zirconium, Aluminum, Cobalt and Gold
2. **Giant-cell granuloma:** Hard Metal (Tungsten carbide and Cobalt)
3. **Foreign-body type reaction:** Copper and Barium

specific immune response. Aluminum, cobalt, gold and zirconium stimulate a delayed-type hypersensitivity response following intradermal injection, analogous to the purified protein derivative, in certain susceptible individuals. Aluminum, cobalt, gold and titanium can also trigger in vitro lymphocyte proliferation.

However, the pathology of Hard Metal Lung Disease (HMLD) is unique in that it is characterized by the presence of "cannibalistic" multinucleated giant cells in air spaces and bronchoalveolar lavage fluid.[8]

CLINICAL FEATURES

Acute pneumonitis is seen in response to high-dose exposures (e.g. copper sulfate solution). Disease symptoms typically begin with the subtle onset of dyspnea on exertion, nonproductive cough, fatigue, low-grade fever and weight loss. In the case of cobalt and copper-associated disease, systemic symptoms such as fever and night sweats may also occur. Vineyard sprayers may present with cough, shortness of breath, recurrent respiratory infections, fever, purulent sputum or hemoptysis.[9] The chest examination may demonstrate fine or dry rales, or it may be normal.

The clinical presentation of HMLD resembles hypersensitivity pneumonitis, with some patients having episodes of work-related subacute disease and some patients evolving, more or less rapidly, to lung fibrosis. Occasionally hard metal alveolitis is accompanied by other inflammatory disorders such as rheumatoid arthritis.[10] One important aspect of HMLD is that the disease may occur after a short duration of exposure, thus suggesting that individual susceptibility, rather than cumulative exposure, plays a major role.[5]

DIAGNOSIS

A careful occupational and environmental history may implicate the etiologic metal involved. The history should include a listing of jobs that entailed metal dust or fume exposures, metals used, and conditions of exposure (use of respiratory protection, availability of exhaust ventilation). Exposure may also be assessed through measurements of urinary and Exhaled Breath Condensate (EBC) concentrations.[11]

Radiology plays an important role, with the disease being frequently noticed on a routine chest X-ray film. Computerized tomography (CT) of the chest reveals the extent of involvement. The chest radiograph demonstrates different patterns of irregular or reticulonodular infiltrates in response to different metals (Table 109. 2).

TABLE 109.2: Chest radiologic abnormalities in different hard-metal diseases

Metal	*Chest Radiologic abnormalities*
Aluminum	Reticular infiltrates, usually bilateral with predominant upper zone involvement
Barium	Small, round or reticular opacities
Cobalt	Round nodular infiltrates; Irregular opacities
Copper	nodular or fine military shadows initially, later progressive fibroids
Gold	Reticular/ reticulonodular interstitial fibrosis
Titanium	Reticular/ reticulo-nodular or nodular infiltrates
Zirconium	Bilateral irregular opacities

High resolution computed tomography may demonstrate increased reticulation, patchy ground-glass opacities, traction bronchiectasis, consolidation and large peripheral cystic spaces, typically distributed in upper and mid lung zones.[12,13]

Patients with suspected disease should undergo pulmonary function tests. These typically show airflow obstruction early in the disease process, with subsequent mixed patterns of obstruction and restriction, and pure restriction in advanced or end-stage disease. Smoking is an important contributory factor to the decline in FEV_1 over time.[14] Hypoxemia can occur with advanced fibrosis in parenchymal disease associated with copper, and rare earth (lanthanide) metals. Pulmonary function tests and blood gases may also be normal, as in the few reported cases of zirconium-associated lung disease.

The definitive diagnosis of granulomatous lung disease is established by lung biopsy. The range of histopathological findings varies from focal peribronchiolar inflammation to diffuse interstitial fibrosis and honeycombing.[15] The real challenge is to link pathology to the exposure of the metal. Typical histological findings include poorly formed non-caseating granulomas infrequently indistinguishable from those found in sarcoidosis or giant-cells in HMLD.[16] Other histologic features include an interstitial mononuclear cell infiltrate, multinucleated giant cells, T-lymphocytes, and varying degrees of fibrosis.

Detection of metal in the bronchoalveolar-lavage fluid, in the granuloma, or by lung tissue particle analysis helps to establish the association of disease with metal exposure, but does not necessarily prove causation. It may be possible to demonstrate a specific immune reaction to the metal by patch testing, as in aluminum, cobalt, gold, or zirconium exposure. *In vitro* lymphocyte proliferation tests to the metal in question, as has been demonstrated with aluminum, cobalt, gold and titanium might help in establishing the presence of a specific immune response.

Occurrence of as well as increased mortality from lung cancer due to chronic hard metal exposure is well established.[17,18] Diagnosis of lung cancer in an exposed individual whenever suspected on the basis of clinical and roentgenological criteria should be confirmed by histopathological examination.

TREATMENT

Primary prevention is the best treatment, given our limited ability to halt or reverse the progression of disease once the patient has progressed to end-stage fibrosis and persistent granulomatous inflammation. The best hope for prevention is to substitute safer working materials, limit the number of exposed workers, and implement tight industrial hygiene controls. Smoking cessation also constitutes an important component of management.

There is limited data suggesting that reducing future exposure to metals can positively affect the course of illness, but doing so is nonetheless considered medically prudent. Medical treatment is indicated in symptomatic patients, and is largely aimed at reducing lung inflammation and palliating the secondary consequences of hypoxemia, pulmonary hypertension, and right heart failure. Corticosteroids are helpful for providing symptomatic relief from acute alveolitis and metal fume fever. Cytokine therapy, such as antitumor necrosis factor-α -receptor blockers may be helpful in the future to inactivate those mediators that participate in the development of fibrosis. Supplemental oxygen, limited use of diuretics, calcium-channel blockers, and angiotensin-converting enzyme inhibitors are well-used second-line therapy for pulmonary hypertension and right-sided heart failure. Pulmonary rehabilitation helps patients to carry out their activities despite of impairment.

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The Health Risks of Asbestos Exposure Inhalation

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INTRODUCTION

The term “asbestos” describes six different occurring fibrous crystals (crocidolite, amosite, chrysotile, anthophyllite, tremolite and actinolite) with a great number of industrial uses. An association between environmental or occupational exposure to asbestos and the occurrence of chest disease is well established in Table 110.1.

The relationship of asbestos exposure to alterations in the pleura, mesothelioma, lung cancer and asbestosis has been clarified in the past decades. Although the case in nearly all instances, direct occupational exposure is not necessary for disease. Unrecognized asbestos exposure may be indirect, occurring in the construction industry, the shipyards or in asbestos workers’ homes. Of particular importance is the latency period between exposure and clinically-detectable disease, typically approximating or exceeding 20 years. When these illnesses are under consideration, a detailed occupational and family history is necessary to recognize the role of asbestos exposure in disease.

During the second half of the last century, regulatory bodies of the world’s developed countries recognized the risks associated with the inhalation of asbestos fibers and acted on this information. Using asbestosis, and to a lesser degree, lung cancer and mesothelioma, as markers for exposures, these adverse health effects have dramatically declined in populations at risk. Yet, this has occurred despite an increase in life expectancy. For example, in 1950, 40 year old white men in the United States were projected to live 31.2 more years. In 2001, this same population had a projected survival of 37.3 years. Non-white men in this age group had a projected survival of 27.3 and 32.5 years at these points in time, respectively.[1] With this increase in life expectancy comes a potential increase in latency period. With this increase in longevity, it is reasonable to expect that workers with asbestos exposure would have a longer time to first, develop disease, and second, progress to more severe disease. Additionally, the population of workers at risk for mesothelioma would have a longer time period to develop this illness and this illness would likely occur more frequently. Similarly, those with asbestos exposure who smoke cigarettes would have a prolonged time to develop lung cancer, even after they stopped smoking. With these insights, if asbestos exposures had remained the same, these additional years of survival would have resulted in more frequent and more severe dust-induced chest illnesses.

TABLE 110.1: Asbestos-related pulmonary effects

1. Asbestosis (asbestos pneumoconiosis)
2. Pleural plaques
3. Pleural effusion (benign)
4. Diffuse pleural thickening
4. Pleural mesothelioma
5. Lung cancer

Yet, the picture that has developed is dramatically different. This is due to a substantial decrease (typically of several orders of magnitude) in respirable exposures. These lesser exposures are reflected in longer survival. Although there are no reports which clearly identify the prevalence of asbestos related illnesses which are truly “representative” of a generation of workers, we have taken the liberty to quote several studies which may be considered "representative" of the decade(s) that the workers were employed and the year of publication. Selikoff, in 1965, reported on a population of asbestos workers with a 40 year latency of asbestos exposure. In this population of 121 workers, 94.2% were reported to have a radiologic diagnosis of asbestosis.[2] Later, in a 1979 report of 359 present and retired shipyard workers with at least ten years of exposure, 44% had parenchymal interstitial disease.[3] More recently, a population of electricians with at least twenty years of union membership, the prevalence of small opacities was 2.1%.[4] These reports show the dramatic decline in dust-induced lung disease. We do recognize the problems in comparing prevalence rates in populations with different lengths of latency; yet, these numbers reflect important changes in the outcome of workers with potential exposure to asbestos. Yet, even with the most recently reported diminished prevalence rates, we cannot dismiss the rate of occurrence of these illnesses.

What caused this dramatic lessening in the number of cases of asbestosis? Regulatory agencies have become sensitized to the adverse respiratory effects of asbestos exposure and responded by lessening permissible exposure limits. Decisions made by governmental agencies regarding standard setting have been driven by epidemiologic studies. These studies have used years of employment and dust measurements as variables and the development of disease (as manifest by decrements in lung function tests [typically, the Forced Expiratory Volume in One Second (FEV_1) and Forced Vital Capacity (FVC)] and the development of chest radiographic [as interpreted by the International Labour Organization (ILO) classification] abnormalities. The notion that these variables determine outcomes in a relatively predictable manner (i.e. dose-dependent) is a key to protecting the worker. Using these data workers have been protected. Yet, summaries by American governmental agencies reflect the continuing adverse effects of dust exposure on the American worker (Fig. 110.1).

Our challenge is not only to detect clinical illness early, but to educate potentially exposed workers and their families about the health risks of asbestos. Prevention of these illnesses will be accomplished only by substituting safe materials and by limiting asbestos exposure in the workplace by appropriate engineering controls.

ASBESTOS FIBERS

Asbestos is classified as serpentine or amphibole, based on structural and chemical properties. Chrysotile is a serpentine asbestos and accounts for 95% of world production. The fibers are long, silky, pliable and heat resistant, but poorly resistant to sea water and chemical digestion. Because of its flexibility, it is commonly woven into textiles. The larger deposits are in Russia's Ural Mountains and in Quebec, although some is found in Vermont. Amphibole asbestos, in contrast to serpentine, is straight and rod-like and resistant to acids, heat and alkali. Crocidolite, amosite and anthophyllite are the common commercial varieties of amphiboles. Crocidolite and amosite are mined in South Africa, and anthophyllite is found in Finland. In Quebec, the asbestos deposit contains 99% chrysotile and 1% tremolite, making this deposit unique. Chrysotile, crocidolite and amosite are the most commonly used fibers in industry. Among the three amphiboles, anthophyllite is used least in commercial preparations due to the short and brittle nature of the fiber.[5]

A summary of its uses throughout time is of interest.[6] Since the beginning of the use of asbestos in industrial applications beginning around 1870, world annual asbestos production has increased from 500 tons until it approximated 5 million tons in 1975, the year of peak production. Since then, the health effects have been better understood and production has declined by 60%. Yet, 2003 statistics show that 2.15 million tons of chrysotile was mined.[7] Asbestos mining is typically an open pit operation where mechanical shovels and bulldozers mine and then load trucks or train cars for transport to a processing mill. The raw material is further processed by fracturing, sorting, and screening to separate the asbestos from undesired ores. Milling further concentrates the fibers by eliminating contaminants and sorting fibers by types and quality.

Although many manufactured products are composed of multiple fiber types, the longest asbestos fibers are used mainly for textiles insulation; intermediate length fibers are used in asbestos cement production and friction and filter production; while the shortest fibers are used in the vinyl asbestos tiles and as an admixture to industrial paints. Mill tailings from the mining process have been used in road construction. In past decades, the major end users have been the construction industry, the shipbuilding industry, and the automobile and railroad equipment industry. Today, much of the insulation and friction materials are made of non-asbestos replacement fiber materials. Potential worker exposures occur during mining, milling, handling, manufacturing processes, and particularly, during the destruction of previously manufactured material (asbestos abatement).

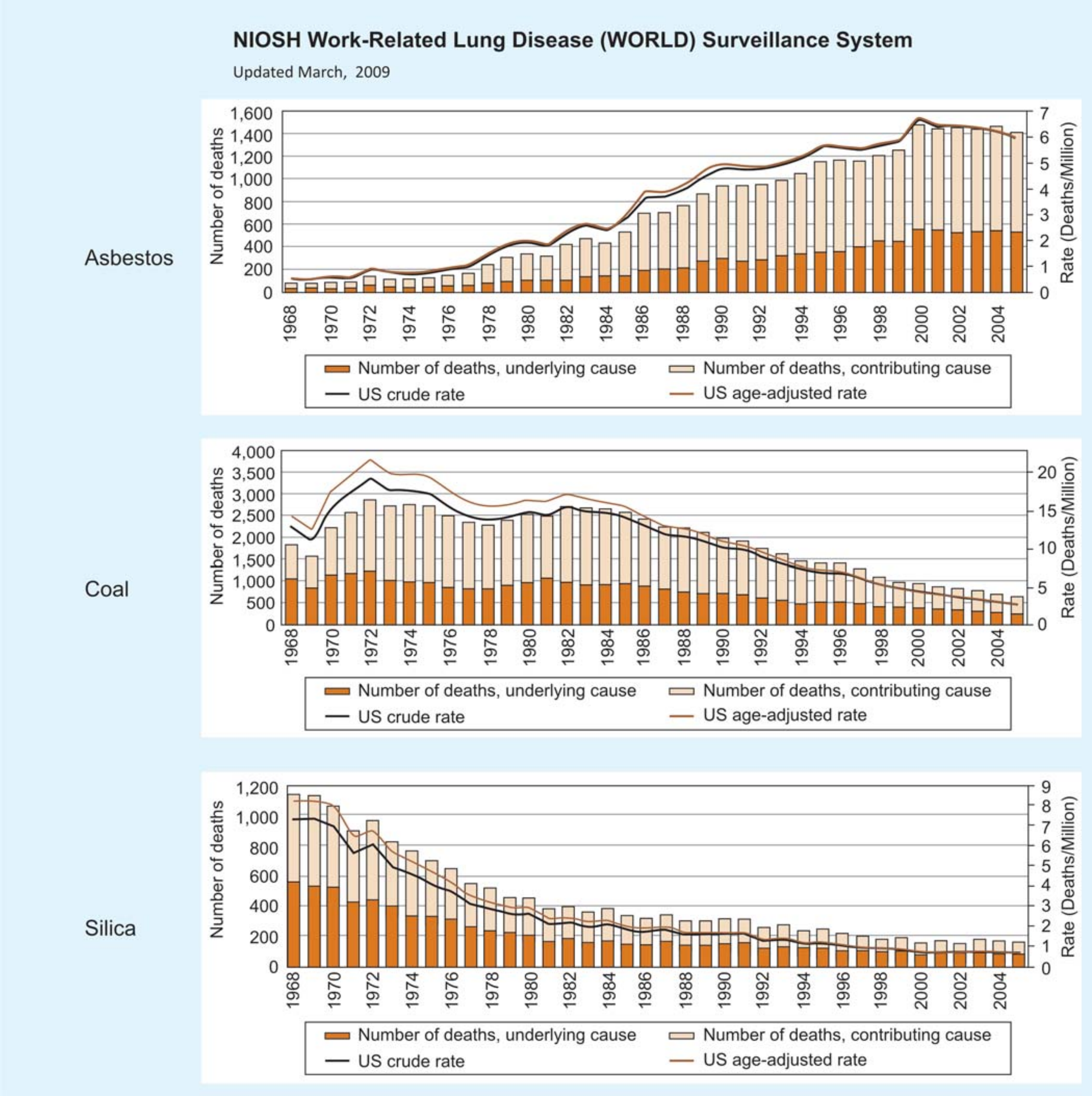


Fig. 110.1: Data from the US National Institute for Occupational Safety and Health show a continuing adverse effect of dust exposures on the health of the American worker. Although the mortality rates attributable to fibrogenic dusts have declined over time, asbestos exposure continues to have the most adverse effect on this population. Website http://www2.cdc.gov/drds/WorldReportData/referenced October 12, 2010

Asbestos is virtually indestructible and remains in the environment indefinitely. Once the fibers are incorporated into a manufactured item, there is little health risk unless the item is disrupted.

Parenchymal Penetration by Fibers

Asbestos fibers which are not cleared by airway cilia penetrate deep into the lung parenchyma. Crocidolite, the thinnest, penetrates deepest; anthophyllite, the widest in diameter, penetrates least; amosite is intermediate in size and penetration. When the chrysotile fiber is long, despite the similarity in diameter to crocidolite, penetration is less than expected due to its serpentine shape. Typically, fibers with diameters greater than 3 µm do not penetrate in the lower lung but those less than 3 µm may penetrate cell membranes, and be carried within the macrophages into the interstitium and pleural space. The length of the fiber is also important. Fibers less than 3 µm in length can be phagocytosed and carried to the lymphatics to be drained, whereas those longer than 5 µm are incompletely phagocytosed and remain in the tissue, sustaining the cellular and molecular events leading to disease. Long fibers are cleared less rapidly than short fibers.[8] For example, fibers that are most carcinogenic for developing mesothelioma have lengths more than 8 µm and diameters less than 0.25 µm.[9] Crocidolite is about 10 times more carcinogenic than chrysotile for mesothelial cells and crocidolite fibers are more prone to induce pleural fibrosis. Lung fibrosis, however, is equally affected by both types of asbestos fibers.[10]

Analysis of lung tissue with identification of asbestos fibers supports the usual clinical methods of diagnosing asbestos-related diseases. Fibers may remain imbedded in the lung for years despite macrophage attempts to engulf and surround them.[11] With time, fibers coated with acid mucopolysaccharides form a matrix for “iron deposition”. Coating of fibers is thought to decrease fibrogenicity. Light microscopy allows visualization these ferritin-protein coated fibers (typically >10 µm in length) which appear as relatively long bead-like structure. Sometimes referred to as “asbestos bodies,” these coated fibers are more appropriately termed ferruginous bodies, as other inhaled fibers (e.g. talc, fibrous glass, cotton and diatomaceous earth) are handled in like manner. Thus, coated fibers are not diagnostic of asbestos, although ferruginous bodies have most commonly been found to have an asbestos core.[12]

Although ferruginous bodies can be found in the lung tissue of virtually all of us, identifying these fibers in digested tissue, sputum, and cells garnered by lung lavage may provide a fundamental index of asbestos exposure.[13-14] In the sputum of asbestos workers, the quantity of ferruginous bodies present has been correlated with duration of asbestos exposure.[15] Ninety six percent of urban dwellers over age 40 had ferruginous bodies present in their lungs. The number of ferruginous bodies was greater in the lungs of blue-collar workers and, in particular, steel workers.[16]

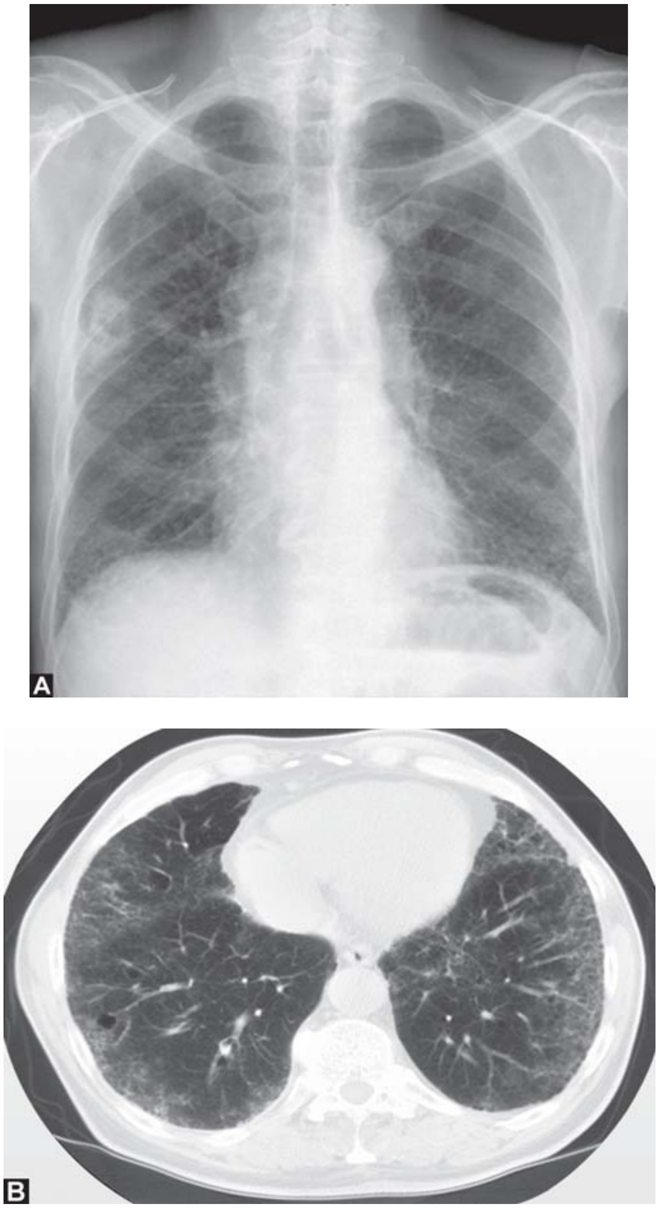
For nonfibrous minerals, it is unusual that particles exceeding 10 microns in diameter would reach the alveoli. Most particles deposited in the alveoli have a diameter of less than 5 microns.[17] However, these considerations do not apply to fibrous minerals such as asbestos. Fiber deposition in the lung is largely ruled by fiber diameter, with fiber length being less important. Fibers 200 to 300 µm long can be found in the lung as their diameter is less than 5 µm. The typical fiber-length of asbestos bodies is 20 to 50 µm, although many fibers less than 5 µm in length can also be found.

Asbestos fibers induce fibrosis and cancers of the lung and pleura.[18,19] Fibrosis begins as an inflammatory reaction which evokes a repair process, resulting in persistent scarring. Cancers begin as a multi-step process in which the target cell Deoxyribonucleic Acid (DNA) suffers increasing amounts of damage (genetic mutations) through a variety of molecular injuries.[20] Experimental animal studies and *in vitro* studies of cell cultures have shown that all of the types of asbestos fibers can cause cell damage which, if sufficiently severe, results in cell death, gene mutation, chromosomal aberration, aneuploidies, and malignant cell transformation.

Asbestosis

Although the prevalence of asbestos-related diseases have become substantially less over time, health issues continue to be recognized, particularly in the older or retired worker. Perhaps the most consequential of these dust diseases is asbestosis, the only major pneumoconiosis to demonstrate an increase in mortality over the past decade.[21] Mortality from asbestosis peaks 40 to 45 years after the workers’ initial occupational exposure to asbestos.[22] Since asbestos consumption increased substantially during and after World War II, with a peak in 1975, followed by a steep decrease beginning in the 1980s, asbestosis-related mortality will remain with us and perhaps even increase for another decade.[23] Asbestos-containing materials that continue to be used in some workplaces and remain in buildings represent a potential risk for the next generation.

The term “asbestosis” refers only to parenchymal fibrosis associated with asbestos exposure. The chronic and progressive inflammation and injury produced by asbestos fibers continues from the time of exposure, through the subclinical phase, to the time when clinical disease is identifiable by the classic methods of chest X-ray and lung function testing, as well as by more investigational approaches such as High Resolution Computerized Tomography (HRCT) scan[24,25] (Figs 110.2A and B).



Figs 110.2A and B: Chest X-ray and CT scan of a 71 year old man with a lung nodule. (A) The chest radiograph shows increased interstitial lung markings at both bases. Mild honeycombing was noted. A cavitary mass is noted in the right upper zone. (B) Slices from the CT scan show fibrotic changes consistent with asbestosis

Signs and symptoms of asbestosis are those of the other diffuse interstitial fibrotic diseases, but may not be present or only minimally noted early in asbestosis. Dyspnea on exertion is the usual symptom of presentation, which worsens as the disease progresses and lung function declines. Non-productive cough and chest pain are present in some cases, but occur late in the disease. When the cough is productive, it is likely attributable to bronchitis. Chest tightness and chest discomfort can be attributed to muscle pain appearing only when the cough and the dyspnea become severe. Hemoptysis is not expected and should be fully investigated as it suggests lung carcinoma. All of these symptoms may occur during the working years or even begin after exposure has ceased, becoming clinically apparent only after retirement.[26]

Persistent crackles are the most important physical finding. They indicate that disease is present and their appearance coincides with detectable changes in lung function and chest radiograph abnormalities, in most cases. They are typically first heard in the lower lateral lung fields in the late-inspiratory phase, and, as the disease progresses, increase in amount to become audible in the mid- and late phases of inspiration. Other adventitious sounds are usually absent. Finger clubbing may be present but does not necessarily relate to asbestosis severity. Cyanosis and reduced chest expansion are late manifestations of the disease.

The diagnosis is clinical and requires a history of exposure with an appropriate latency period, chest radiographic features consistent with asbestosis,[27] and the absence of other illnesses which might explain the radiologic features.[28,29] Idiopathic pulmonary fibrosis or lung fibrosis attributable to connective tissue disease is often part of the differential diagnosis. Although signs and symptoms of lung disease and respiratory impairment may be present, this is not a requisite for the diagnosis (Table 110.2).

The chest X-ray classically shows irregular basilar opacities which, in time, may progress to honeycombing.

TABLE 110.2: Clinical manifestations seen in some patients with asbestosis

1. Subjective respiratory complaints
2. Restrictive pulmonary function tests (FVC < 80% predicted)
3. Finger clubbing
4. Basilar crepitations
5. Chest radiograph with increased basilar lung markings
6. Known asbestos exposure

It commonly takes 15 or more years of exposure for these parenchymal changes to become detectable on the chest roentgenogram. The radiographic specificity for asbestosis, which may be identical to other diffuse fibrotic processes, is enhanced when bilateral pleural thickening and, in particular, when pleural calcification accompanies basal fibrosis.

The use of the Computed Tomography (CT) scan has not been shown to be justified in the periodic examination of asbestos exposed workers, but it has a place in the clinical investigation of these individuals. For example, it can better define pleural based abnormalities. When lung cancer or mesothelioma is considered, the CT scan better defines the anatomic extension of disease. Compared to the conventional CT scan, HRCT scan has improved our assessment of the interstitium and allows us to better appreciate interstitial and emphysematous changes.[30] Although the pulmonary abnormalities seen on HRCT are non-specific and cannot be attributed to asbestosis without characteristic pleural plaques and/or a history of significant asbestos exposure, the HRCT scan in asbestosis shows characteristic features.

When asbestosis becomes clinically important, it is classically associated with restriction of lung volumes (TLC<80% predicted). Although a decrease in small airway flow rates, due to peribronchial accumulation of asbestos fibers with associated fibrosis, may occur, smoking plays an independent role in the development of airway obstruction in heavily exposed workers.[31-33] Serial follow-up of workers with asbestosis showed that the decline in FVC was more than expected due to aging alone. A fall in diffusing capacity was the most sensitive measurement of a decrement in lung function, while the FEV_1, peak flow rate and pO_2, showed little change over time.[34] Grossly, the extent of fibrosis in the asbestotic lung varies from minimal amounts at the bases (in a subpleural distribution) to a diffusely fibrotic, shrunken lung. Progressive massive fibrosis occurs rarely and, if present, suggests mixed dust exposure.

Microscopically, asbestosis is fibrosis associated with asbestos bodies (by light microscopy) or uncoated asbestos fibers (by transmission electron microscopy). Both fibers and fibrosis must be present. Dust accumulation and fibrosis occurs at the level of the respiratory bronchiole, and may have features thought to sometimes be consistent with respiratory bronchiolitis. The alveolar septae become thickened and infiltrated with mononuclear cells, neutrophils and macrophages. With progression, diffuse alveolar wall thickening occurs with replacement of parenchyma by collagen. The severity and extent of the asbestos induced fibrotic process in a lung specimen correlated with other parameters of disease severity, such as the radiograph and lung function tests.[35]

The most likely respiratory illness which can be mistaken for asbestosis is Idiopathic Pulmonary Fibrosis (IPF). There are several differences aside from the absence of asbestos fibers in IPF. First, the interstitial fibrosis of asbestosis is accompanied by very little inflammation; second, the fibroblastic foci that are seen in IPF, a disease with a much more rapid progression that asbestosis, is absent in asbestosis; and third, asbestosis is almost always accompanied by mild fibrosis of the visceral pleura, a feature that is rare in IPF.[36]

There are important questions concerning the development and progression of asbestosis. Specifically, is there an effective therapy? Does removing the worker with asbestosis from the work environment affect progression? Once recognized, asbestosis can be a chronic and progressive disease. The evolution of asbestosis has changed significantly since the original report in 1907 by Murray who reported 10 workers with asbestosis who died before age 30.[37] Corsican asbestos workers have been studied twice. First when almost 80% of the workers had no radiographic evidence of disease and later, despite no further exposure, when only 34% had no radiographic evidence of disease.[38] Epidemiological studies of asbestos exposed individuals beginning in the 1970s have repeatedly documented a higher incidence of asbestosis and lung cancer among workers with greater cumulative dose.[39] Currently, with improved industrial hygiene, the long latency period, and early disease recognition when there is only a minimally abnormal chest radiograph (ILO category 1 pneumoconiosis), most cases are recognized after age 50 and fewer than 20% of cases so, recognized progress.

The medical management of the patient with asbestosis is supportive. Steroids are not helpful. There is experimental evidence to support ceasing exposure reduces the rate of progression.[40,41] Once diagnosed, the worker must avoid further exposure to asbestos dust.

Pleural Effusions

Although the mechanism is not understood, pleural effusions can be attributed to asbestos exposure. These effusions may be clinically manifest as being without symptoms with radiologic features of a blunted costophrenic angle as the sole manifestation of the inflammatory process to a “full-blown” bout of pleurisy with chest pain on inspiration, fever, dyspnea and a substantial collection of hemorrhagic fluid in the affected pleural space. The effusions are exudative in nature and are typically a “diagnosis of exclusion.” These may occur in individuals who have a history of asbestos exposure and a latency period most often of approximately ten to fifteen years from initial exposure, although sometimes less (such effusions as recognized to be the earliest occurring among the numerous presentations of asbestos induced chest effect).[42] These may be attributed to asbestos after chemical and cellular assessment of the fluid in the pleural space, as well as a sample of the pleura, provides no clear diagnosis. This may require serial chest radiographs over an observation period of two or three years as these effusions typically resolve slowly and spontaneously over a period of months.[43,44]

Asbestos pleural effusions do not predict the development of lung cancer, pleural plaques or mesothelioma, although exudative effusions often accompany lung cancer as well as mesothelioma.[45,46] Not surprisingly, these exudative effusions leave a "scarred" pleural space as they resolve. This is manifest by the radiographic appearance of obliteration of the costophrenic angle and described as diffuse pleural thickening.

Diffuse Pleural Thickening: Fibrosis of the Visceral Pleura

Diffuse pleural thickening is a disease of the visceral pleura. It is not specific for asbestos exposure and is often associated with fibrosis due to an inflammatory reaction caused by tuberculosis, surgery, hemorrhagic chest trauma, or drug reaction. In addition the radiologic features of pleural thickening were more than three times more likely in obese (BMI > 30 kg/m^2) asbestos workers.[47]

In association with asbestos exposure, the mechanisms which cause diffuse pleural thickening are unknown, but it appears to be the result of exudative benign pleurisy in most cases. In other cases, where there is no history of a previous episode of benign pleurisy, perhaps the confluence of pleural plaques or the extension of subpleural parenchymal fibrosis into the visceral pleura has caused diffuse thickening. In the most aggressive cases, diffuse pleural thickening can extend into the interlobular spaces of the lung and affect the fissures, leading to restriction of lung expansion, even in the absence of interstitial lung fibrosis.[48] Although it had been originally thought that those who develop diffuse pleural thickening had greater exposure to asbestos than those who developed pleural plaques, no difference in asbestos burden in those with plaques vs. those with diffuse pleural thickening was shown by calculating exposure ratings from exposures in the trade within the shipyard and years employed in the trade[49] (Figs 110.3A to C).

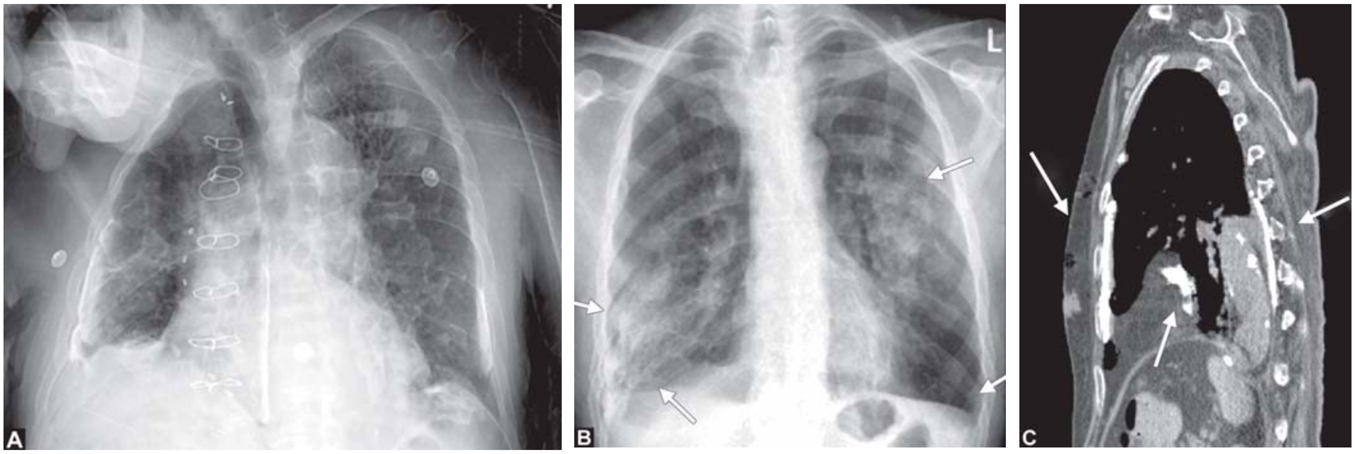
Diffuse pleural thickening may be responsible for dyspnea on exertion and perhaps a dry cough. Decreased respiratory excursion may be noted if the lung is "trapped" and moves little on the affected side. Diffuse pleural thickening may restrict lung function modestly if limited, but if extensive and bilateral, this may cause a significant restriction of lung function due to a "trapped lung" and result in respiratory insufficiency and failure in some instances. Although the radiographic features of diffuse pleural thickening often appear to show a more extensive pleural effect compared to the radiographic features of benign pleural plaques, data show no difference in mean exposures between workers with these two types of radiographic features. A wide distribution of exposures was recognized in both groups.

On the radiograph, diffuse pleural thickening appears as a continuous, smooth pleural opacity extending more than one-fourth of the pleural surface with blunting of the costophrenic angle. If diffuse pleural thickening is bilateral, the foremost concern is asbestos exposure. The relationship between these radiographic changes and asbestos is a clinical perception and does not require histologic confirmation unless malignant pleural disease is considered. Because this primarily affects the visceral pleura in the posterior and posterolateral lower zones, the CT scan provides a better visualization than the chest radiograph. Diffuse pleural thickening can be complicated by extension of fibrosis in the interlobar and interlobular fissures to form crow's feet (a focal abnormality of the visceral pleura which appear as small, pleural and parenchymal fibrous strands). Rounded atelectasis (the folded lung) is also known as Blesovsky's syndrome and is thought to be the result of visceral pleural fibrosis which has been "drawn back" into the lung.[50]

Pleural Plaques (Fibrosis of the Parietal Pleura)

One of the radiographic hallmarks of asbestos exposure is pleural plaques. These are located on the parietal pleura, are not associated with pleural adhesions, and cause no pulmonary function impairment. Workers with pleural plaques are without symptoms or signs of chest disease.

The pathogenesis of these plaques is unclear. Short and thin fibers are found in the pleural space soon after inhalation exposure. The most likely means of transport is via the lymphatics with probable additional contributions of gravity and respiratory motion.[51] Thomson has suggested that inhaled fibers gradually penetrate toward the base and periphery of the lung in a migration propelled by the continual movement of the lung.[52] He



Figs 110.3A to C: These three chest radiographs show features emphasizing diffuse pleural thickening. The first radiograph shows extensive pleural changes in an asbestos-exposed worker who has had previous coronary artery bypass surgery. Specifically, there is calcified pleural thickening in both right and left pleural bases and lower pleural margins. In addition, there are calcified *en face* pleural plaques most notable on the left chest and a discrete calcified pleural plaque along the left chest wall. The second radiograph shows extensive pleural calcifications with obliteration of both costophrenic angles. Particularly noticeable is a calcified discrete pleural plaque on the right chest wall. The final figure is a chest CT scan (sagittal cuts) showing heavily calcified pleural plaques on left side (along the anterior chest wall, the posterior and outlining the basal lobule). Calcifications of the descending aorta is also noted

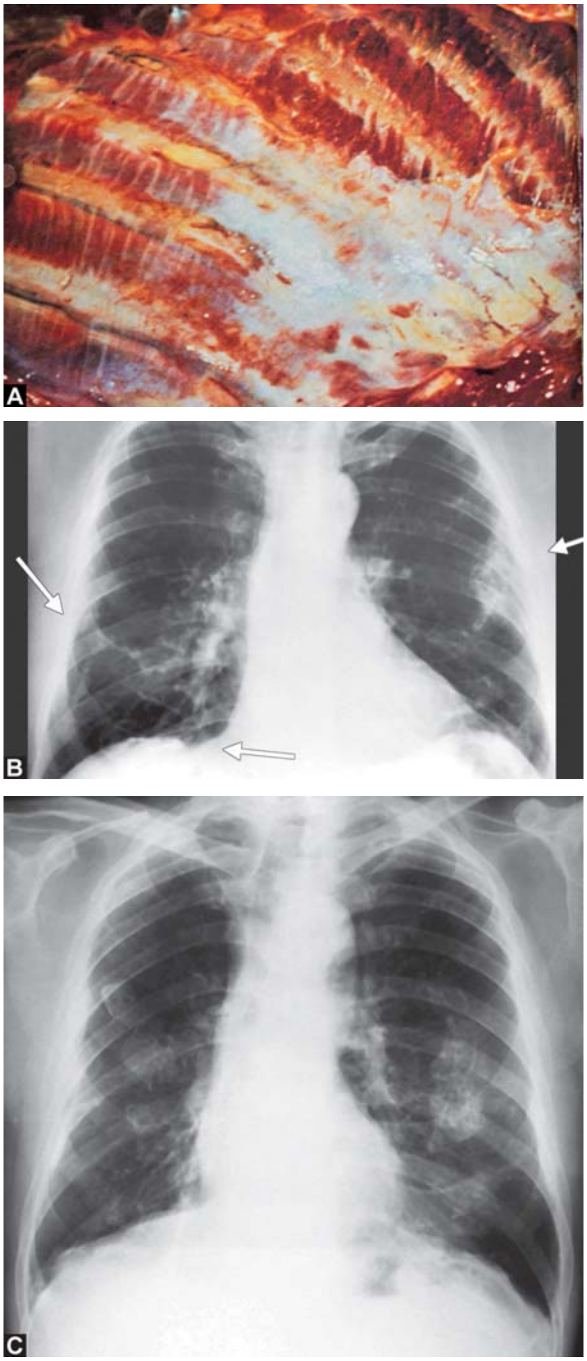
hypothesized that the common basal and posterior pleural plaques are a result of these areas being dependent when the subject is upright and during sleep. The tendinous part of the diaphragm, the ribs and the vertebral bodies block fiber penetration, and thus pleural plaques are typically located over these structures. Perhaps the thin and pointed nature of the fibers in the pleural space facilitate tissue penetration, scratching of the pleural tissue, and initiation of an inflammatory reaction, followed by organization, all leading to the pleural plaque. Even though pleural plaques are strongly associated with past asbestos exposure, they may occur in subjects with low-level or even sporadic asbestos exposure (based on fiber counts collected by broncho-alveolar lavage) using high resolution CT scans to identify the extent of fiber involvement.[53]

Grossly, plaques are firm, raised areas with a nearly white, glistening surface. Microscopically, collagen fibers are oriented in a parallel fashion in the sub-mesothelial layers of the parietal pleura at the level of the costal margins, the diaphragms, and the para-spinal areas. They are covered by a normal mesothelial lining which does not contribute to the development of the plaque. They can be found in the pericardium and, less often, in other mediastinal pleura. Visceral pleural plaques occur much less frequently, but can extend in the interlobar fissures. Therefore, the plaque is really extra-pleural.[54] This, plus the slow, nonexudative growth of the plaque may explain the lack of adhesions. Pleural calcification occurs in areas of collagen degeneration and implies that the plaque has been present for 20 or more years.[55] Generally, neither asbestos bodies nor asbestos fibers are found in the plaques. Although they serve as markers of asbestos exposure, there is no evidence to suggest that pleural plaques are premalignant forms of mesothelioma.

The earliest finding on the chest radiograph of a pleural plaque is frequently a thin line of soft-tissue density at the lateral margin of the seventh or eighth rib. This early change may be difficult to distinguish from normal "companion" shadows. The routine chest radiograph defines only 8 to 15% of all pleural plaques.[56] Oblique views may assist in their recognition. The conventional CT scan recognizes plaques much earlier and at a less well defined stage than the chest radiograph. Diaphragmatic plaques which were not always well appreciated with the conventional CT scan are better evaluated with the HRCT. Computed tomography scans can clearly differentiate plaques from extrapleural fat pads, a sometimes difficult distinction on the plain chest radiograph. Furthermore, in the presence of extensive and calcified pleural plaques, the CT scan permits a clearer appreciation of the lung parenchyma than the plain radiograph (Figs 110.4A to C).

Malignant Mesothelioma

Malignant pleural mesothelioma arises from the mesothelial cells of the pleura. Tumors may be solitary

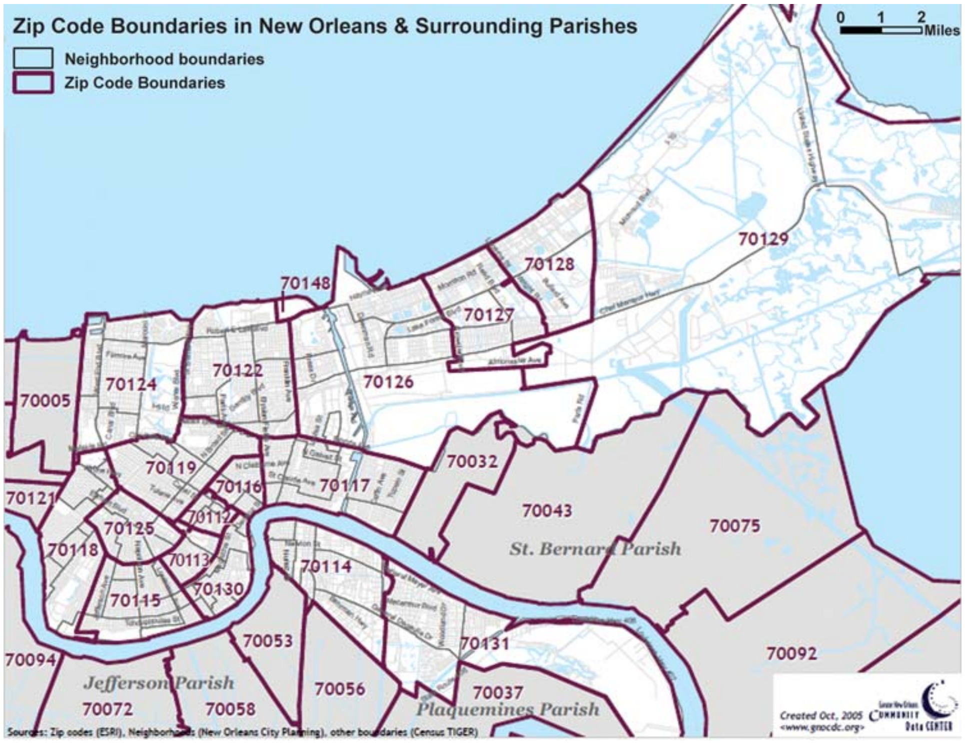


Figs 110.4A to C: The first figure (A) shows a parietal plaque on the thoracic wall with an irregular thick plaque. (Photograph from the textbook Asbestos Related Disease: Clinical, epidemiologic, pathologic, and radiologic characteristics and manifestations. American College of Radiology, 1982). The first radiograph (B) shows pleural thickening along both lateral chest walls with shows a calcified pleural plaque of the right hemidiaphragm. The figure (C) shows several calcified *en face* discrete pleural plaques located on the chest wall, bilateral calcified pleural thickening along the lateral chest wall, and bilateral diaphragm thickening

or diffuse. Solitary mesotheliomas are benign, well-circumscribed, variable in size and usually fibrous in histologic type, although epithelial elements may be present. They are unrelated to asbestos exposure and curable by surgical excision. It is a rare tumor but with increasing incidence and a poor prognosis.

Diffuse mesothelioma has a gross appearance which is more diagnostic than its variable histologic appearance.[57] In its early stages, it appears as multiple gray or white nodules on the pleural surface (Fig. 110.7). It spreads along the pleural surface, encasing the lung with a resulting loss of volume. Distant metastases beyond the regional Iymph nodes are rare, unless advanced disease is present. The tumor has a predilection for growth along incision or biopsy sites. This malignancy spreads by direct extension into adjacent structures of the chest wall, interlobar fissures, lung parenchyma, mediastinum, pericardium, diaphragm, esophagus, large vessels of the mediastinum, contralateral pleura and the peritoneal cavity (Fig. 110.8). Death is usually caused by restriction of one or more of these vital structures. Malignant mesothelioma is of peritoneal origin in less than 25% cases. In the abdomen, the gross appearance of the tumor is quite similar with direct invasion of the abdominal structures. Microscopically, malignant mesothelioma may have one of three histologic patterns: Epithelial, sarcomatous or mixed. Usually, one pattern predominates, but elements of the other two may be present.[58]

Although inhalation of asbestos fibers is a major risk factor for the development of mesothelioma, not all mesothelioma are associated with asbestos fiber inhalation. Exposure to amphibole fibers is much more likely to induce mesothelioma than exposure to chrysotile fibers, yet all of the commercially available fibers have been recognized to cause mesothelioma.[59,60] The relationship between mesothelioma and asbestos exposure was first well documented in 1960.[61] A study of 17,800 asbestos insulators uncovered 66 mesotheliomas.[62] Most occurred 30 or more years from onset of exposure. Persons having household contacts with asbestos workers are at increased risk for development of mesothelioma.[63] Residents of communities where asbestos is mined/processed may also be at increased risk (Fig. 110.5). Mesothelioma is exceedingly rare in the non-asbestos exposed population, and the estimated mortality rate due to mesothelioma is one in 10,000 deaths per year in the general population.[64] Over-all, in the absence of asbestos exposure, malignant mesothelioma is a rare disease with an incidence of one to two cases per year per million people in the general population of North America.


Zip Code Boundaries in New Orleans & Surrounding Parishes
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Jefferson Parish
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Plaquemines Parish
Created Oct, 2005 <www.gnocdc.org>
Community Data Center
Sources: Zip codes (ESRI), Neighborhoods (New Orleans City Planning), other boundaries (Census TIGER)

Fig. 110.5: A 28-year-old accountant presented with dull chest pain for several months. Evaluation showed a large pleural effusion and diagnostic work-up showed malignant mesothelioma. Lung tissue assessed for asbestos fibers showed two different types in the lung. Importantly, when asked, she reported that she had recently finished her CPA (Certified public accountant accreditation) and had no known exposure to asbestos. The story was a puzzle until the MDs realized that her two places of residence in her life were several blocks from an asbestos cement manufacturing plant that had ceased operation in New Orleans several years earlier

Using the Louisiana state registry, we showed that there was a cluster of mesothelioma in women (but, not men) residing in this 70116 zip code in the previous decade, with a decrease in the number of cases as one went further away from this address. This led us to conclude, based on epidemiologic data, that the risk for developing mesothelioma may well have been associated with the presence of the asbestos cement plant in the residential area

In the asbestos exposed populations, the rates can be 5 to 20 fold higher, with a gradient of 10 to 1 for crocidolite to chrysotile exposures.[65]

Symptoms develop insidiously and include progressive dyspnea and weight loss. Most patients with mesothelioma cite chest pain, often only partially relieved by analgesics, as the reason that they consult a physician. The presenting sign is usually a unilateral pleural effusion. As the disease progresses, affected supraclavicular nodes may become palpable and ribs may become tender as a result of local tumor invasion. Both superior and inferior vena caval obstruction can occur with resultant congestion, edema, and ascites. Digital clubbing may be present.

Malignant mesothelioma should be considered in the differential diagnosis of all cases of explained exudative pleural effusion, particularly if asbestos exposure is documented. Clinical clues suggesting mesothelioma include contralateral pleural plaques and pleural calcification. In fact, among workers with asbestosis and/or asbestos-related pleural disease, there has been a significant increase in the risk for mesothelioma.[66-68] The issue under discussion, at least some of these reports, is the adequacy of accurately identifying plaques by chest radiograph.[69-70] Commonly, mesothelioma is seen in the absence of basilar interstitial fibrosis, a classic finding of asbestosis.[71]

During thoracentesis, it may be difficult to enter the pleural space due to thickened pleura. The effusion is exudative, viscous and very cellular, with normal, malignant and inflammatory cells. Cytologic examination of the fluid is often of limited diagnostic value because it is frequently difficult to differentiate benign from malignant mesothelial cells. Hyaluronic acid may be greatly elevated in effusions associated with malignant mesotheliomas.[72] Because of rapid fluid accumulation,

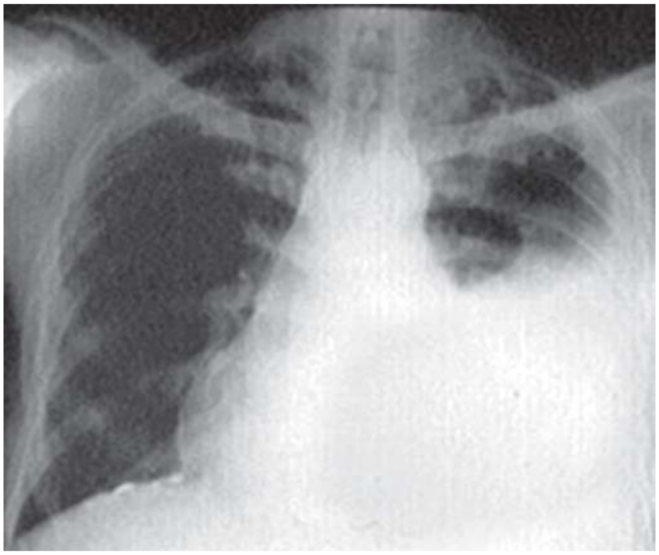

Fig. 110.6: This radiograph shows a large left-sided pleural effusion. Following thoracentesis, the left lateral chest wall showed a "bumpy" nodular appearance. Histologic staining of the mass showed malignant mesothelioma with associated. Note displacement of the heart to the right and calcifications on the right hemidiaphragm

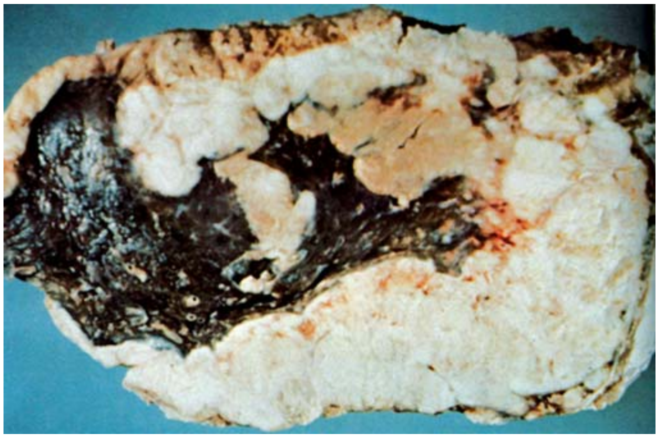

Fig. 110.7: This lung was removed at autopsy from an insulator with a 35 year history of asbestos exposure. The lung is encased by the gray-colored mesothelioma. (Photograph from the textbook Asbestos Related Disease: Clinical, epidemiologic, pathologic, and radiologic characteristics and manifestations. American College of Radiology, 1982)

repeated thoracentesis may be necessary to palliate dyspnea.

There is no method for the early recognition of mesothelioma. Although an open thoracotomy with pleural biopsy may well be needed to provide adequate amounts of tissue to establish a certain diagnosis, recent recommendations suggest that an earlier and equally reliable diagnosis may be gained through the use of thoracoscopy (except in cases of pre-operative contraindication).[73] In addition, because standard staining procedures are insufficient in approximately 10% of cases, these consultants propose using specific immunohistochemistry markers on pleural biopsies. No staging system exists for mesothelioma. The authors propose use of the most recent TNM-based classification for lung cancer for mesothelioma and propose a three step pre-treatment assessment. The patient's performance status and histological subtype are currently the only prognostic factors of clinical importance in the management of Malignant Pleural Mesothelioma. Other potential parameters should be recorded at baseline and reported in clinical trials. Malignant pleural mesothelioma exhibits a high resistance to chemotherapy and only a few patients are candidates for radical surgery. To date, surgery, radiotherapy, chemotherapy, and, of late, immunotherapy or cytokine therapy, or a combination of the above, have been equally unsuccessful in curing this disease although may improve prognosis for a period of time. Gene therapy has not yet reached clinical practice.[74] Patients who are considered candidates for a multimodal approach to therapy should be included in a prospective trial at a specialized center.

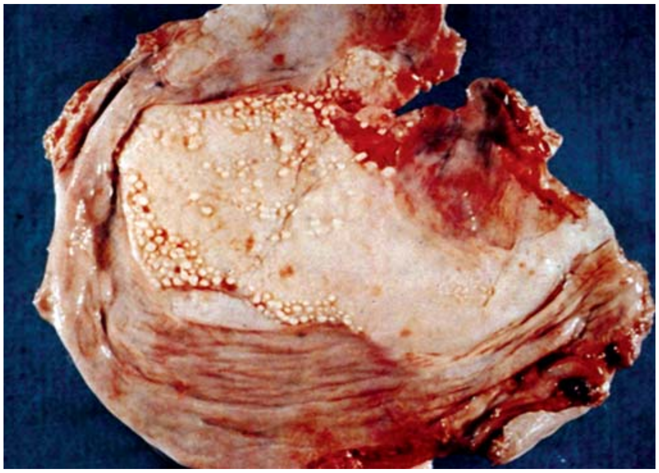

Fig. 110.8: This photograph shows the peritoneal surface of the diaphragm of a pipefitter with a 30 year asbestos exposure history. The main tumor mass was within the peritoneal cavity and involved the small intestine and pelvis. The discrete white nodules reflect seeding of the mesothelioma along the inferior aspect of the diaphragm. (Photo from the textbook Asbestos Related Disease: Clinical, epidemiologic, pathologic, and radiologic characteristics and manifestations. American College of Radiology, 1982)

Lung Cancer

An association between asbestos exposure and bronchogenic cancer was first suggested in 1935, and, since that time many studies have documented this relationship.[75] The persistence of asbestos in the lung parenchyma results in a lifelong exposure to this carcinogen. Thus, despite removal of the worker from a contaminated environment, the worker's lungs are continually exposed and the risk for cancer increased. In a series reported several years ago, 60% of English workers were disabled due to asbestosis and died of lung cancer.[76]

Our understanding of the way that asbestos induces lung cancer is incomplete.[77] Some consider asbestos to be a tumor promoter on the basis of its weak activity in standard tests which address a carcinogen's potential (i.e. its ability to produce chromosomal abnormalities). Based on this perspective, the fibers increase the susceptibility of the lung to other carcinogens. Others consider asbestos to be a tumor initiator and note the excess number of lung cancers in animals not exposed to other carcinogens and the excess of lung malignancies in lifetime non-smokers. A separate, and quite contentious issue, reflects whether asbestosis is necessary for the genesis of lung carcinoma. This is supported by epidemiological studies which have shown an excess number of lung cancers in a great majority of reports addressing the outcomes of the most heavily exposed workers with the highest prevalence of radiographic opacities consistent with asbestosis.[78] However, alternative views contend that lung cancers occur in the absence of radiologic or histologic evidence of asbestosis and that the extent of asbestos exposure, the risk for developing asbestosis, the effects of cigarette smoking and the ensuing risk for lung cancer all run parallel and increase with time, making the measurable risk for asbestosis alone, as it applies to lung cancer, difficult to separate from these other parameters.[79-82] Discussion continues on this topic.

Our understanding of asbestos-related lung cancers in the absence of clinically recognizable asbestosis is further complicated by the multiplicative risk of smoking. In another study of the same workers, the risk of lung cancer in cigarette smoking asbestos workers was compared to a group without asbestos exposure.[83] Asbestos workers who smoked one pack of cigarettes per day had an 87 fold increase in the risk of developing lung cancer compared to nonsmoking, non-asbestos exposed controls. In nonsmoking asbestos workers, this risk was only five-fold. This has led to the postulate that the exposure to smoking and to asbestos causes a multiplicative risk for lung cancer. More recently, data from different asbestos exposed populations and the risks for lung cancer were measured. Although the fiber dose required to develop lung cancer was similar among different populations of asbestos insulators, it was very different among populations of workers exposed to asbestos in the manufacture of textiles and in workers employed in the manufacture of asbestos cement. The disparities are not clear and have led many to challenge the hypothesis that there is not a "multiplicative risk," but rather a synergistic effect of asbestos exposure and cigarette smoking altered by other interacting elements in the causation of lung cancer. Rather suggestions regarding smoking history; fiber type; underlying obstructive lung disease; exposure to contaminant metals, ionizing radiation, and chemicals such as benzopyrene and polycyclic aromatic hydrocarbons; the presence or absence of asbestosis and the question of individual susceptibility have been considered as possible explanations for these differences.[84]

Asbestos-related cancers are not distinct in type, nature, or their location within the lung from those solely associated with cigarette smoking. The histologic distribution of asbestos-related cancers approximates 35% epidermoid, 25% small cell, 30% adenocarcinoma and 10% large cell carcinoma, a distribution similar to the cell types of cancer in those who smoke without asbestos exposure.

Asbestos-related lung tumors present in the same manner as lung tumors caused by other carcinogens, except when the symptoms of asbestosis are present. In the presence of asbestosis, it is accepted that lung cancers should be compensated. In the absence of asbestosis, compensation has been debated, some refusing compensation for all cases, others favoring compensation for cases of long exposure (about in excess of 20 years). A detailed discussion of this is beyond the scope of this review.

An Assessment of the Extent of Asbestos-Related Disease in India

Compared to the United States, where a great amount of asbestos was used during World War II and continued to be used until the 1970s, a significant amount of the consumption of asbestos in India began later on. In the US, annual consumption approximated 40,000 metric tons in 1920. This gradually increased to 100,000 metric tons by 1940, and then increased again to 500,000 tons yearly from 1950 until 1970 with the peak being 803,000 tons in 1973. Asbestos has not been mined in the United States since 2002, so the United States is dependent on imports to meet manufacturing needs. Asbestos consumption in the United States in 2009 was estimated to be 715 tons. Roofing products were estimated to account for about 65% of US consumption and other applications, 35%.[85]

In India, the timeline is very different. In one report, approximately 125,000 metric tons were used in 1995 with a gradual yearly increase until utilization reached 200,000 tons consumption per year in 2003.[22] In a second report dated 2003, the annual consumption of asbestos in India was cited to be less and to approximate 100,000 metric tons. One-fifth of this amount was mined in India, with the rest being imported, a great percentage from Russia and Canada.[86] A more recent unofficial report stated that India's asbestos use has risen to 300,000 metric tons yearly. Importantly, since 2003, companies no longer need a license to import chrysotile, so it may be more difficult to track usage.[87] A great percentage of the asbestos used in India is mixed with cement to form roofing sheets. Although the epidemic of asbestos-related disease in the US appears to be slowing, this pattern of asbestos usage suggests that the Indian epidemic is closer to its beginning.

In the absence of banning the use of asbestos, control of asbestos dust exposure in the workplace is the most effective way to prevent disease. In the past, although peak asbestos fiber counts in the workplace air sometimes exceeded 100 fibers/cc of air, more typical exposures ranged from 5 to 20 fibers per cc. The current allowable US limit to airborne exposures is 0.1 fiber per cc of air expressed as an 8 hour time-weighted average with a maximum exposure of limitation of 1.0 fiber per cubic centimeter of air (1 f/cc) as averaged over a sampling period of 30 minutes for all fiber types.[88] In India, asbestos exposure is regulated under the Factories Act (1948), in which asbestosis is listed as a notifiable disease in the schedule 3 of the Act.[89] Under this act, the limit of exposure is 1 f/cc. Asbestos is also regulated under the Environment Protection Act (1986) which sets a limit of 4 f/cc. for environmental emissions.[90]

Two reviews provide considerable insight into the prevalence of asbestosis in India, although in other reports, authors are increasingly vigorous in maintaining that asbestosis occurs much more commonly than it is reported.[87,91-94] One report states that as of 2005, approximately 100,000 workers have been exposed to asbestos, and less than 30 workers have been compensated. This same report recognized 41 workers with asbestosis in one asbestos processing plant where asbestos brought into the workplace in bags is processed and made into finished products such as asbestos textiles and brake and clutch linings.[95] A 1996 epidemiologic study reported lung impairment and radiologic abnormalities in 54.8% of asbestos millers and 19.5% of asbestos miners.[96] In some workplaces exposures are excessive. In a study of asbestos cement factory workers, exposures were two to three times higher that the Threshold Limit Value (TLV) among asbestos pipe cutters, but below the TLV in other areas. In this group, the FVC was less in the group employed 16 to 20 years, but in workers employed more than 20 years, the mean values of all pulmonary function parameters studied were reduced, implying a "mixed" defect in lung function. When smokers were compared to non-smokers, there was no measurable effect.[97] In another report of asbestos miners, exposures were below the permissible exposure limit in the mine, but the ambient exposures in the mill were 200 to 400 f/cc.[98] These exposures were lessened to 15 to 20 f/cc. with appropriate engineering controls.[99] Others have reported grossly increased exposures in asbestos milling.[100] With such exposure data it is not surprising that a 1989-1990 report by the Indian National Institute of Occupational Health (NIOH) showed an asbestosis prevalence of 4% among miners and 21% among millers.[101] The prevalence of asbestosis in asbestos cement factories and the asbestos textile industry workers is variably described from 3% to 9%.[102,103]

It has been very difficult to estimate the predicted number of mesothelioma cases and when these cases may reach their peak. In the US, about 2,000 annual deaths from mesothelioma are anticipated in coming years. This year, in 2010, approximately 700 cases are anticipated in Australia. In the Netherlands, it has been predicted that pleural mesothelioma will peak in 2028, with nearly 900 cases. In France, the number of annual deaths attributable to mesothelioma is expected to peak in 2020 at 2,200 cases.[104] Unfortunately, with the lack of reliable reporting of diseases such as mesothelioma and the continuing use of asbestos, it is not possible to make such assessments in the Indian population.[105] Yet, it is reasonable to be concerned that this disease will persist.

CONCLUSION

To begin, the reader should be reminded that the best indicator of past asbestos exposure (the gold standard) remains the detailed work history. If the exposure history is not clear, the presence of pleural abnormalities of diffuse pleural thickening or pleural plaques can serve as a surrogate for past asbestos exposure. In the rarest of occasions, an open lung biopsy with assessment of the mineral content of the lung is possible.[106]

Although a great number of articles address the adverse respiratory health effects associated with asbestos exposure, numerous questions regarding the determinants of pleural disease (specifically, mesothelioma and pleural plaques) and how fibers interact with the pleural space remain. Specifically, why some workers with similar workplace exposures have very different radiographic manifestations is not understood. Some develop pleural plaques, while others may have an exudative pleural effusion which may end up with diffuse pleural thickening. How do pleural plaques develop when there is only minimal evidence of inflammation in the pleural space? How does the persistence of fibers in the lung of one worker result in mesothelioma while in another there is no visible effect?

Next, it is reasonable to state that there is a sufficient amount of data to justify the current exposure regulations which protect the worker from the development of asbestosis. Yet, there is no exposure evidence available which addresses the maximal allowable levels of asbestos exposure which will protect the worker from the development of pleural changes, mesothelioma, or the risk of lung cancer. Asbestos exposure regulations are not based on these features of exposure.

Finally, it remains unclear how asbestosis apparently transforms into lung malignancy. Yet, even more unclear is how fibers which may cause inflammation, but no discernable lung disease, increase the risk of malignancy.[107] Overall, this appears to be increasingly consequential. In the past, the weight of evidence about the relationship between asbestos exposure and lung cancer appeared to favor the conclusion that asbestosis was necessary to attribute lung cancer to asbestos exposure. At present, this conclusion has been increasingly challenged as research continues.

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Occupational Asthma

Gajanan S Gaude

INTRODUCTION

Physicians commonly encounter patients who develop or show increased severity of asthma during their adult working life. It is important to determine in these situations whether work is causally related to the development of asthma. Indeed, asthma is now the most common cause of work-related respiratory disease in the industrialized countries. Occupational asthma in fact is a silent disease, frequently seen, but seldom considered. Occupational asthma is estimated to constitute an average of 15% of adult asthma and an even more of new-onset asthma in adults.[1]

HISTORICAL ASPECTS

Ramazzini provided clinical descriptions of Baker's asthma and farmer's lung in his treatise, "De Morbis Artificum" in 1713. Only in 1920s, greater details on occupational asthma appeared with the recognition that exposure to many substances, such as hay, grains, pollens, dusts and animals could provoke the attacks of rhinitis and wheeze. The term "occupational asthma" was coined by Von Pirquet in 1906. These disorders were attributable to the proteinaceous High Molecular Weight (HMW) or Low Molecular Weight (LMW) reactive chemicals. Following the World War II, the surge in the industrial growth led to the introduction of a plethora of reactive chemicals into the workplace leading to an increase in the symptoms of occupation-related asthma.

DEFINITIONS

Occupational asthma is characterized by wheezy breathlessness occurring after exposure to a sensitizer at work. It may also include subjects with prior asthmatic symptoms whose symptoms subsequently worsen as a consequence of sensitization in the workplace. It is defined as a disease characterized by variable airflow limitation and/or Nonspecific Bronchial Hyperresponsiveness (NSBH) due to causes and conditions, which are attributable to a particular occupational environment and not to stimuli encountered outside the workplace.[2] It includes both the immunological and nonimmunological causes:

i. Immunological occupational asthma occurs upon exposure to an agent after a latent period of immune sensitization.
ii. Nonimmunological asthma may or may not occur after a latency period of exposure to an agent(s), which does not induce immune sensitization as determined by currently available technology. It has also been defined by the presence of reversible obstruction of the airways associated with bronchial hyperresponsiveness caused by the inhalation of dusts, gases, fumes or vapors that are produced at or incidentally present at the workplace.[3] It excludes bronchoconstriction caused by exercise or cold air. Preexisting asthma does not preclude the development of work-related asthma.

The American College of Chest Physicians (ACCP) consensus statement on occupational asthma tries to differentiate between work-exacerbated asthma and occupational asthma.[4] Work-related asthma is a broad term that refers to asthma that is exacerbated or induced by inhalation exposures at the work place. The term "work-exacerbated" asthma refers to asthma triggered by various work-related factors (e.g. aeroallergens, irritants or exercise) in workers who are known to have preexisting or concurrent asthma (e.g. asthma that is occurring at the same time, but is not caused by workplace exposures.) Occupational asthma refers to asthma or the recurrence of previously quiescent asthma (e.g. asthma as a child or in the distant past that has been in remission) induced by either sensitization to a specific substance [e.g. an inhaled protein (HMW protein of > 10 kd) or a chemical at work (LMW agent)], which is termed sensitizer-induced occupational asthma or by exposure to an inhaled irritant at work, which is termed irritant-induced occupational asthma.

Sensitizer-induced occupational asthma presents with a latency period includes those causative agents (proteins and some chemicals) for which sensitization can be demonstrated (typically by antigen-specific IgE) in most persons with asthma due to exposure to that agent. It also incorporates occupational asthma caused by those agents (usually reactive chemicals) for which an immunologic mechanism is strongly suspected, yet an antigen-specific immune response cannot easily be tested in most of the affected workers. The most definitive form of irritant-induced asthma is Reactive Airways Dysfunction Syndrome (RADS), which is described as acute onset of asthma after a single, very high irritant exposure. Work exacerbated asthma and occupational asthma may coexist in the same worker. In contrast to work-exacerbated asthma, the onset of asthma due to work exposures in a person with a history of asthma in the past or during childhood is considered more likely as the new-onset occupational asthma and not work-exacerbated asthma; the recurrent onset of asthma unrelated to work and subsequent work exacerbation is also possible.

EPIDEMIOLOGY

It is the most common form of occupational lung disease in many Western countries, having overtaken the pneumoconiosis owing to improved control of exposure to silica, asbestos and coal dust. There are no long-term prospective studies that deal with occupational asthma. Nearly all the epidemiologic studies have relied on subjective data in identifying asthma. It has generally been accepted that at least 9 to 15% of adult asthma can be attributed to work place exposure, although recent data indicate that 25% or more of de novo asthma may have occupational basis.[5,6] The reported incidence of occupational asthma was 13 cases per million workers in South Africa, while it was approximately 6% of all asthma patients in a large university hospital respiratory clinic in Zambia.[7] Statistics from around the world indicate that a high percentage of adults with asthma miss work in a 12-month period because of their asthma: 25% in the United States, 17% in Western Europe, 23% in Central and Eastern Europe, 27% in Asia-Pacific and 30% in Japan.[8] Incidence of occupational lung diseases, including occupational asthma in India is on the rise.[9] Indian industry remains labor intensive, often employs relatively inexpensive and hazardous technology due to financial constraints. This is especially true for the unorganized small scale sector. There are very few studies on the prevalence of occupational asthma in India. A clinical survey done in two silk filatures industry revealed that 36.2% of the persons engaged in the processing of natural silk suffered from bronchial asthma, while 16.9% of the total subjects had asthma of occupational origin.[10] The overall prevalence data remains underestimated principally because of the lack of an appropriate reporting system.

WORK-EXACERBATED ASTHMA

Work-Exacerbated Asthma (WEA) is a condition associated with the worsening of asthma attributable to workplace conditions. It occurs among people with asthma whose onset occurred before entering the suspected job (i.e. preexisting asthma) or while in the suspected job, but with onset not attributable to workplace conditions (i.e. coincident or concurrent asthma). Symptoms can be confounded by exposures to cigarette smoking (or other irritants) or in association with hobbies or businesses run from homes that have irritating or allergenic environmental stimuli. Work-exacerbated asthma may account for much greater morbidity and productivity losses than occupational asthma.

AGENTS CAUSING OCCUPATIONAL ASTHMA

Occupational asthma may encompass both immunological and nonimmunological causes:[11]

i. Immunological (allergic) occupational asthma occurs upon exposure to an agent after a latent period of immune sensitization to a substance or material present at the work site characterized by variable work-related airflow limitation and the presence of specific/nonspecific airway hyperresponsiveness. In sensitized subjects, reexposure to a small amount of the causative agent leads to the occurrence of asthma.

ii. Nonimmunological (nonallergic) occupational asthma is due to an outstanding workplace irritant exposure and develops without a preceding latent period of exposure to an agent(s), which does not induce immune sensitization and is distinguished by persistent nonspecific airway hyperresponsiveness. This category includes irritant-induced asthma or RADS, which may occur after a single or multiple exposures to nonspecific irritants at high concentrations.[12] Two distinguishing features are pertinent to this classification of occupational asthma – latency and specific airway reactivity. In RADS, the exposure is characteristically acute, singular and extreme in nature, but asthma developing after lesser exposures and occurring over a more prolonged period of time has been intimated. In both allergic and nonallergic asthma, pathologic changes depict bronchial mucosa injury and inflammation.[13]

The major risk factor for occupational asthma is the extent of exposure to the sensitizer. The workplaces that allow high and frequent exposure of workers to airborne sensitizers may expect a high rate of respiratory problems. Atopy increases the risk of an individual becoming sensitized and contributes to an early sensitization and early occurrence of symptoms.[14] Smoking increases the risk of sensitization and the development of IgE antibodies.[15] The diagnosis should be confirmed objectively.

Most of the occupational agents causing asthma have known or suspected allergic properties. These agents are divided into two groups: those with HMW and those with LMW (< 1,000 daltons).

High Molecular Weight Compounds

Occupational agents, such as the proteins, polysaccharides and peptides induce allergic response by producing specific IgE antibodies and sometimes, specific IgG antibodies (Table 111.1). In most instances, positive immediate skin test reactions can be elicited and specific IgE antibodies to these antigens can be demonstrated. These patients are usually atopic with the history of allergic rhinitis or eczema. They usually describe asthma symptoms occurring within a few minutes of exposure. There is a good evidence to suggest that specific IgE antibodies to the hapten-protein conjugate are responsible for the patients' symptoms. Occupational asthma due to IgE-dependent etiological agents mostly affects the atopic subjects.

1. *Animal Products:* Laboratory animals are commonly used for experimental purpose. The most common cause of asthma is rats, followed by mice and rabbits. The allergens are usually found in the excreta and secreta of these animals.[16]
2. *Plant Proteins:* Dock workers are exposed to various cereals that can cause, apart from occupational asthma, different syndromes as a result of exposure to organic dust, including allergen-induced airway obstruction and a febrile alveolitis-like condition. Cereals and flours along with isocyanates are the old agents known to cause respiratory symptoms. Wheat is the most commonly incriminated cereal, but soya is also highly allergenic. Bakers are at the risk of developing sensitization not only to various cereal flours they handle at work, but also to storage mites, various other added protein products and enzymes (á-amylase is the most common) that are added to offer better control of processing.[17] Other food additives, such as hemicellulase and papain, used as enzymes in bakeries, can also cause sensitization.

   Gums derived from plants contain high polymer carbohydrates that produce mucilages when they react with water. Common examples include gum acacia or arabic gum, used in the food and pharmaceutical industries; tragacanth, used mainly in printing; karaya, grown in India and used instead of tragacanth. Guar gum, another natural gum, is reported to be responsible for asthma in the carpet-manufacturing industry.[18]
3. *Enzymes:* Association of exposure to detergent enzymes with asthma, nasal and ocular symptoms among workers involved in the manufacture of detergents has been known for several years. These workers show positive skin test reactivity to *Bacillus subtilis alcalase* and develop an immediate or late asthmatic reaction on inhalation challenge.[19] Various occupational allergens of plant and flower origins, beans and gums, can cause occupational asthma. Many ubiquitous allergens can, at times, be considered as occupational allergens. This is the case of grass pollens for municipal workers cutting lawns or mites for hotel employees making beds.[10]
4. *Fish Proteins:* Workers at food processing units develop occupational asthma. Oyster handlers are found sensitized to the "hoya" or "sea-squirt" contaminating oysters, and develops symptoms of rhinitis and asthma. Processing of prawns and snow

TABLE 111. 1: Occupational allergens: High molecular agents

Class	*Agent*	*Occupation or Industry*
Animal proteins	Laboratory animals (hairs, urine, serum, pelts)	Drug, research, breeders
	Bovine proteins	Dairy workers
	Egg white/yolks	Egg processing workers
	Prawns	Prawns workers
	Crabs, prawns, sea squirt	Snow crab workers
	Chicken	Poultry workers
	Pigeon, parakeets	Breeders
	Salmon, trout	Food processing
	Horses	Veterinarians
Plant proteins	Cereal grains, grain dust	Granary workers, millers
	Wheat and rye flour	Bakers, millers
	Buckwheat	Food processors
	Hydrolysed gluten	Food workers, bakers
Enzymes	Subtilisin	Detergent
	Trypsin (hog)	Drug
	Pancreatin	Drug, medical
	Bacillus subtilis	Food processors
	Fungal amylase	Bakers
	Flaviastase	Pharmaceutical
	Pepsin	Pharmaceutical
Legumes	Coffee beans	Food processors
	Soybeans	Farmers, dockworkers
	Castor beans	Fertilizer workers
Seeds	Cotton seeds	Bakers, fertilizer workers, cottonseed oil producers
	Linseed	Linseed products
	Flaxseed	Flax workers
	Tea leaves	Tea processing workers
Insects and ascarides	Grain mites	Granary workers, farmers, dock workers
	Silk (silkworm moth, larvae, eggs)	Sericulture industry workers
	Maggots	Fisherman
	Mealworms	Bait/grain workers
	Cockroaches	Laboratory workers
	River fly	Power station workers
	Locust	Laboratory workers
Enzymes (plant)	Papain	Food processors
	Bromelain	Food processors
Vegetable gums	Gum acasia	Confectionary, pharmaceutical
	Karaya	Food, hair dressers
	Tragacanth	Printing, hair dressers
	Guar	Carpet manufacturing
	Quillaja	Saponin workers
Miscellaneous	Grains	Farmers, distribution workers
	Tobacco leaf	Tobacco farmers and processors
	Garlic	Food workers
	Latex	Surgical gloves manufacturers
	Psyllium	Pharmaceutical
	Fungal spores and antigens	Farmers, biotechnology

crabs can lead to occupational asthma due to the inhalation of vapors released during boiling.

Low Molecular Weight Compounds

Many low molecular weight compounds (MW<1,000 daltons) have been shown to cause occupational asthma in various industries (Table 111.2). In some instances, the compounds have been shown to act as haptens that combine with carrier protein molecules as allergens. The most well-known compounds in this group include acid anhydrides, metals, such as platinum and some pharmaceutical products.

1. *Wood Dusts:* Many different species of wood have been identified as being associated with occupational asthma. Western red cedar is the most common wood dust studied and is the most common type of occupational asthma in the Pacific Northwest. Red cedar asthma affects 4 to 14% of the exposed population, depending on the type of industry and the level of dust exposure.
2. *Metals***:** Exposure to metals may occur not only in metal mining and metallurgical industries, but in a number of other trades, such as welding and soldering. Platinum-induced asthma has been recognized for a long time. Platinum salts, particularly the halides, are more potent in inducing sensitization and asthma than any other metallic salt. In some chemical plants, the cumulative risk for sensitization can be as high as 51% within five years.[20] Smoking is a strong risk factor for a positive skin prick test and predisposes for the development of asthma. A variant of occupational asthma has been reported among pot room workers in aluminum smelters who report respiratory symptoms during a shift at work. The cause of pot room asthma is not known. The occurrence of nickel-induced asthma compared to contact dermatitis among exposed workers is rare. Exposure to zinc and chromium can also lead to asthma in addition to contact dermatitis.
3. *Diisocyanates:* Diisocyanates are used extensively in a number of important industries all over the world. They are used in the production of rigid and flexible foams as protective coatings for electric wiring, for painting automobiles, as adhesives and binders in foundries, as liners for mine and grain elevator chutes, soles of shoes and spandex fibers. All these chemicals have N=C=O groups that are highly reactive and explain their sensitizing properties. The prevalence of diisocyanate-induced occupational asthma is from 5 to 10%.[14] Bronchial biopsies of patients with diisocyanate-induced asthma have shown absence of bronchial IL-4 RNA message, irrespective of response to inhalation challenge, suggesting that this is a non-IgE-mediated disease. Specific IgG and monocyte chemoattractant protein-1 have also been incriminated.
4. *Fluxes:* Colophony is widely used as a flux in electronic industry. Colophony is obtained from pine trees containing abietic acid. The prevalence of work-related respiratory symptoms among electronic workers was 22% and was related to the degree of exposure.[21] Half of the workers with colophony-induced asthma continued to have symptoms even four years after the cessation of exposure.
5. *Anhydrides:* Acid anhydrides are used in making alkyd and epoxy resins. Epoxy resins are widely used in adhesives, casting, coating and sealants, whereas alkyd resins form the base for paints, varnishes and plastics. Acid anhydrides can give rise to hypersensitivity reactions in the exposed population. Phthalate anhydride has long been known to cause occupational asthma and rhinitis. Trimellitic anhydride exposure is associated with asthma, rhinitis, late respiratory systemic syndrome and pulmonary disease-anemia syndrome.[22]

PATHOGENETIC MECHANISMS OF OCCUPATIONAL ASTHMA

Occupational asthma is probably the result of multiple genetic, environmental and behavioral influences and has serious medical and socioeconomic consequences. There are two basic variants of occupational asthma based on its pathogenesis. The allergic variant can be further divided into classic IgE-mediated and polyimmunologic forms. The nonallergic variant can be divided into reactive airways dysfunction syndrome, pharmacologic bronchoconstriction and reflex bronchospasm. Even if the precise causative mechanism of occupational asthma is unknown, several mechanisms have been proposed, i.e. immunological, pharmacological, genetic, and airway and neurogenic inflammation. More than one mechanism may be operative in occupational asthma.

Immunological Mechanisms

Immunologic mechanisms seem to be operative in most of the cases of occupational asthma. In fact, occupational asthma caused by the exposure to HMW compounds is mostly IgE-mediated, while those due to the exposure to LMW compounds is rarely so. During the latency

TABLE 111.2: Occupational allergens: Low molecular agents

Class	*Agent*	*Occupation or Industry*
Wood dusts	Western red cedar (plicatic acid)	Carpenters, saw mill workers
	African maple, ramin wood	Wood workers
	California red wood	Wood workers
	Oak	Wood workers
	Mahogany	Wood workers
Antibiotics	Penicillin	Pharmaceutical
	Spiramycin	Pharmaceutical
	Tetracycline	Pharmaceutical
	Cephalosporins	Pharmaceutical
	Methyldopa	Pharmaceutical
	Piperazine hydrochloride	Chemist
Metal salts	Platinum salts	Platinum refining
	Cobalt	Hard metal workers
	Nickel	Metal plating, welding
	Chromium	Cement tanning
	Aluminum	Aluminium refining
	Vanadium	Vanadium refining
Anhydrides	Phthalic anhydride	Plastics, drugs
	Trimellitic anhydride	Epoxy resins, plastics
	Tetrachlorophthalic anhydride	Epoxy resins
Diisocyanates	Toluene diisocyanate	Isocyanate and urethane manufacturing, adhesives
	Methylene diphenyl diisocyanate	Foundry workers, polyurethane foam
	Hexamethylene diisocyanate	Paint, plastics
	Naphthalene diisocyanate	Plastics
	Iosophorone diisocyanate	Plastics
Dyes	Azo- and anthraquinone, methyl blue, black G-R	Cloth dying
	Paraphenylene diamine	Fur dying
	Persulfate, henna	Hair dressing
Chemicals	Formaldehyde	Laboratory workers
	Glutaraldyhyde	Laboratory workers
	Cyanoacrylate esters	Adhesive use
	Azodicarbonamide	Foam manufacturer
	Formalin	Fur, tanning, insulation
	Hexachlorophene	Hospital staff
	Paraphenylene diamine	Fur dyers
Insecticides	Organophosphates	Farmers, manufacturers
	Pyrethin	Fumigation
Fluxes	Colophony	Electronics
	Amino ethyl ethanolamine	Aluminium soldering
	Fluoride	Aluminium refining
Miscellaneous	Sulfonechloramide	Pharmaceutical, cotton
	Piperazine hydrochloride	Pharmaceutical
	Alpha methyl dopa	Pharmaceutical
	Ethylenediamine	Hair dressing, plastics, rubber
	Ammonium thioglycolate	Beauty operators

period, allergens are processed by alveolar macrophages that present the antigens to the T-helper cells that in turn stimulate B cells to produce specific IgE. Sufficient quantities of antibodies are generated to sensitize circulating basophils as well as the mast cells.[23] High molecular weight agents act as complete antigens, whereas LMW chemicals must first react with autologous or heterologous proteins to produce a functional allergen. Crosslinking of allergens with a specific IgE antibody on the surface of mast cells, basophils and possibly macrophages, dendritic cells, eosinophils and platelets gives rise to a cascade of events that is responsible for inflammatory cell activation. There is subsequent synthesis and/or release of preformed and newly formed inflammatory mediators that then orchestrate the inflammatory reaction.

Pharmacologic Mechanisms

Certain agents in the work place may directly induce bronchoconstriction. Exposure to organophosphates, inhibitors of acetylcholinesterase, causes immediate symptoms of asthma. It has also been suggested that some agents, such as isocyanates and plicatic acid, act through a pharmacological mechanism. Isocyanates may act as beta-2-adrenergic blocking agents and plicatic acid is able to activate complement. The clinical importance of pharmacological mechanisms in occupational asthma is unclear. It is likely that the pharmacological properties of some of the agents in the work environment may interact and potentiate the immunological response in these individuals.[24]

Neurogenic Inflammation

The beta-adrenergic receptor is closely associated with adenylatecyclase, an enzyme present in the plasma membrane of many cells that indirectly controls processes, such as active secretion, transport and storage of carbohydrate. Mast cells in the lungs of asthmatics may have lower concentration of cAMP, which results in the release of the vasoactive mediators that cause asthmatic reaction. An abnormality in the beta-adrenergic receptors has been noted in patients who had asthma from toluene diisocyanate. In addition to the cholinergic and adrenergic mechanisms, Nonadrenergic-Noncholinergic (NANC), neural pathways involving the sensory nerves have been shown to be important in human lungs.[25] This network of unmyelinated sensory nerves contains potent peptides, including substance P, neurokinin A and a calcitonin gene-related peptide. These neuropeptides may play a role in the development of airway inflammation. Dusts, chemicals and other irritants stimulate the sensory nerves to release substance P and related neuropeptides. It has been observed that airways of patients with severe asthma do not contain Vasoactive Intestinal Peptide (VIP) in bronchial mucosa. The absence of this peptide, which is known to relax airways, could amplify the effects of constrictor agents. Inflammatory cells (mast cells, eosinophils, neutrophils) release numerous peptidases that rapidly breakdown VIP. This may be like "taking the brakes off" cholinergic nerves, resulting in an exaggerated reflex cholinergic bronchoconstriction, and contributes to bronchial hyperresponsiveness.[26].Tachykinins (TK) have the ability to affect multiple cells in the airways and to cause responses, such as cough, mucus secretion, smooth muscle contraction, plasma extravasation and neutrophil adhesion. These effects are termed "neurogenic inflammation".

Excitatory neuropeptides, including substance P, neurokinin A and calcitonin gene-related peptide are characterized by rapid onset smooth muscle contractile effects. They constitute unmyelinated sensory nerves and display inflammatory effects. Substance P causes airway smooth muscle contraction, stimulates mucus secretion, increases microvascular permeability and exudation of plasma into the airway lumen, degranulates mast cells, and possibly has chemotactic properties. Neurogenic inflammatory responses are presumably protective in nature. When neutral endopeptidase is inhibited by inhibitors or by exposure to cigarette smoke, respiratory viral infections or inhalation of chemicals (such as toluene diisocyanate), neurogenic inflammatory response is exaggerated.[27] Occupational stimuli which act on capsaic insensitive primary afferents and/or inhibit neutral endopeptidase, could trigger neurogenic inflammation and precipitate asthma.

Genetic Mechanisms

Some of the genetic abnormalities observed in occupational asthma, might provide a means to understand better the interaction between a susceptible genotype and multiple environmental factors. Several models of interactions have been proposed.[28] Not only the gene-environment interactions, but also gene-gene, gene-gene environment, and gene-environment-environment interactions may contribute to the risk of developing asthma. Genetic studies performed in platinum refinery workers suggested that the relative risk associated with the HLA phenotype was greater at lower levels of exposure, indicating that the strength of this association varies inversely with the intensity of exposure to the sensitizing agent.[29] It has been suggested that the most important gene variants for asthma are polymorphisms that exert their influence on the network system controlling biological responses to asthma-related exposures.[30] It has been proposed that specific HLA class II alleles could be involved in susceptibility or resistance to isocyanate-induced asthma, suggesting that the basic molecular and cellular mechanisms of occupational asthma induced by low molecular weight compounds are immunological, as in IgE-mediated asthma, in which the association with HLA class II genes is well-documented.[31] Occupational asthma induced by isocyanates and IgE-mediated asthma differs in terms of their association with particular HLA class II alleles or haplotypes.

DIAGNOSIS

A high degree of suspicion must be maintained in the evaluation of a patient of working age who develops asthma or notices a significant deterioration of preexisting symptoms. In most instances, the diagnosis of occupational asthma can be strongly suspected from the history alone, by finding a temporal relationship between symptoms and occupational exposure.

History and Physical Examination

The history should elicit the features of a work-related airway disease and provide clues to the linkage to one or more suspected work exposures. As expected, the history has a high degree of sensitivity but a low specificity for the diagnosis of occupational asthma. A thorough occupational history starts with a detailed chronologic history of the patient's jobs and exposures.

Patients with occupational asthma may have very typical symptoms of cough, wheezing, and dyspnea and may be able to associate the onset of symptoms to a specific exposure at the workplace. As the condition progresses over several months, symptoms tend to become more severe, to start earlier and last longer, to have nocturnal symptoms, and to impinge on the weekends. If the condition is not recognized and the cause eliminated, continued exposure will often lead to persistent severe asthma indistinguishable from that occurring in a nonoccupational asthma.[4] Remissions initially occur on holidays, but even this feature may disappear after a sufficiently prolonged exposure.

The physical examination may be specific but tends to be insensitive. It is important to establish objectively a relationship between work and asthma symptoms. Specific challenge tests or occupational exposure tests are often considered a reference standard for the diagnosis of occupational asthma. American College of Chest Physicians,[4] recommends that in individuals with suspected sensitizer-induced occupational asthma, in addition to carefully documenting the occupational history, one should perform additional objective tests when feasible (e.g. serial Peak Expiratory Flows (PEFs), serial methacholine challenges, immunologic assessments, induced sputum testing, and specific inhalation challenge testing) to improve the diagnostic probability. Since there are no physical examination findings specific for asthma and because work-related wheezing is difficult to detect, repeated pulmonary function testing (both at and away from work) is usually required in order to make the diagnosis of occupational asthma.

Pulmonary Function Testing

Pulmonary function studies are indispensable in the diagnosis and assessment of the severity of occupational asthma. Most importantly, there should be no doubt that reversible airflow obstruction exists. Before one can label a person suffering from occupational asthma, he should be diagnosed to be indeed suffering from asthma, which can be done by routine spirometry with bronchial reversibility pattern. A change of more than 15% in Forced Expiratory Volume$_1$ or Forced Vital Capacity (FEV$_1$ or FVC) from baseline values, or improvement in FEV$_1$>200 ml over baseline is the diagnostic of asthma. Once the diagnosis of asthma is achieved, the next important aspect is the documentation of work-related changes in pulmonary function. A single measurement of pulmonary function is not helpful in diagnosing occupational asthma. Pulmonary function measured on a day away from work may be normal in up to half of those with occupational asthma. Serial measurement of spirometry when the patient has been away from work for a time and repeated when the patient returns to work, if coupled with an appropriate change in symptoms, may help to confirm an association with the work environment.[32] Preshift and postshift measures of FEV$_1$ are not generally helpful to either confirm or refute a diagnosis of occupational asthma. The availability of portable, inexpensive devices has allowed physicians to monitor PEF at work and away from work. Coupling PEF monitoring and changes in Nonallergic Bronchial Responsiveness (NABR) for periods at work and away from work has also been proposed for the diagnosis of occupational asthma. A serial peak flow meter recording is most frequently used and is the most easily accessible test. The best time to identify changes in PEF from workplace exposures is when the patient with underlying asthma is as stable as possible. A more sophisticated method of analysis of PEFR, which is based on a computer-generated discriminant analysis (OASYS-2; OASYS Research Group, Midland Thoracic Society; Birmingham, UK) can also be used and this is now commercially available and uses a different method of plotting results.[32a]

The currently recommended method is for the patient to record his or her peak flow at least four times daily (on awakening, middle of work shift or lunch, end of work shift and before bed). At each time point, patients should perform the maneuver three times and record each result in a log. The optimal duration of the recording is for at least 2 weeks at work, including the weekends, followed by one to two weeks away from work. At present, a graph of the daily maximum, mean, and minimum flow is inspected visually to check for deterioration at work and improvement away from work. The results can be plotted and then visually interpreted to determine whether there is a pattern of worsened PEF during work weeks compared with days or weeks off work.

Nonspecific Bronchial Inhalation Challenge

The measurement of bronchial responsiveness may be beneficial in the assessment of the patient with occupational asthma. A positive challenge result supports a clinical diagnosis of asthma when baseline pulmonary function is normal. A negative study however, does not rule out asthma, particularly when the patient has been away from exposure for a period of time. Serial measurements of airway responsiveness in conjunction with prolonged recording of PEF provide the objective evidence of sensitization with the occupational agent. It can also serve as a good guide to the initial dose of occupational agent that can be safely given during a specific bronchial provocation test.

Skin Test and Serology

Skin testing with common allergens, such as the house dust, danders, and grass and tree pollens may be useful in determining the atopic status of an individual. In few circumstances, especially with high molecular compounds, appropriate extracts of potential occupational allergens are available for skin testing.[33] Skin testing with flour and wheat has a sensitivity of 96% and specificity of 81% for Baker's asthma.[34] Extracts of animal products, flour, coffee and castor beans have been shown to cause immediate skin test reactions in susceptible individuals. An important practical limitation is the general lack of standardized commercial skin test reagents for many occupational proteins. Nevertheless, non-standardized commercial reagents are widely available and can be used for skin-prick tests of food (e.g. wheat, rye extracts) and laboratory animals (e.g. mouse, rat and guinea pig).

Total serum IgE may be useful in monitoring the patients. The use of immunologic testing in the diagnosis of allergic occupational asthma is limited. Specific antibodies, such as IgE antibodies to various occupational allergens may be demonstrated by radioallergosorbent test and enzyme-linked immunosorbent assay. Although serologic testing is highly specific, it is often less sensitive indicator of sensitization than skin testing.

Specific Inhalation Challenge Testing

This test is still considered the gold standard in the confirmation of the diagnosis of occupational asthma. Originally performed in the laboratory and aimed at mimicking work exposure, it can also be done at the workplace. It is necessary to identify the substance at fault. In this test, the patient is exposed to the suspected sensitizer in a way in which he might be exposed at the workplace, although in a setting where symptoms are controlled and lung functions measured.

The most usual response to a challenge test is an immediate fall in flow rates, lasting for up to an hour. Typical patterns of bronchial reactions have been described.[35] Immediate reactions are those that shows maximal response 10 to 30 minutes after exposure, with complete recovery within one to two hours; they are actually the most dangerous, as they can be severe and unpredictable, stressing the importance of progressive exposure. Late reactions develop slowly and progressively, either one to two hour (early late) or four to eight hour (late) after exposure; they may occasionally be accompanied by fever and general malaise. They generally respond well to an inhaled beta 2-agonist, although the response may be of shorter duration in some subjects. Dual reactions can also occur.

In general, the diagnosis of occupational asthma can be firmly established in subjects who develop an asthmatic reaction with a greater than 20% fall in FEV, following exposure to sub-irritant level of an offending agent. However, a negative challenge test cannot exclude the diagnosis of occupational asthma with certainty.

MANAGEMENT

The algorithm for approach to the management of a patient with occupational asthma is shown in Figure 111.1. The mainstay of treatment of occupational asthma

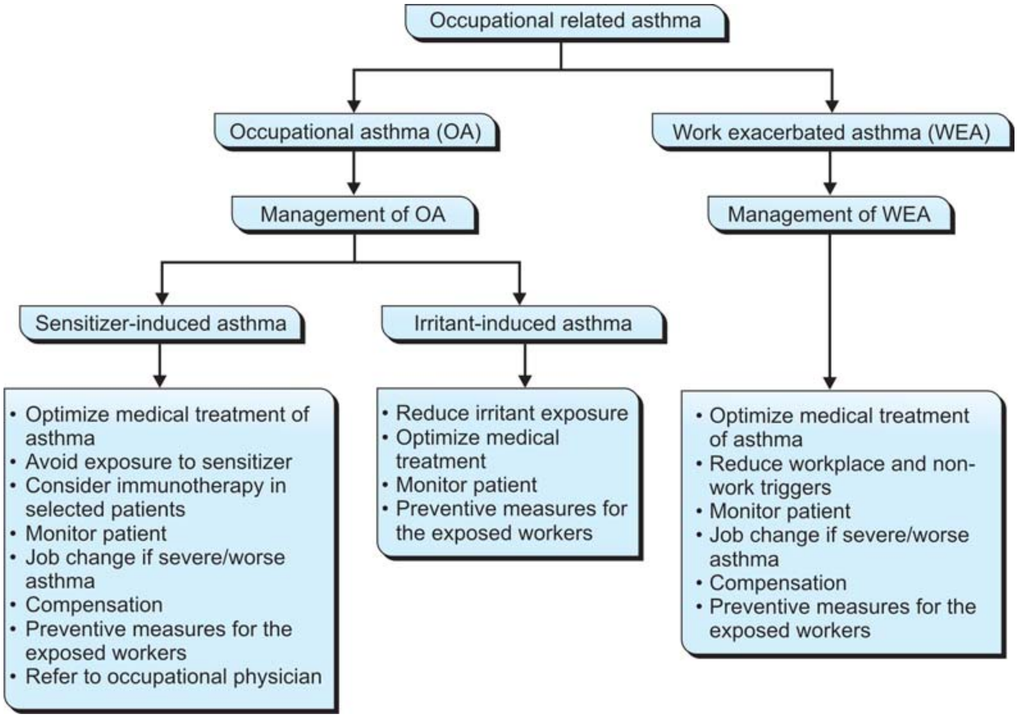
Occupational related asthma
Occupational asthma (OA)
Work exacerbated asthma (WEA)
Management of OA
Management of WEA
Sensitizer-induced asthma
Irritant-induced asthma
• Optimize medical treatment of asthma
• Avoid exposure to sensitizer
• Consider immunotherapy in selected patients
• Monitor patient
• Job change if severe/worse asthma
• Compensation
• Preventive measures for the exposed workers
• Refer to occupational physician
• Reduce irritant exposure
• Optimize medical treatment
• Monitor patient
• Preventive measures for the exposed workers
• Optimize medical treatment of asthma
• Reduce workplace and non-work triggers
• Monitor patient
• Job change if severe/worse asthma
• Compensation
• Preventive measures for the exposed workers

Fig. 111.1: Approach to the management of a patient with occupational asthma
Adapted from Reference no. 4

is prompt diagnosis and removal of the worker from further exposure to the inciting agent if substitution with a less hazardous substance is not possible. This is crucial in cases of sensitizer-induced occupational asthma, because even a very low exposure may trigger asthmatic reactions, including acute severe asthma attack. In most of the cases, the ideal solution is for the patient to be redeployed by the employer to a different work in a place where further contact with the sensitizer is not possible. If this is not possible, in many cases, the patient may need to work elsewhere, although this often entails financial hardship and an issue of litigation.[36] In some cases, workers with irritant-induced or work-aggravated asthma may continue to work in their usual jobs if the exposure to the inciting agent is diminished via proper engineering controls or by using respiratory protective equipment.[37] In the case of exposure to organic substances e.g. animal antigens and wood dusts, it may be possible to combine good local exhaust ventilation, partial enclosure of processes, and respirator use to reduce exposure, sufficient enough for the person to continue to work along with the use of medication. In such situations, patients should continue anti-inflammatory medicines and monitor their peak flow rates on regular basis. In cases of sensitization to LMW agents like isocyanates, acid anhydrides and colophony, redeployment or change of job is generally required.[36]

The management of occupational asthma does not differ significantly from the management of asthma that is not work related. The patient should be made aware of the need to balance future employment prospects against future risk. Once the diagnosis of occupational asthma has been made, the information should be given specifically (preferably in writing) to the patient who should be advised that the prognosis is improved by early complete removal from exposure. Continued exposure to the sensitizing agent may lead to greater airway inflammation and potentially, more airway remodeling and lower FEV_1.[38] When patient is unwilling or unable to leave a job, the initiation of anti-inflammatory and bronchodilator therapy may be the only management option available to the clinician, although the patient should be educated to understand that continued exposure may lead to a worse outcome; it is essential that patients have careful medical monitoring so that any worsening of asthma can be detected early and further interventions applied. It has been demonstrated that inhaled corticosteroids induce a small, but significant overall improvement in patients with sensitizer-induced occupational asthma after withdrawal from exposure. Inhaled corticosteroids have been found to be more beneficial if administered earlier rather than later after the diagnosis is established.[36]

Allergen immunotherapy is a possible treatment option for patients with sensitizer-induced occupational asthma, but there is limited evidence to support its efficacy.[39] Immunotherapy could be considered in settings where occupational asthma due to a specific allergen has been established, when only one or a few allergens are clinically linked to disease, when the avoidance of the triggering allergen is impossible, and when standardized allergens extracts are available for treatment. There are a limited number of studies of immunotherapy with allergens of potential occupational relevance such as for natural rubber latex for health care workers, venom from stinging insects for beekeepers, wheat for bakers, grass or ragweed pollen for outdoor workers and cat allergen for animal workers. Subcutaneous immunotherapy has been shown to be effective in reducing workplace symptoms, specific skin reactivity and medication use, but has not yet been shown to improve the clinical course of occupational asthma.[40,41]

PROGNOSIS

The long-term consequences of occupational asthma are variable and require prolonged follow-up. Symptoms due to occupational asthma may remit when the condition is diagnosed early and the worker is removed from further exposure. More commonly, the occupational exposure leads to persistent symptoms and permanent bronchial hyperresponsiveness.[42] A favorable outcome is noted with a shorter duration of symptoms before the diagnosis, relatively normal pulmonary function and a lesser degree of bronchial responsiveness. Persistent symptoms after the cessation of exposure were associated with a longer duration of symptoms, abnormal pulmonary function and more marked levels of bronchial responsiveness.

PREVENTION

As all occupational asthma cases are potentially preventable and given the high incidence of disease worldwide, better prevention efforts are required. Control of the exposures causing asthma is the most direct way of reducing the number of incident cases. No control measure can be assumed to eradicate asthma short of elimination of the causal agent.[43] Consideration should be given to the surveillance of exposed workers, especially in the first two years of work, preferably by a simple questionnaire of nasal and respiratory symptoms. [36]

Primary Prevention

Elimination of the sensitizing agent is the most secure way of preventing exposure. Substituting a new agent for the causative one in the workplace should be emphasized as the first step in the primary prevention. Other methods of primary prevention includes the reduction of exposure to the sensitizing agent, restriction of employment to the sensitizing environment, control of smoking and other respiratory irritants, and use of respiratory protection devices such as respirators.[43,44] Despite some important efforts with regard to HMW sensitizers, more exposure-response data on LMW sensitizers and irritants are critical to develop effective primary prevention programs. [45]

Secondary Prevention

Secondary prevention aims at early detection of asthma especially among workers in high-risk industries, such as the spray painting industry, where there is a high exposure to diisocyanates.[43] Periodic screening tests should be used to identify the persons at risk during the employment. A wide variety of questionnaires can be used for the symptomatology. Spirometry and immunological tests, where available, are to be used for the identifications of the asthma for the persons at risk.[4] Hence the main objective of secondary prevention is to evaluate the workplace to identify and prevent other cases of occupational asthma in the same setting.[46]

Tertiary Prevention

Tertiary prevention applies to individuals who have already been diagnosed with occupational asthma. It includes the institution of appropriate treatment and an effort to prevent permanent asthma by early removal from exposure.[47] Unfortunately, although this leads to symptomatic improvement, it may not prevent the development of persistent asthma.[48]

Another essential component in the prevention of occupational asthma is the surveillance for occupational asthma in the workplace. Risk assessment in the workplace is designed to minimize workplace risk associated with various hazards.[49] Engineering controls should be instituted in order to lower the risk of exposure to irritants and sensitizers, when substitutes cannot be found. Fundamental to this process is to identify all potential inhaled hazards and to assess the associated risk in that particular workplace. For example, isocyanate spray paints are hazardous when inhaled, but probably pose little risk when in solution form prior to activation.[50] It is the act of mixing these chemicals with an activator and aerosolizing these while spraying that is associated with a significant risk.

SUMMARY

Occupational asthma is currently the most common form of occupational lung disease in the developed world. The prevalence of this disease is likely to remain high for many years to come, because about 250 industrial agents are known to cause the disease and new chemicals are continuously being introduced into the workplace. Early in disease onset there is often an association with the workplace, although this relationship may wane over time and continued exposure. The diagnosis is generally established on the basis of suggestive history of a temporal association between exposure and the onset of symptoms and objective evidence that these symptoms are related to airflow limitation. Occupational asthma management differs from environmental asthma in two important ways. The first is the emphasis on functional outcomes. The goal and mark of successful therapy are improved work capacity and return to work. The second difference incorporates a public health approach to treatment. If the patient is exposed and has disease, then coworkers may also develop disease. Control of occupational asthma rests on the control of exposure by restricting the patient from direct or indirect exposure to the inciting chemical or process. Prevention of new cases is the best approach to reducing the burden of asthma attributable to occupational exposures.

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112

Hypersensitivity Pneumonitis

PS Shankar

DEFINITION

Hypersensitivity Pneumonitis (HP) or extrinsic allergic alveolitis is a complex group of immunologically-mediated alveolar and interstitial lung disorders caused by repeated inhalation of a wide variety of airborne allergens. Several different kinds of environmental, occupational and recreational organic antigens, as well as the low-molecular weight chemical agents are responsible for hypersensitivity reactions in significant numbers of affected individuals to which they have been previously sensitized.

Most of these conditions exhibit similar clinical features, which develop several hours following environmental exposure.

HP was first observed by Jon Finsen in 1874 in the farmers of Iceland who inhaled hay that had been molded in the barn. Later, it was recognized in British farmers following work with hay and was described as farmer's lung in 1932 by Campbell.[1] Since the environmental antigens are ubiquitously distributed, this form of interstitial lung disease is more frequently recognized in the recent decades. New examples of HP are constantly being added due to changing environmental exposure.

ETIOLOGY

The inhaled antigens leading to development of HP can be classified as bacteria, fungi and their components (spores, mycelial fragments, degraded substrates and toxins), animal proteins and low-molecular weight chemicals (Table 112.1).

TABLE 112.1: Some of the common antigens responsible for different hypersensitivity pneumonitis

Causative agent	*Examples*
Bacteria	Thermophilic actinomycetes *Bacillus subtilis* *Klebsiella* spp *Pseudomonas* spp *Streptomyces alba* *Epicaceum nigrum* *Mycobacterium avium* complex
Fungi	*Aspergillus* spp *Alternaria* *Trichosporon cutaneum* *Cephalosporium* spp *Cladosporium* *Penicillium*
Animal proteins	Avian, Bovine, Porcine material, feather, silkworm larvae and insect material
Chemical sensitizers	Isocyanates, acid aldehydes, pyrethrum

A wide variety of antigens, usually organic compounds of biological origin from bacteria (thermophilic actinomycetes, *Bacillus subtilis)*, fungi (*Aspergillus* species, *Trichosporon cutaneum*) moulding stored vegetable matters (hay, barley, bagasse) and animal protein (avian, bovine, porcine or insect material) and reactive low-molecular weight chemicals used in industry, such as isocyanates are responsible for initiating hypersensitivity pneumonitis (Table 112.2). The changing practices of agriculture and industry have resulted in recognition of newer forms of HP.

TABLE 112.2: Common hypersensitivity disorders and their relationship to different exposures and antigens

Exposure	*Antigens*	*Diseases*
Mouldy hay[2]	Thermophilic actinomycetes	Farmer's lung
Mouldy bagasse[3]	Thermophilic actinomycetes	Bagassosis
Mouldy compost and mushroom[4]	Thermophilic actinomycetes	Mushroom worker's disease
Contaminated barley[5]	*Aspergillus clavatus*	Malt worker's lung
Compost[6]	*Aspergillus* spp.	Compost lung
Esparto grass[7]	*Aspergillus* spp.	Esparto dust lung
Soy sauce brewing[8]	*Aspergillus* spp.	Soy sauce lung
Contaminated humidifiers, air conditioners, heating systems[9]	Thermophilic actinomycetes	Ventilator lung
Domestic birds[10]	Bird proteins	Bird fancier's lung
Pigeon droppings[11]	Serum, feathers, droppings	Pigeon breeder's disease
Parakeets[12]	Serum, feathers, droppings	Budgerigar fancier's lung
Silkworm larvae[13]	Silkworm larvae proteins	Sericulturist's lung
Grains[14]	Grain weevil	Grain lung
Isocyanates[15]	Altered proteins	Hypersensitivity pneumonitis
Wood cutting[16]	Plant protein	Woodman's disease
Contaminated metal working fluid[17]	*Pseudomonas* spp	Machine operator's lung
Detergent enzymes[18]	*Bacillus subtilis*	Detergent worker's disease (washing powder lung)
Contaminated basement[19]	*Cladosporium* spp, *Penicillium* spp	Basement lung
Contaminated hot tub water[20]	*Mycobacterium avium* complex	Hot-tub lung
House dust[21]	*Trichosporum asahii*	Japanese summer house hypersensitivity pneumonitis

The risk of development of HP depends on the nature of inhaled antigen, the circumstances of exposure and the immunologic status of the host. The exposure is often to a complex mixture of antigens and not to a single antigen.[22]

The reaction occurs in a person, previously sensitized by exposure to the antigen and it does not depend on the constitutional makeup of the individual. The condition develops predominantly in non-atopic persons who may become sensitized to organic dust due to repeated exposure. An acute allergic alveolitis develops from exposure to high concentrations of antigen, repeated exposures to smaller amounts of dust is likely to cause chronic disease. The bacterial and fungal antigens found in the internal environment offer ideal circumstances for their proliferation. Inhalation of such material incites a hypersensitivity lung disease. Indoor bacteria (*Bacillus subtilis*), which thrive at lower temperature can lead to the development of HP.

Farmer's lung is the classical example resulting from exposure to mouldy hay, straw or grains. When the hay has been harvested while damp and stored under conditions of high humidity and temperature in barns and grain storage silos, it facilitates proliferation of the thermophilic actinomycetes-*Micropolyspora faeni* (now called *Saccharopolyspora rectivirgula*) in the organic matter. These spores are about 1 micron in diameter. The inhalation of dust from mouldy hay while feeding the live-stock, handling of mouldy straw or during threshing of mouldy grain crop, allows entry of the spores into the respiratory tract and their deposition in the alveoli in large amounts. The antigens liberated from such material leads to widespread reaction mediated by precipitins. The condition is seen in agricultural workers who handle mouldy hay or other mouldy vegetable products.

There are many similar diseases resulting from exposure to organic dusts. The thermophilic actinomycetes - *M. faeni* is considered responsible for bagassosis and mushroom picker's lung. The former appears following the inhalation of mouldy overheated sugarcane bagasse and the latter from mouldy mushroom compost dust. Those exposed to mouldy barley, mouldy cheese or coffee bean result in the manifestation of malt-worker's disease, cheese worker's lung and coffee worker's lung, respectively, where the *Aspergillus clavatus*, *Penicillium casei* and coffee bean dust act as sensitizing antigens.

People exposed to pigeon droppings and budgerigar (turkey pigeon) droppings are sensitized to avian serum proteins and result in pigeon fancier's lung and budgerigar lung disease, respectively. Improperly maintained or contaminated air conditioners or humidifier systems in offices and factories can provide a suitable environment for the growth of thermophilic actinomycetes.

HP induced by chemicals is relatively less common, compared to those induced by microbial and animal proteins. Isocyanates such as toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), hexamethylene diisocyanate (HDI) and 1,5 naphthalene diisocyanate (NDI), used in the production of polyurethane polymers, are the commonly reported chemicals responsible for HP.

PATHOGENESIS

Pathogenesis of hypersensitivity pneumonitis involves a complex sequence of immunologic events in a susceptible and sensitized host. It does not develop on the atopic background. The condition is neither associated with eosinophilia nor raised levels of IgE. The sensitization results from an earlier exposure to antigen (organic dust). Following an intense reexposure to such an antigen, there is interaction of the antigen and the "memory" system. There is formation of precipitins and complement fixing antibodies and they form immune complex aggregates of antigen-antibody to bring about systemic and pulmonary reactions.

The demonstration of precipitins against the thermophilic actinomycetes in the serum and a delay of three to eight hours before the onset of symptoms following exposure to the antigen suggest that the pulmonary and systemic disturbances are as a result of an immune complex-mediated Arthus reaction. The immune complexes are not demonstrable in the alveolar septa or in the granuloma. It is considered that there is a mononuclear leucocyte-mediated component in the pathogenesis of HP.

A delayed type hypersensitivity reaction also to a certain extent is likely to be responsible for the development of chronic disease.[23] Animal models support the importance of cell-mediated immunity.[24] This view is strengthened by the presence of a higher proportion of lymphocytes in the bronchopulmonary lavage fluid. It implies that a local sensitivity may play an important role in the development of the disease.[25]

Though a large number of persons get themselves exposed to a given antigen and develop antibodies to that antigen, only a small number of them develop symptoms. Probably it is dependent on host susceptibility and the amount of antigen inhaled. The host susceptibility may also depend upon the differences in the persistence of noxious agent, environmental factors, the polymorphism and other genetic factors.[26-29] Some of the HPs, such as the farmer's lung are known to have familial aggregation, suggesting the importance of genetic predisposition.

PATHOLOGY

Following antigen exposure, the inhaled antigen reaches the alveolar space where it crosses the alveolar endothelium and binds to circulating antibody creating immune complexes that get deposited in the lung. There is an inflammatory response. The acute phase is mediated by neutrophils and the chronic phase by lymphocytes and macrophages in the form of a delayed-type hypersensitivity response. This is likely to lead to the formation of granuloma and progress to fibrosis.

Acute HP is characterized by diffuse alveolar damage with necrosis. There is an acute inflammatory infiltrate. Pathologic abnormalities are observed in subacute and chronic forms of the disease. Subacute form is characterized by the irregular areas of patchy consolidation with a centriacinar distribution. There are interstitial lymphocytic infiltrates, cellular bronchiolitis and loosely formed non-necrotizing granulomas. The small and poorly circumscribed granulomas consist of the aggregates of lymphocytes, plasma cells, macrophages and multinucleated giant cells. Presence of eosinophils and neutrophils are not characteristic. There is interstitial fibrosis with honeycomb changes in the chronic forms of disease. These changes are similar, irrespective of the causative antigens.

CLINICAL PRESENTATION

Hypersensitivity pneumonitis is a multifaceted clinical syndrome, which may mimic almost any interstitial lung disease, some infectious diseases and even bronchiolar disorders.[30] It presents predominantly with symptoms of dyspnea and cough. The condition may have an acute, subacute, or chronic onset. However, the manifestations frequently overlap. The manifestations are systemic and pulmonary. The systemic reactions are indistinguishable from that of infection.

High intensity short duration exposure leads to acute hypersensitivity pneumonitis. Acute condition presents with fever, chills, dyspnea, myalgias, arthralgias, headache, cough and chest tightness, 4 to 8 hours following a heavy exposure to the antigens. The symptoms peak in 6 to 24 hours following the exposure. Generally, the attack is self-limited and resolves in 1 to 3 days, following removal of the patient from the source of antigens. The continued exposure results in the persistence of symptoms. Physical examination usually reveals the presence of fever, tachypnea and bibasilar crackles.

The subacute form of disease is characterized by a slowly progressive symptomatology interspersed by discrete attacks of respiratory symptoms following heavy antigen exposure. In subacute form, the clinical features develop insidiously over a period of weeks. Cough and dyspnea are generally prominent. In some patients, the subacute form of the disease may permit the occurrence of an acute presentation especially if exposure to antigen persists.

In chronic condition, the level of antigen exposure is generally much lower and persistent. The respiratory manifestations develop slowly over months or years without any discrete attack suggesting the antigen as an offending agent. The patients suffer from increasing breathlessness, nonproductive cough and weight loss. Fever is usually absent. Examination reveals the presence of tachypnea and bibasilar crackles. Digital clubbing is uncommon. It is worth noting that the acute forms do not necessarily evolve into a chronic form of disease. It is intriguing why the consequences of antigen inhalation and the natural history of the disease process exhibit variations among individuals with the similar levels of the same antigen exposure. Moreover, only few individuals exposed to the antigens develop HP.

The clinical manifestations depend on the periodicity and the intensity of exposure. It may be either intermittent and heavy exposure or regular exposure in smaller dosages. Those who are exposed for limited duration intermittently to a relatively heavy concentrations of antigen as in the case of farmers involved with the mouldy hay and the pigeon fanciers engaged with cleaning of the pigeon lofts, manifestations that occur three to four hours after exposure reach a maximum in seven to eight hours and subside within 24 hours. The patient is able to associate his symptoms with the dust exposure. The incidence of serious disability can be stopped if the exposure is avoided or terminated. In those who expose continuously to smaller concentrations of antigen as seen in budgerigar fanciers, there is no acute history, and the features develop insidiously and progress to gross irreversible changes with fibrosis. The features of cor pulmonale and right ventricular failure ultimately supervene.

INVESTIGATIONS

Patients with acute HP exhibit polymorphonuclear leucocytosis without eosinophilia. Bronchoalveolar lavage (BAL) fluid shows the presence of neutrophils initially.[31] Later, it is replaced by lymphocytes. These lymphocytes are made up of $CD8^+$ lymphocytes.[32] During acute HP, there is increase in erythrocyte sedimentation rate and the inflammatory markers, such as the C-reactive protein. BAL lymphocytosis may persist for a long period of time after removal of antigen exposure.

The chest radiograph may be normal especially if obtained during an asymptomatic phase. In an established and symptomatic case, the radiograph shows the presence of patchy or diffuse infiltrates. Advanced cases exhibit pulmonary fibrosis with linear interstitial opacities, distortion, volume loss, and honeycombing. In acute HP, chest radiographs demonstrate a fine micronodular pattern or diffuse patchy ground-glass opacity.[12] They are characteristically seen in the lower lobes. These shadows resolve completely following cessation of exposure. HP is not associated with pleural effusions or thickening, and hilar or mediastinal lymphadenopathy. High resolution computed tomography (HRCT) is highly sensitive than the plain chest radiographs in detecting changes in the lung interstitium. It characteristically shows small, indistinct nodules, ground glass infiltrates and air-trapping.

In subacute form of disease, small nodules and fine linear opacities may be seen. In chest radiographs, chronic HP reveal the evidence of interstitial fibrosis manifested by diffuse linear and nodular radio densities. There is volume loss and honeycombing. These changes are predominantly noted in the upper lobes than in the lower lobes. There is evidence of pleural effusion or thickening. HRCT shows multiple, centrilobular nodules throughout the lung fields. These radiological ground glass opacities lead to volume loss and honeycombing.[33] Emphysematous changes may be seen in the lower lung zones in nonsmokers.

Exposure to an antigen is confirmed by the presence of elevated titers of serum antibodies (IgG, IgM and IgA). They can be demonstrated by utilizing ELISA, indirect immunofluorescence, complement fixation, latex agglutination or agar-diffusion methods. It suggests that the patient has been exposed to the suspected antigen and has mounted an immune response. The presence of antibody merely indicates the occurrence of exposure and sensitivity and not necessarily the disease.[34] It should be noted that the serum antibodies tend to disappear following the cessation of exposure to antigen. Several different cytokines involved in the disease pathogenesis have been demonstrated to rise in HP.[35,36] At present, they have no role in the diagnosis or clinical assessment of disease.

Pulmonary function tests may be normal or show restrictive, or mixed restrictive and obstructive patterns of defects. In acute HP, there is restrictive defect with a decreased forced vital capacity, total lung capacity and diffusion capacity. Mild obstructive defect may be seen due to bronchiolitis obliterans. The diffusing capacity is generally decreased. Arterial hypoxemia is evident especially after exercise.[37] The pulmonary function tests may be within normal limits in subacute HP. Chronic HP reveals both restrictive and obstructive defects. There is decreased diffusing capacity and hypoxemia. HP should be considered in differential diagnosis in nonsmoking individuals presenting with airflow limitation. Skin tests demonstrate immediate or delayed type of hypersensitivity against the suspected antigens. However, it has not shown its usefulness as often there are nonspecific reactions. Inhalation challenge tests for suspected antigens may be helpful in confirming the diagnosis.

Lung biopsies from patients with chronic HP show chronic interstitial inflammation with infiltration of plasma cells, macrophages and lymphocytes. They are found adjacent to the bronchioles. There are poorly formed, noncaseating granulomas without any necrosis. There may be bronchiolitis, bronchiolitis obliterans and sometimes with organizing pneumonia. In addition, there are varying degrees of interstitial fibrosis. Transbronchial lung biopsies may fail to provide sufficient material for the histopathologic study, open lung biopsy is preferred in such a situation.

DIAGNOSIS

The diagnosis of hypersensitivity pneumonitis is considered as one possibility in most cases of undiagnosed interstitial lung diseases. The patient has to be questioned about potential occupational and home exposures. A detailed history with special reference to the appearance of symptoms and the work history and activities of the person has to be obtained. History of exposure to pets (particularly the birds), chemicals used in gardening, and the details of indoor environment have to be obtained. Acute hypersensitivity pneumonitis is often confused with pneumonia, secondary to viral or mycoplasma infections. Recurrent episodes of similar symptoms should suggest hypersensitivity disorder of the lungs and search should be made for the relevant exposure. The clinical diagnosis of the HP is made on the basis of diagnostic criteria (Table 112.3). The diagnosis is confirmed if four major and at least two minor criteria are present, in the absence of other disease with similar findings.[38]

TABLE 112.3: Diagnostic criteria for hypersensitivity pneumonitis

Major criteria

1. History of compatible symptoms that appear or worsen within hours after antigen exposure
2. Exposure confirmation based on history, environmental investigations, serum precipitin testing and/or BAL antibody
3. Compatible abnormalities on chest radiograph or HRCT
4. BAL lymphocytosis
5. Compatible histologic changes on biopsy, and
6. Positive natural challenge(reproduction of symptoms and laboratory abnormalities after exposure to the suspected environment) or by controlled inhalation challenge

Minor criteria

1. Basilar crackles on lung examination
2. Decreased diffusion capacity, and
3. Arterial hypoxemia at rest or with exercise

Differential diagnosis is important from few other syndromes, which may present with similar clinical manifestations. For example, inhalation of organic dusts may result in organic dust toxic syndrome (ODTS), which unlike HP, may occur in any individual without any prior sensitization. The condition may be noted in a large number of people exposed to a great amount of organic dust. Patients suffering from this experience fever, dyspnea and nonproductive cough. There is leucocytosis and BAL fluid reveals presence of neutrophils. The condition is not associated with any characteristic radiologic abnormalities. It does not lead to any permanent lung damage.[39]

Exposure to the etiological agents of humidifier lung may also result in a non-HP syndrome, the humidifier-fever. Again, the sensitization is not required. The condition exhibits with fever, chills, myalgias, arthralgias, headache, malaise, cough and dyspnea. These features are noted 4 to 12 hours following exposure. There is leucocytosis. The clinical manifestations recede in 12 to 24 hours after cessation of exposure.

Chronic HP exhibits with features of Idiopathic Pulmonary Fibrosis (IPF). The hypersensitivity pneumonitis is distinguished from IPF on the basis of a detailed history of occupational and vocational history. One should make every effort to establish a link between a particular exposure either at work or at home and earlier episodes of similar manifestations. Further, it should be possible to demonstrate the presence of serum antibody to an agent known to cause hypersensitivity pneumonitis. IPF, on the other hand, is a progressive disorder without any recognizable exposure or antibody response.

Proof of repetitive symptoms, laboratory and radiological abnormalities associated with exposure to a particular environment helps in arriving at a diagnosis of hypersensitivity pneumonitis. It has to be confirmed by the demonstration of abnormal white cell count, abnormal chest radiograph or HRCT scan, decreased diffusing capacity or arterial hypoxemia. Lung biopsy confirms the diagnosis.

PROGNOSIS

Hypersensitivity pneumonitis pursues a variable course. If the condition is recognized early, the recovery is generally expected. Generally, the manifestations of acute HP regress after a short interval following stoppage of exposure. Pulmonary functions return to normality within 2 weeks after an acute attack. When the acute attacks are recurrent, the symptoms may persist and lead to progressive lung impairment. The subacute or chronic HP exhibits insidious onset of symptoms. Often the conditions are recognized later in the course of illness, it makes the prognosis unfavorable. The condition may exhibit features of emphysema in later stages of farmer's lung disease or fibrosis in bird breeder's disease.[40,41] Continued exposure to an inciting antigen leads to an accelerated decline in lung functions.

PREVENTION

Hypersensitivity pneumonitis is essentially preventable by avoiding the inciting antigens. The acute episodes are self-terminating and subside if the patient is removed from the antigen-containing environment. Those who continue to be exposed to the antigen for a prolonged period of time develop symptoms insidiously and exhibit a progressive functional deterioration with the development of structural changes within the lung.

The drying of hay minimizing its moisture content and pretreatment of sugarcane bagasse reduces the occurrence of farmer's lung and bagassosis, respectively. The avoidance of birds is essential in bird fancier's lung disease.

MANAGEMENT

Early diagnosis of HP is essential as it facilitates the avoidance of suspected antigen. Avoidance of the offending antigen forms the cornerstone of therapy. It may necessitate change in occupation and hobbies to enable complete avoidance of antigens. There is a need to bring about change in the work environment and improve ventilation so as to minimize exposure. Efforts are made to minimize growth of an offending organism in the environment and removal of the contaminated source. The workers should wear properly fitted masks during exposure.

Persons suffering from acute manifestations respond to administration of corticosteroids. However, the utility of corticosteroids in chronic condition is not proven. A short course of corticosteroids hastens recovery and further stoppage of exposure to dust in the early stages revert the lung to the original condition. Prednisolone, 40 to 60 mg daily is given to achieve an improvement. It is continued for two or more weeks or until there is resolution of clinical and radiological abnormalities. The dose is then gradually tapered after demonstrating objective improvement in pulmonary functions. Bed rest and supplemental oxygen inhalation are advocated. When irreversible fibrosis has developed as in budgerigar's disease, steroids are not helpful and the withdrawal from contact with budgerigars shows limited improvement. The removal of contaminated air-conditioner or humidifier is essential to prevent humidifier pneumonitis.

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Toxic Inhalations and Thermal Lung Injuries

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INTRODUCTION

The airways and lung parenchyma are in constant contact with the external environment and thus are especially vulnerable to damage by toxic or irritant substances released in the atmosphere. A person can be exposed to such toxic materials as a result of industrial disasters,[1,2] occupational exposures,[3,4] recreational mishap,[5] natural catastrophe,[6] chemical warfare[7] and acts of terrorism.[8, 9] The inhalation of smoke results in a series of pathophysiological events involving the respiratory and circulatory systems. Upper airway injury is mainly due to heat damage. The lesions of the tracheobronchial and parenchymal areas are mostly related to the chemicals present in the inhalants. Lung damage may take place even after a single exposure to an irritant gas, fume or vapor. Within seconds of exposure to an inhaled toxin, pathological events occur that may cause immediate distress, systemic illness lasting days or even lead to the development of chronic lung disease. Clinicians need to be aware of the mechanisms, natural history, treatment and prevention of inhalation injury due to different agents so that they can manage individual patient accordingly.[10,11] Pulmonary responses based on consequences of exposure are listed in Table 113.1.

DETERMINANTS OF INHALATIONAL LUNG INJURY

A variety of factors determine the pathological changes of a toxic inhalation, viz. the size of inhaled particles, solubility of the inhaled substance in water, concentration of the inhalant in ambient air, duration of exposure, presence or absence of ventilation and a variety of host factors (age, smoking status, comorbid diseases, use of respiratory protection and perhaps even genetic susceptibility).[12,13] The size of aerosolized particles is of critical importance in inhaled toxin pathogenesis, as it determines the nature and site of injury. In general, larger aerosolized particles are more likely to deposit on the nasopharynx via impaction and may not gain access to the lower airways, while smaller particles are able to penetrate smaller airways and effect toxicity at the level of the alveolus. Particles of over 10 μm are lodged in the upper respiratory tract, while those less than 0.5 μm are usually exhaled. Thus, particles between these sizes are inhaled into the bronchi and if less than 3 μm, into the alveoli, causing diffuse damage. Water solubility plays a key role in determining where inhaled gases/particles get deposited in the respiratory tract.[11] Highly soluble agents (e.g. hydrochloric acid, sulfur dioxide, ammonia and aldehydes) have an early effect (within minutes of exposure) and cause acute irritant injury to the mucous membranes. This results in damage and related symptoms of the conjunctiva, nose and upper airway, but spare the lower respiratory tract. Those with low solubility (e.g. nitrogen dioxide, nitrous oxide, phosgene and ozone) cause no symptoms in upper airway and predominantly penetrate into the lower airways. Hence, they cause delayed onset irritant effects in bronchi, terminal bronchioles and alveoli. Because of the delayed effects and symptoms, exposure is often not noted early by the subject and exposure can thus be prolonged and more damaging.[14]

TABLE 113.1: Consequences of exposure

S.No.	Diseases	Common Agents
1.	Upper respiratory tract diseases	
	a. Rhinitis and laryngitis	a. Dust from flour, latex, pollens, ammonia, SO_2, ETS, hypochlorous acid
	b. Rhinorrhea	b. Cold air, carbaryl, malathion, parathion
	c. Ulceration and perforation of nasal septum	c. Arsenic, copper dusts, chromic acid and chromates
2.	Airway diseases	
	a. Asthma	a. Acid anhydrides, aldehydes, chlorine, dust from flour, latex, pollens, isocyanates
	b. Bronchitis	b. SO_2, rock and mineral dusts
	c. Bronchiolitis	c. Acetaldehyde, ammonia, chlorine
3.	Interstitial diseases	
	a. Pulmonary fibrosis	a. Asbestos, crystalline silica, talc
	b. Alveolar proteinosis	b. Fine crystalline silica dust
	c. Lipoid pneumonia	c. Oily metal working fluids
	d. Hypersensitivity pneumonitis	d. Fungi, thermophilic bacteria
	e. Granulomatous diseases	e. Beryllium
	f. Inhalation fever	f. Ameba, fungi, cotton dust, freshly generated zinc fumes
4.	Chronic obstructive pulmonary disease	Coal dust, cotton dust, cadmium, crystalline silica
5.	Lung cancer	Asbestos, arsenic, mustard gas, radon progeny, cadmium, crystalline silica

SO_2: Sulfur dioxide, ETS: Environmental tobacco smoke

CLINICAL PRESENTATIONS OF INHALATIONAL INJURY

Upper Airways

The effects of acute inhalation injury on the upper airways range from simple, transient irritation to airway compromise.[11-15] The initial nasal mucosal response to inhaled toxins is typically sudden and short-lived compared with the distal airways and hence, chronic pathology is unusual. Characteristic tissue injury ranges from slight edema of the nasopharynx and larynx to epithelial ulceration and frank hemorrhage. Once the airway epithelium is compromised, it fails to function as a protective barrier against the environment. Underlying inflammatory cells, nerves, muscles and blood vessels become exposed, which makes it sensitive to further lower concentrations of irritants. Substances that are inhaled into the nose are perceived as olfactory stimuli (olfactory nerve) or irritant stimuli (trigeminal, glossopharyngeal and vagus nerves).

Patients with the acute exposure of irritant substances to the upper airways present typically with complaints of burning sensations of the nasal passages and throat, copious sputum production, coughing and sneezing. Other symptoms include burning of the eyes, profuse lacrimation, headache and dizziness. Besides these, exposed persons can present with life-threatening airway obstruction due to reflex bronchoconstriction, laryngospasm/glottic closure, mucosal edema, increased secretions and sloughed epithelial cells. The larynx, which has the smallest cross-sectional area in the respiratory tract, causes a narrowing of air stream where air velocity increases eddies form and particulate matter gets deposited, which further predispose to laryngospasm. Along with the upper airways, epithelial injury can occur in the conducting airways by acute toxic inhalation which exposes submucosa to dangerous effects of toxins. Mild irritant effects include tracheitis and bronchitis. Irritation and inflammation can aggravate underlying airways disease, such as chronic obstructive pulmonary disease (COPD) or bronchial asthma. The resulting edema, inflammation and bronchoconstriction may be life-threatening. The airways are also vulnerable to infections and other environmental pollutants due to the loss of the epithelial barrier. The smooth muscle of the airways can be hyperresponsive following the irritant exposure. The injury to the conducting airways may manifest as intrathoracic airflow obstruction, hours after the initial insult and patient may present with dyspnea or chest tightness and wheezing. Chronic effects of irritant injury to the conducting airways include chronic bronchitis and tracheitis. If individuals have a pre-existing airway disease, the irritant exposure may cause more severe disease.[16]

Reactive Airways Dysfunction Syndrome (RADS)

An acute, excessive exposure to a number of chemicals, regardless of whether or not the agent has the potential to induce sensitization, can result in RADS.[17-19] The diagnostic criteria for RADS are given in Table 113.2.[20] The interval between the time of the exposure and the appearance of asthma symptoms in RADS is very short, often just a few hours. Subjects develop asthma-like symptoms within 24 hours after the single exposure. The agents that cause RADS include high-level exposure to an irritant gas, vapor or fume-like uranium hexafluoride gas, floor sealant, spray paint containing significant concentrations of ammonia, heated acid, 35% hydrazine, fumigating fog, metal coating remover and smoke. The exposure induces persistent nonspecific bronchial hyperresponsiveness. Bronchial biopsy demonstrates bronchial epithelial cell injury and bronchial wall inflammation with lymphocytes and plasma cells, but without eosinophils. At the time of medical examination, all subjects show a positive methacholine challenge test with PC20 of 8 mg/mL. There is a lack of any specific underlying host susceptibility (e.g. cigarette smoking, pre-existing lung disease or atopy). Chest radiographs may be normal and pulmonary function tests are normal or show mild airflow limitation. Subsequently, most persons with RADS require antiasthma medications that they were not taking before the exposure.

TABLE 113.2: Diagnostic criteria for RADS

1. Absence of pre-existing respiratory disorder, asthma symptoms or a history of asthma in remission
2. Exclusion of conditions that may mimic asthma
3. Exposure to an irritant vapor, gas, fumes or smoke in very high concentrations
4. Onset of asthma symptoms within minutes to hours and <24 hours after a single exposure or accident
5. Positive methacholine challenge test
6. Pulmonary function test to document airway obstruction (may or may not be present)
7. Exclusion of another pulmonary disorder

Irritant-induced Asthma

Patients not meeting the criteria of RADS are categorized as having irritant-induced asthma.[21] These patients usually have history of repeated episodes of less massive exposures and develop symptoms after a lag of several days.[20] Repeated exposures to irritants lasting days or weeks are required before the development of asthma.

Bronchiolitis Obliterans

Bronchiolitis obliterans is a disease where there is damage to the epithelium of the small conducting airways and frequently of the adjacent alveolar tissue that progresses to inflammation; the clinical consequence of this injury is irreversible airway obstruction. Although there are several patterns of primary bronchiolitis, constrictive bronchiolitis (also called obliterative bronchiolitis or bronchiolitis obliterans) is the most pertinent in inhalation injuries. Constrictive bronchiolitis often accompanies connective tissue disorders. Other causes are infections, chronic hypersensitivity pneumonitis, drugs and organ transplantations. Inhalational bronchiolitis obliterans evolves after inhaling an irritant gas, fume, vapor (and rarely dust), such as nitrogen dioxide, sulfur dioxide, ammonia, chlorine, phosgene, hot gases or fly ash. There were sporadic cases of bronchiolitis obliterans among nylon-flock workers, workers who sprayed prints onto textiles with polyamide-amine dyes, battery workers exposed to thionyl chloride fumes and workers in the food-flavoring industry.[21-24]

There is a classic three-phase pattern of response to gaseous exposures, such as nitrogen dioxide. Within first-four to six hours, upper airway symptoms predominate if the exposure is due to a more water soluble gas, such as sulfur dioxide; not as much upper airway symptoms take place when the gas was less soluble, such as with nitrogen dioxide. The exposure also causes diffuse alveolar damage that leads to a second phase characterized by the acute respiratory distress syndrome (ARDS), which develops within the first 24 hours. After resolution of ARDS, there is a third phase (perhaps several weeks after the exposure); where there are 7 to 10 days of minimal respiratory symptoms and then a gradual progression of shortness of breath. In most cases, constrictive bronchiolitis is progressive and poorly responsive to corticosteroids. Progressive airflow limitation may result in respiratory failure and death.[25-27]

Chest radiography may be normal or show only nonspecific abnormalities. There may be variable amounts of hyperinflation, peripheral attenuation of the vascular markings and sometimes, nodular or reticulonodular opacities. If serial radiographs are available, progressive hyperinflation can be appreciated. There may be changes consistent with bronchial wall thickening and bronchiectasis. A more sensitive diagnostic tool is high-resolution computed tomography (CT) scans, which typically show diffuse mosaic areas of decreased attenuation and vascularity, evidence of air-trapping (accentuated on expiratory views) and peripheral cylindrical bronchiectasis. Pathologically, constrictive bronchiolitis is characterized by peribronchiolar fibrosis with scarring of the bronchiolar lumen. The fibrosing inflammatory process surrounds rather than fills the lumen, resulting in extrinsic compression and obliteration of the airway. There are subtle and often patchy areas of fibrosis that may be missed if lesions are inadequately sampled. Therefore, transbronchial lung biopsy is a relatively insensitive diagnostic tool and usually a surgical lung biopsy is necessary.

Acute Respiratory Distress Syndrome

Although all toxic inhalants are capable of producing distal airway disease at extreme concentrations and durations, the gases most likely to do so are those with low water solubility, such as phosgene and nitrogen dioxide, which bypass reflex bronchoconstriction and absorption by upper airway mucosa.[27] The initial pathological events in distal airways are caused by the cellular toxicity of the inhaled agent and its derivatives, which compromise the impermeability of the alveolar-capillary interface. Some of this cytotoxicity may be derived indirectly from reactive oxygen species released from activated inflammatory cells. In the absence of an intact alveolar-capillary interface, profound pulmonary edema may develop that impairs gas exchange and can prove fatal. The severity of this pulmonary edema, which typically presents after a latent period of several hours following the initial insult, is likely dose related. This process may cause no more than slight dyspnea and cough with a mild alveolar infiltrate or may progress via diffuse alveolar damage to ARDS.

SPECIFIC INHALED TOXINS

Bhopal Methyl Isocyanate Disaster

The world's worst chemical industrial disaster occurred at Bhopal (India) on the night of 2nd to 3rd December, 1984. The leakage of the gases took place at a pesticide plant from a buried stainless steel tank in which 42 tons of Methyl Isocyanate (MIC) had been stored. This episode resulted in the immediate death of approximately 2,500 people and the exposure of over 3,50,000 people in the Bhopal City, comprising of over 8,00,000 inhabitants.[28-30] The main symptoms on the initial day were breathlessness (99%), cough (95%), throat irritation or choking (46%), chest pain (25%) and hemolysis (12%).[31] Many patients had features suggestive of pulmonary edema with froth coming out of the mouth immediately after the exposure (Fig. 113.1). Radiological studies done 72 hours after the leakage mainly showed alveolar and interstitial edema.[32] The predominant type of ventilatory defect, one to three months after exposure was combined obstruction and restriction.[33,34] Open lung biopsies, six to eight months after the exposure showed thickened alveolar walls, macrophages in the alveoli, some interstitial fibrosis and destructive changes in the terminal bronchioles with exudates in the lumen, a picture, which was suggestive of bronchiolitis obliterans.[28]

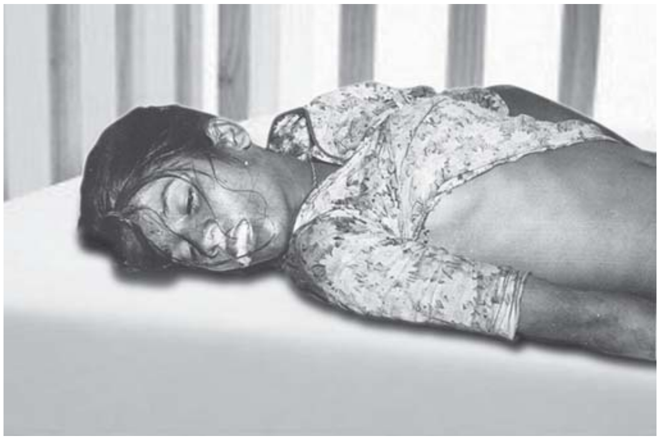

Fig. 113.1: One of the victims died due to MIC exposure with froth coming out of the mouth and nose

Bronchoalveolar lavage (BAL) studies of 1 to 2½ years after exposure to the gas had shown an increase in cellularity in the lower respiratory tract (alveolitis) of the severely exposed subjects.[35] The increase in cellularity in severely exposed nonsmokers was due to the abnormal accumulation of macrophages suggesting a subclinical alveolitis. Bronchoalveolar lavage studies repeated in these subjects 1.4 ± 0.6 years after the first lavage had revealed that the lower respiratory tract inflammation had progressed from initial macrophage alveolitis to macrophage-neutrophilic alveolitis.[36] Bronchoalveolar lavage studies in a new group of subjects 5.1 ± 1.0 years after exposure had confirmed chronic inflammation of the lower respiratory tract as evidenced by macrophage-neutrophilic alveolitis in these subjects as well.

Clinical, radiographic and pulmonary function abnormalities were found to persist in these subjects.

Fibronectin (FN) levels in BAL fluid had been found to be elevated in 29.3% of subjects.[36] Total lung inflammatory cells and absolute numbers of macrophages and lymphocytes in BAL fluid increased as the severity of exposure increased. There was a significant increase in lung eosinophils as time passed.[37] Forced Expiratory Volume in One Second/Forced Vital Capacity% (FEV_1/FVC%) was significantly lower as severity of exposure increased. Bronchoalveolar lavage neutrophils, both percentage and absolute numbers showed significant negative correlation with FEV_1% predicted. Neutrophil percentage was negatively correlated with FEV_1/FVC%. Radiographic abnormalities were associated with decline in FEV_1% predicted.[37]

Clinical, radiological and pulmonary function changes were noticed 4.7 ± 1.4 years (range three to seven years) after exposure. Obstructive ventilatory defect was seen in 33% and restrictive defect in 16% of the individuals. Pulmonary function abnormalities were predominantly seen in subjects severely exposed to the gas.[38] Computed tomographic evidence of pulmonary fibrosis was also described in a patient with toxic gas exposure.[39] Small airways obstruction was found to persist among survivors of the disaster even 10 years following the gas leak.[40] These studies suggest that the pulmonary function abnormalities persisted in subjects exposed to the gas and that irreversible changes in pulmonary function occur in subjects who had severe exposure.[37] Thus, a single massive exposure to the gas in Bhopal has resulted in residual lung damage especially obstructive airways disease.

Nitrogen Oxides (NO_x)

The main sources of nitrogen oxides are from automobile engines, combustion of coal and petroleum and smoking of cigarette. Mining, acetylene welding and manufacture of explosives are other sources from industrial settings. Inhalation of concentrated nitrogen dioxide gas released from decomposing nitrogenous material in silos leads to "silo-fillers" disease in farmers. Nitrogen oxides can occur as nitrogen dioxide, nitrous oxide, nitrogen peroxide and other nitrous oxides. Nitrogen dioxide is a red/brown pungent gas.

The initial effects of nitrogen dioxide exposure are relatively benign but at very high concentrations may result in cough, fatigue and occasionally nausea.[41-44] With high-intensity exposure, patients may experience headache and chest tightness, although these symptoms tend to resolve promptly. Nitrogen dioxide is less irritating to mucosal surfaces than other toxic inhalants. Symptoms typically abate initially, however, an intense pulmonary edema consistent with ARDS develops after a few hours due to increased capillary permeability following extensive damage to vascular and airway epithelium. Patients who survive are at an increased risk for the development of bronchiolitis obliterans and bronchiolitis obliterans organizing pneumonia, one to four weeks following exposure.

Sulfur Dioxide (SO_2)

Sulfur dioxide is a byproduct of the combustion of fossil fuels, i.e. coal and petroleum. It is often used as a preservative in alcoholic beverages and fruit. Ore smelting, sugar refining and the bleaching of wool and wood pulp, volcanic eruptions are other important sources. Sulfur dioxide is a major component of air pollution smog. Sulfur dioxide is a heavy, colorless and highly water-soluble gas that has the distinct, pungent odor of burnt matches. It settles in the ground due to its high density and dissipates slowly from the sites of release. Sulfur dioxide reacts with the water present on mucous membrane to form sulfuric acid, which causes local tissue destruction. Sulfuric acid further dissociates into hydrogen ions, sulfite and bisulfite, which can then react with oxygen to produce reactive oxygen species; ensuing lipid peroxidation may be a contributing mechanism of injury to immediate tissues and elsewhere.[45-47]

Symptoms of SO_2 inhalation include dyspnea, burning of the nose and throat, rhinorrhea, cough and airway obstruction. Proximal airway injury is characterized by acute denudation of the airway mucosa without inflammatory cell infiltrates. When lower airways are exposed, alveoli are filled with fluid due to noncardiogenic pulmonary edema and a clinical picture consistent with ARDS develops. Extremely high-intensity acute exposures can lead within minutes to death from respiratory failure. Reactive airways dysfunction syndrome and bronchitis can also occur. Sometimes, there may be initial recovery followed several weeks later by the onset of irreversible airflow obstruction due to bronchiolitis obliterans.

Phosgene ($COCl_2$)

Phosgene is released due to the production of pesticides, polyurethane resin, toluene di-isocyanate, pharmaceutical products and dyes. It can also be released accidentally via the heat decomposition of various solvents, paint removers, dry cleaning fluids and methylene chloride. Individuals may not be aware of exposure to phosgene because of its properties of being colorless, lacking a strong odor (in high concentrations it is reported to smell like moldy hay, new-mown hay or green corn) and not irritating to the nasal and oral mucosa. It was used as chemical warfare agent in World War I because it showed the above mentioned properties.

Phosgene reacts with water to form hydrochloric acid and carbon dioxide, resulting in local epithelial necrosis. Its lack of irritability in the upper airways ensures the passage of the gas to the alveoli inflicting significant damage in alveoli.[48,49] Phosgene also causes tissue damage by rapidly acetylating the amino, hydroxyl and sulfhydryl groups of proteins, resulting in protein denaturation and structural compromise of cell membranes, leading to a breakdown of the blood-air interface. Lipid peroxidation has also been shown to occur and antioxidant therapy has been shown to attenuate its effects in animal models.

Victims may present with chest tightness, wheezing or cough or sometimes may be asymptomatic. Post-exposure, there may be a variable latent period of up to 48 hours before the onset of symptoms of pulmonary edema/acute lung injury. The duration of this latent period is thought to be inversely proportional to both the severity of exposure and the ensuing severity of disease. The patient experiences dyspnea, cough and respiratory distress, and rales and cyanosis may also be present. Dyspnea or radiographic evidence of pulmonary edema within four hours after exposure indicates a worse prognosis and warrants treatment in an intensive care unit. Although, survival for patients with acute phosgene exposure is good, numerous long-term sequelae have been reported, including prolonged exertional dyspnea, chronic bronchitis and emphysema.

Ozone (O_3)

Ozone is highly toxic to respiratory tract. It is an important oxidant pollutant in smog. It is widely used in water purification systems and is a byproduct of electric currents passing through air, as in welding and corona wires of photocopying machines. It is also used for the bleaching of fabrics and the manufacture of plastics. Ozone is a colorless, odorless gas having low water solubility. This leads to a lack of early irritating warning effects and an increased probability of damage to the conducting airways and lower respiratory tract. Ozone exposure results in the formation of free oxygen radicals and lipid peroxidation, which causes oxidative cellular damage. Severe exposures can cause dyspnea, cyanosis and pulmonary edema.[50,51] At higher doses, ozone exposure has been found to be associated with the development of RADS.

Ammonia (NH_3)

Anhydrous ammonia (NH_3) is a colorless gas with a strong odor. It is generally stored and transported under pressure as liquid. It is used as a household cleaner and in industries as a chemical coolant for refrigeration, as fertilizer, as fixative in photocopiers and in the manufacture of polymers and explosives. Small amounts are naturally present in the atmosphere as products of the putrefaction of vegetables and animal proteins. Most inhalation exposures are the result of accidental releases, including tank leaks and transportation mishaps, as well as from exposures that occur in the industrial workplace. Accidental releases of anhydrous ammonia caused by explosions or other accidents can lead to severe chemical inhalation injury as well as dermal and conjunctival burns because of the strong alkaline properties of ammonium hydroxide and hydroxyl ions formed in an exothermic reaction when ammonia reacts with water on the surface of mucous membranes.

Anhydrous ammonia and ammonium hydroxide have an affinity for mucous membranes that leads to liquefactive necrosis and full thickness tissue destruction. The resulting injury, typical of alkali burns, penetrates deeply. The initial injury to the mucosa of the oropharynx can cause edema, hemorrhage, sloughing of tissue and increased secretions that can bring about fatal upper airway obstruction. Ammonia is directly caustic to airways at concentrations of 1000 ppm and higher. Although concentrated at the proximal airways, the effects of ammonia have been observed at all levels of the respiratory tract. The penetration of the gas to the smaller airways and alveoli is a function of its concentration and the duration of exposure.

Inhalation injury with ammonia can lead to pharyngitis, laryngitis/tracheobronchitis, hemoptysis, pulmonary edema, bronchiolitis and bronchopneumonia. Chronic sequelae include bronchiectasis, RADS and COPD.[52-54] Occurrence of interstitial lung disease has been seen in survivors following a single exposure to ammonia. A biphasic pattern of pulmonary response to ammonia inhalation has been reported, characterized by initial, acute pneumonitis that may clear over the next two to three days, followed in some individuals by the gradual development of airway obstruction and respiratory failure. There may be a relationship between the bacterial superinfection after exposure and the ensuing development of bronchiectasis. The most common causes of death are laryngeal edema and obstruction, noncardiogenic pulmonary edema and extensive pneumonic complications.

Chlorine, Chloramines and Hydrochloric Acid

The first reports of chlorine toxicity were during its use as an agent of chemical warfare in World War I. Exposures to chlorine occurs in industrial settings where chlorine is used in the manufacture of paper, cloth, antiseptics and other products. Household exposure has been observed due to the liberation of chloramines and other toxic chlorine derivatives from the reaction of chlorine-containing products (e.g. hypochlorite bleach) with ammonia or products containing hydrochloric or phosphoric acids. Numerous exposures to chlorine gas have been reported to occur near swimming pools where chlorine-releasing agents (e.g. calcium hypochlorite and chlorinated isocyanuric acids) are used in water purification.

Chlorine gas is a greenish-yellow gas that has strong irritant and odor. A slight mucous membrane irritation of eyes, nose and throat occurs at concentrations of 1 to 3 ppm and noticeable irritation occurs at brief exposure of 3 to 6 ppm. The pathogenicity of chlorine gas occurs directly from elemental chlorine's effects on the respiratory tract and indirectly from its reaction with water to form hydrochloric acid (HCl) and hypochlorous acid (HOCl). Hyrdrochloric acid and HOCl possess considerable water solubility and are responsible for the tissue damage of the upper airways and ocular conjunctivae. Irritation to trigeminal nerve endings caused by these compounds can cause a reflex bronchoconstriction that may contribute to compromise in airway diameter. In addition to cause the tissue coagulation typical of acid exposures, these compounds ionize and enter cells, where they may form reactive oxygen species. Although, lower respiratory tract irritation has been reported following high-level of exposure, only less than 5% of inhaled chlorine gas penetrates beyond the upper airways. Fatal dosages from chlorine inhalation have ranged from 50 to 2000 ppm.

The immediate clinical manifestations of acute chlorine exposure are typical of its irritants effects, viz. rhinitis, cough, dyspnea, wheezing and chest tightness along with conjunctivitis and skin irritation. Lower respiratory tract may be affected in the form of pneumonitis and pulmonary edema. Acute respiratory symptoms are more prevalent and severe among patients who already have chronic respiratory disease. Respiratory sequelae of chlorine gas exposure have been described since the years following the use of the gases in World War I. Long-term pulmonary sequelae have included both restrictive and obstructive processes, frequently resolving to normal function within a month and almost always before two years following exposure.[55-58] Reactive airways dysfunction syndrome may be infrequent sequelae of high-level exposures to chlorine.

Cadmium

Cadmium is used in nickel cadmium batteries and is also found in alkaline accumulators, electroplating, bearings, solders and as a barrier around nuclear fission generators. It is present in many metal ores and cadmium-containing pigments are used in paints, artists' colors, rubber, plastics, printing inks, wallpaper, leather, glass and enamels. Most inhalations occur to workers who are involved with soldering, brazing, smelting and refining. The mechanisms involved with the acute lung injury due to cadmium inhalation are not well defined. Postmortem examinations of individuals who died after accidental acute inhalation exposure have revealed tracheobronchitis, consolidated lungs, denuded bronchial epithelium, intra-alveolar hemorrhage and the presence of macrophages in the alveolar spaces. It is known that cadmium inhibits the synthesis of plasma alpha 1-antitrypsin, which may explain the correlation between cadmium exposure and the later development of emphysema.[59]

When cadmium-containing materials are heated, cadmium vapors and cadmium oxide fumes are released. These can produce a systemic flu-like syndrome, which resembles metal fume fever. They are asymptomatic for several hours before developing fever, malaise and myalgias. These constitutional symptoms are often accompanied by or shortly followed by respiratory distress including cough, chest tightness and dyspnea. Cadmium exposure can also lead to a severe pneumonitis which can progress to ARDS, pulmonary hemorrhage and eventual death from respiratory failure. Cadmium may be detected in the urine.[60]

Mercury

Mercury is used in mining operations, dental amalgams, jewellery production and light bulb manufacturing. It is present in the form of environmental hazard as a component of thermometers, sphygmomanometers and other specialized equipment. Like phosgene and cadmium, mercury vapor has little or no immediate upper airway or mucosal surface irritant effects. As a result, exposed individuals may inadvertently remain in an area where the harmful vapors are present. The toxicity of mercury vapors within the lung is thought to be due in part to the irritant effects of oxidized mercurous and mercuric ions and the disruption of enzyme systems containing sulfhydryl groups. Mercury coagulates protein, blocks cellular metabolism of carbohydrates at the pyruvic oxidase level and as a result produces metabolic acidosis. Lung pathology following acute exposure reveals pulmonary edema, capillary damage and the desquamation and proliferation of airway epithelium followed by an obliteration of airspaces.[61, 62]

Inhalation of mercury vapors causes cough, dyspnea and respiratory distress developing over a 24-hour period. These initial symptoms may be accompanied by fever, nausea, vomiting, diarrhea and a metallic taste in the mouth, similar to what is often experienced by individuals with metal fume fever. In fact, mercury vapor inhalation can be mistaken for metal fume fever or influenza. However, symptoms of mercury vapor inhalation do not spontaneously resolve as with metal fume fever. Like cadmium, the pneumonitis due to mercury exposure may progress to ARDS and respiratory failure, sometimes accompanied by pneumothorax. Death has been preceded in several reports by tension pneumothorax. Inhaled mercury vapor is absorbed rapidly into the blood, where it can cause systemic toxicity in the form of renal, hepatic and nervous system pathology. Patients surviving the acute injury typically experience resolution of their symptoms within one week, but have also progressed to develop interstitial fibrosis. Mortality due to exposure may be increased in children.

Zinc Chloride

Zinc chloride is formed when zinc oxide is ignited with hexachloroethane. The smoke obscures vision, resulting in directional disorientation and the individual is unable to quickly escape the area of exposure. Zinc chloride ($ZnCl_2$, or hexite) is a major ingredient of smoke bombs/smoke-generating devices. Zinc chloride is in particulate form with an average particle size of 0.1 µm and hence, it penetrates to the lower respiratory tract. After depositing on the airway and alveolar surfaces, zinc chloride reacts with water to form hydrochloric acid and zinc oxychloride. This directly causes irritation of exposed mucosal surfaces and is the probable mechanism behind the diffuse lung injury observed on exposure. Zinc chloride inhalation is followed by tracheobronchitis and pneumonitis. Patients experience cough, dyspnea and chest tightness followed by a period of relative stabilization before progressing to ARDS.[63,64] Chest imaging may be normal initially, but can reveal pleural effusions, pneumomediastinum and bilateral infiltrates consistent with pneumonitis. Prominence of ground glass opacities observed on high-resolution CT imaging may be predictive of severity of exposure and length of hospital stay. Urine zinc levels are useful for confirming the diagnosis of zinc inhalation toxicity.

Tear Gas

"Tear gas" is the name, collectively given to the disabling chemical irritants of which there are more than a dozen chemicals, but the five commonly used chemicals are: 2-chlorobenzylidene-malonitrile (CS, Tear gas), 1-chloroacetophenone (CN, mace), dibenz-1,4-oxazepine (CR, Fire gas), oleoresin capsicum (OC, pepper) and Pelargonic Acid Vanillylamide (PAVA).[65] All these agents are used by military and law enforcement agencies to control crowds and individuals, making use of their intense and immediate irritant effects on mucous membranes and lacrimal glands. The tear gas affects the exposed cutaneous and mucous membrane surfaces.[66] Exposure to any of them results in immediate rhinorrhea, mucositis, chemical conjunctivitis and profuse lacrimation. Immediate pulmonary effects include an intense burning sensation in the upper airways, reflex airway constriction, chest tightness, dyspnea and cough.[67,68] Exposure may also provoke nausea, headache and photophobia. Severity of response depends on the concentration of the agent used, duration of exposure and presence or absence of ventilation and protective breathing apparatus. The effects of tear gas are predominantly due to its upper airway irritant effects and thus lower airway injury and parenchymal disease is rarely observed. Some exposed persons may develop severe pulmonary disease in form of pneumonitis, pulmonary edema and reactive airways dysfunction syndrome. In asthmatic individuals, it may precipitate acute bronchospasm.

World Trade Center Disaster

The World Trade Center (WTC) in New York was struck by two commercial jets on 11th September, 2001, leading to the collapse of three skyscrapers. As a result, 2,751 persons, including 373 firefighters from the New York City Fire Department (FDNY) died. The WTC collapse has produced a massive exposure to respirable particulates, with the larger-size fractions having a pH ranging from 9 to 11 leading to an alkaline burn of the mucosal surfaces.[69] The survivors, both rescue workers and bystanders, were exposed to respirable particulates and combustion byproducts.[67] Induced sputum from FDNY workers had shown high levels of particulates and evidence of continuing inflammation 10 months after exposure to WTC dust.[70] Intense short-term exposure to materials generated during the collapse has been shown to be associated with bronchial responsiveness and development of asthma.[71] Respiratory symptoms, either new or increased in severity have been described in FDNY rescue workers, other exposed workers and residents.[72] During the first year post-September, 2001, there was a parallel decline in both FEV_1 and FVC resulting in a low FVC and normal FEV_1/FVC in the FDNY rescue workers and in non-FDNY rescue/recovery workers raising the possibility of interstitial lung disease in exposed subjects.[71,73] However, pulmonary function evaluation during the first seven years postexposure in FDNY rescue workers had shown that airways obstruction was the predominant physiologic abnormality.[74]

SYSTEMIC ILLNESSES FROM INHALED TOXINS

Systemic flu-like illness lasting less than two days has been observed in patients exposed to organic dusts and fumes of heated metals and fluorocarbons. These are known as inhalational fevers and are of three types, viz. metal fume fever, polymer fume fever and organic dust toxic syndrome (ODTS). The course of the disease is self-limited and appears to be cytokine mediated.

Metal Fume Fever

Metal fume fever (MFF) is a self-limiting inhalation fever attributed to a number of metal oxide fumes. The history is characterized by fever, headache, myalgia, fatigue and dyspnea. Other features include cough, thirst, a metallic taste, salivation and a neutrophilic leukocytosis. Metal fume fever is an important occupational-related illness classically associated with zinc oxide fume exposure from welding galvanized steel or brass.[75,76] It is also seen in association with high temperature zinc coating processes and metal pouring in brass foundries. Magnesium and copper oxide fumes are more rarely the causative agents. Metal fume fever has been known by a number of other names: Brazier's disease, smelter shakes, brass chills, zinc chills, welder's ague, copper fever, foundry fever and Monday morning fever. Radiography may demonstrate bilateral diffuse infiltrative pulmonary lesions. Pulmonary function tests demonstrate a significant reduction in vital capacity, transfer factor and arterial oxygen partial pressure. Urine and plasma metal levels may be increased. Onset is typically rapid, occurring between three and ten hours after exposure. Spontaneous recovery occurs within 24 hours. No long-term complications are known.

Specific fumes that have been blamed include those of beryllium, cadmium, copper, magnesium, nickel, silver and zinc. Welders are at the highest risk for metal fume fever contraction, although it has been reported in other metal working occupations, including soldering, brazing, cutting, metalizing, forging, melting and casting. Episodes of varying severity of metal fume fever may be experienced by between 20% and 35% of all welders. Repeated exposure may lead to tachyphylaxis. The name "Monday morning fever" refers to the recurrence of acute disease on return to exposure following a short period of absence. Metal fume fever is generally thought to have no long-term sequelae. An association between it and the later development of occupational asthma has been observed.[77,78] The pathogenesis of metal fume fever appears to involve an increase in proinflammatory cytokine activity in the lung; increased BAL fluid concentrations of tumor necrosis factor (TNF), interleukin-6 (IL-6) and interleukin-8 (IL-8) have been reported in subjects exposed to zinc oxide fumes, probably produced by pulmonary macrophages.[79] Of the numerous components of metal fumes, it appears to be the soluble transition metal particles, which generate reactive oxygen species and deplete glutathione stores that are responsible for the fumes' cytotoxicity. A proposed mechanism of the observed tolerance to metal fumes involves the increased synthesis of toxic metal-binding protein metallothionein in exposed patients.[80]

Diagnosis is based on clinical suspicion, clinical findings and rapid resolution. Evidence of possible exposure is critical. Treatment is symptomatic. The syndrome needs to be differentiated from serious MFF seen after military smoke exposure, which typically has a biphasic response with severe relapse 24 to 48 hours after initial remission.[81] It should also be differentiated from true chemical pneumonitis after metal fume exposure.

Polymer Fume Fever

Polymer fume fever, a syndrome similar to but less common than metal fume fever. Fluorocarbon polymers are a class of compounds that are commonly used as nonstick coatings on cooking equipment (e.g. polytetrafluoroethylene [PTFE, or Teflon]), but are also used in mold-release sprays, lubricants and fabric or leather treatments. Heating of fluorocarbon polymers produces fumes that contain carbonyl fluoride, perfluorinated alkanes, hydrofluoric acid and carbon dioxide. Polymer fume fever presents similarly to metal fume fever: Initial symptoms include dry throat, rhinitis, chest tightness and conjunctivitis. Constitutional symptoms (fever, chills, and myalgias) typically follow exposure by about four to eight hours and spontaneously resolve within one day.[82,83] As with metal fume fever, a leukocytosis is observed concurrent with the patient's constitutional symptoms. Individuals with pre-existing obstructive lung disease may experience worsening obstruction after recurrent exposures to polymer fumes. Pneumonitis is more frequently observed than with metal fume fever, perhaps due to release of hydrofluoric acid. Tachyphylaxis, a hallmark of metal fume fever, is not observed in polymer fume fever, suggesting that different mechanisms are responsible for the two diseases. As with metal fume fever, the systemic response to particle inhalation appears to be cytokine mediated. Although exposure to pyrolized fluoropolymers occurs in industrial settings where it may be immediately suspected in the context of respiratory complaints, it also occurs in homes.

Organic Dust Toxic Syndrome

Organic dust toxic syndrome (ODTS) is a self-limited syndrome characterized by fever with chills, malaise, myalgia, headache, dyspnea, chest tightness, dry cough and nausea. The syndrome usually begins within hours of an exposure to high concentrations of organic dust. Organic dust is defined as solid particles of 0.1 to 50 microns or larger in diameter that are produced by some mechanical process, such as crushing, grinding, abrading or blasting and suspended in air. The physical and chemical compositions of organic dusts vary and are affected by the dust source, geographic region, temperature, humidity and other factors. Grain dust constituents include fractured grain kernels, trichome particles, insects or insect parts, silica, bacteria and molds and chemical residues.[84-87] Organic dust toxic syndrome typically resolves spontaneously within 48 hours following exposure. Agricultural workers are at the highest risk for contracting ODTS, as it commonly follows exposure to hay or corn silage-containing silos, spoiled animal feed and swine confinement facilities. Other settings of ODTS have included a storehouse containing moldy oranges, a waste-sorting plant, a print-shop in which an air humidifier was colonized with gram-negative bacteria, fungi and amoeba and following exposure to wood chip mulch. The exact mechanisms of toxicity are not known, but endotoxin, fungal spores or mycotoxins are believed to play a role and the mechanism is nonimmunogenic. The amount and duration of exposure are important. Grain dust extracts have been shown to cause alveolar macrophages to produce IL-1, IL-6 and TNF-α, which are endogenous pyrogens. Cytokine expression increases following organic dust exposure. This especially includes proinflammatory cytokines, such as TNF-α and interleukin-6 (IL-6), suggesting a means by which local activation of innate immunity may provoke the observed systemic manifestations. Interleukin-1 is also thought to play a critical role in ODTS development. An intriguing correlation has been observed between patients with celiac disease and the development of ODTS, suggesting that some underlying disorder, perhaps hyperactivity of innate immunity, may increase the patient's susceptibility to both.

Patients with ODTS frequently present with no findings on chest examination, although bibasilar crackles and scattered wheezes may be appreciated. A neutrophil predominant leukocytosis is frequently found and mild hypoxemia and bilateral infiltrates on chest X-ray have been reported. Although, bronchoalveolar lavage may initially reveal the predominance of neutrophils, a lymphocytic response may come to dominate the BAL cellular population. ODTS needs to be clinically distinguished from hypersensitivity pneumonitis (HP), which is also provoked by inhaled organic dusts. Development of HP usually requires repeated exposures, although it can occur following a single acute exposure. Onset may follow such an exposure or may be insidious. HP may result in permanent pulmonary sequelae following even a single occurrence. Unlike with ODTS, the chest X-ray often shows infiltrates, severe hypoxemia, prior sensitization to antigens in the organic dust and there may be significant sequelae in HP. HP is also usually associated with a positive precipitin test and provocation testing may be helpful in diagnosis. The early BAL findings in ODTS are overwhelmingly neutrophilic, unlike the lymphocytic findings in HP. Treatment of ODTS is symptomatic. Unlike with HP, corticosteroids appear to be of only marginal benefit in the treatment of ODTS.

SMOKE INHALATION LUNG INJURY

Smoke inhalation injury, either by itself or in the presence of a burn, is now well-recognized to result in severe lung-induced morbidity and mortality. The most common cause of death in burn centers is respiratory failure.[88-90] The composition of smoke, which leads to lung injury, varies according to the materials that are involved. Common components of smoke are carbon dioxide, carbon monoxide, hydrogen cyanide, oxygen radicals, ammonia, sulfur dioxide, aldehydes, acrolein, aromatic hydrocarbons and phosgene. Carbon monoxide toxicity is one of the leading causes of death in fires.[91,92] Whereas oxygen is used during combustion, carbon monoxide is released, because it is a basic byproduct of combustion.[93] Carbon monoxide is rapidly transported across the alveolar membrane and preferentially binds with the hemoglobin molecule in place of oxygen. In addition, carbon monoxide shifts the hemoglobin-oxygen dissociation curve to the left, thereby impairing oxygen unloading at the tissue level. The result is a major impairment in oxygen delivery.

Direct heat injury caused by the inhalation of air heated to a temperature 150°C or higher ordinarily results in burns to the face, oropharynx and upper airways (above the vocal cords). Even superheated air is rapidly cooled before reaching the lower respiratory tract because of the tremendous heat-exchanging efficiency of the oropharynx and nasopharynx. Heat and especially the chemicals in smoke produce an immediate injury to the airway mucosa, resulting in edema, erythema and ulceration. Although these mucosal changes may be anatomically present shortly after the burn, physiologic alteration may not be present until the edema is sufficient to produce clinical evidence of impaired upper-airway patency. This may not occur for 12 to 18 hours. The presence of a body burn magnifies the injury in direct proportion to the size and depth of the skin burn.[94-96] The epithelial cells in the pharynx respond by increasing mucus production, which can then be found in the lower airways often in obstructive mucus clots. Another compounding injury is any face or neck burn that will produce marked anatomic distortion and in the case of the deep neck burn, external compression on the larynx. A more superficial burn causes massive external edema, but may produce much less mucosal edema and airway compromise. The local edema usually resolves in four to five days. Exposed individuals present with symptoms of obstruction, namely, stridor, dyspnea, increased work of breathing and eventually cyanosis.

Smoke is composed of two phases: a gas and a particle phase. The gas phase contains a number of volatile water-soluble compounds, such as acrolein, chlorine, hydrochloric acid, sulfur compounds, as well as carbon monoxide, carbon dioxide and cyanide gas.[97] Large quantities of short-acting oxidants and oxidant precursors are also present. These compounds have been reported to produce proximal airway damage. The gas phase of smoke also contains unusually long-acting oxidants, which can reach distal lung tissues. These agents produce local-airway injury. The vapors, in large part, are mucus membrane irritants leading to intense bronchorrhea, bronchoconstriction and airway edema. The process often peaks hours after injury, although patients with pre-existing airway reactivity can develop very early intense bronchoconstriction.[98,99] The particle phase of smoke is composed of carbon particles, 0.1 to 10 µm in diameter, on which are adherent many of the compounds found in the gas phase along with heavy metals and other oxygen radical-producing compounds and lipid-soluble compounds like the aldehydes.

Some of the gas compounds like phosgene can also bind to the carbon. Particle size and tidal volume determine their distribution in proximal versus distal lung. Once particles adhere to lung tissue, the injury from adherent toxins, including oxidant release, can occur over hours to days, resulting in progressive cellular injury and in case of severe injuries, mucus membrane destruction can occur. The particles phase injury of smoke produces severe injury. The degree of exposure to the lung is dependent on particle size and breathing pattern.[100] The degree of deposition in distal lung is accentuated by deeper breaths, as would be evident in a hypoxic patient or a patient attempting to actively escape the insult. As opposed to the gas phase, which is short-lived, the particulates can adhere to the mucosa and perpetuate the local tissue injury. Particulate clearance, in turn, is impeded by the impaired mucociliary action perpetuating the injury. Consequent to smoke inhalation injury, there is clinical evidence of continued respiratory compromise namely, dyspnea, tachypnea, diffuse wheezing and rhonchi, which precede radiographic changes. The evidence on radiography of lung damage is usually that of diffuse atelectasis, pulmonary edema or bronchopneumonia.

APPROACH TO A VICTIM OF INHALATION INJURY

Accurate history is of great help for diagnosing the type of inhalation injury in order to find the likely agent/chemical involved and for anticipating the complications accordingly. Depending on the type of presentation, the person can be classified as acutely ill or stable.[101] Acutely ill person will require battery of tests, such as arterial blood gas analysis, chest roentgenogram, blood and urine levels of suspected chemical (e.g. mercury, zinc, etc.), CT scan and bronchoscopy. In case of person being stable clinically, he can undergo pulmonary function tests in addition to the above tests, which can help in diagnosing RADS and bronchiolitis obliterans.

MANAGEMENT

The victim has to be removed immediately from the site of leakage or fire so as to minimize the exposure and to characterize the agents involved.[102] This is followed by thorough decontamination by removing all clothing, which has trapped chemicals in it. If they are outdoors, they should move away from the source of contamination till they reach a safe place. If they are indoors, close all doors and windows and shut down all heating and cooling systems to minimize the entry of contaminants from outside. Individuals suspected to be exposed to chemical contaminants should immediately remove the contaminated clothing and should be irrigated with water and washed with soap and water.[103] The victim is then assessed for the signs of severe injury, which include altered mental status, respiratory insufficiency, cardiovascular instability, convulsions and unconsciousness.

Initial supportive therapy should be focused on airway patency, ventilation and circulation. At the same time, patient must be examined for burns, trauma and other injuries. When poisoning by chemicals is suspected, routine emergency guidelines should be followed which include consideration towards administration of naloxone to patients who have an altered mental status and respiratory depression. Some chemicals cause systemic intoxication and may require treatment with antidotes.[103] Diazepam, cyanide antidote kits, atropine and pralidoxime are the most important drugs, which should be present for managing such emergencies. Airway compromise and respiratory insufficiency may warrant high flow oxygen, intubation or tracheostomy. Patients going into ARDS will require mechanical ventilation as per the ARDS protocol, including low tidal volume, high frequency ventilation. Inhaled or systemic corticosteroids and inhaled bronchodilators are useful in the management of bronchospasm.

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Drug-Induced Respiratory Disease

William J Martin II

INTRODUCTION

Drug-induced respiratory disease is it sufficiently common that clinicians need to consider in the differential diagnosis of most acute and chronic respiratory and pleural disorders. The challenge is to consider its possibility when taking the history of the patient. If a good history is not taken and the possibility of drug-induced respiratory disease not considered, the diagnosis is invariably missed and a potentially reversible respiratory disorder can become chronic and lead to progressive disability and death. Thus, despite the various diagnostic clues from tests and imaging modalities, there is nothing more important in making the diagnosis of drug-induced respiratory disease than an accurate history of medication use and the consideration that the medication use might be the cause of the respiratory distress.

There are more than 300 drugs associated with respiratory toxicity[1] and the list is only going to grow as more therapeutic agents are brought to the market. Clinicians often rely on their personal experience or those of their colleagues to suspect the possibility of a drug-induced lung reaction. As noted above, this is the most important step in the diagnosis and management of patients with adverse drug reaction involving the respiratory system. In the past, a clinician might review several of the excellent textbooks or recent reviews to see if an association exists between a specific medication and respiratory toxicity.[1-5] Today, it is much simpler with access to the web site www.pneumotox.com[6] for an excellent and easy method to access up-to-date information on drug-induced lung reactions.

Thus, this chapter will not focus on presenting an exhaustive list of drugs or medications associated with adverse respiratory reactions as those lists are available elsewhere and are everchanging; rather, the chapter will provide an approach focused on certain drug classes known to cause lung disease, specific examples of drugs that illustrate the typical clinical presentation and finally, an approach to clinical management that can be adapted to the evaluation of most patients who present with symptoms or findings, consistent with drug-induced respiratory disease.

DRUGS ASSOCIATED WITH RESPIRATORY TOXICITY

Cancer Chemotherapy Agents

There are several ways to organize one's approach to the assessment of drug-induced respiratory toxicity. Although the list of possible drugs that cause adverse lung and pleural reactions is long, one can organize the drugs into broad categories that reflect their general class of use (Table 114.1). From this, one can find well-described examples of the most common adverse drug reactions that most clinicians will see during the course of their professional career.

Cancer chemotherapeutic agents, including radiation were among the first class of drugs or agents to be recognized as cause of respiratory toxicity (Table 114.2). Busulfan, one of the early alkylating agents, was first described in 1970s as a cause of diffuse lung disease, leading to progressive fibrosis and death.[7,8] Since then, many cancer chemotherapy agents have been implicated

TABLE 114.1: Drug-induced respiratory disease

> 300 drugs associated with pulmonary toxicity
- Cancer chemotherapy
- Antibiotic/antimicrobial
- Anti-inflammatory
- Cardiac
- Illicit
- Miscellaneous

TABLE 114.2: Cancer chemotherapy

• Busulfan	• Methotrexate
• Melphalan	• Procarbazine
• Cyclophosphamide	• Hydroxyurea
• Bleomycin	• ARA-C
• Nitrosurea e.g. BCNU, CCNU	• Mitomycin-C
• Chlorambucil	• Radiation

in respiratory toxicity, not only complicating the cancer treatment regimen, but limiting additional therapeutic approaches to controlling cancer growth.[9,10] Thus, the need to understand the mechanisms of chemotherapy-induced lung disease is critical to provide better strategies to maximize the antitumor effect and to minimize the pulmonary complications for the patient (Fig. 114.1).

One of the typical examples of respiratory toxicity from cancer chemotherapy occurs with bleomycin, an antibiotic derived from *Streptomyces verticillus*, which is an effective cancer chemotherapy agent, especially for germ cell tumors of the testes and lymphomas.[11-13] It has been recognized since the 1960s that the drug can generate oxygen radicals and damage deoxyribonucleic acid (DNA)[13] (Fig. 114.2). This property makes it effective to kill cancer cells, but may also serve to injure critical alveolar lining cells and endothelial cells in the lung, which may result in acute lung injury and death. This process may account for the reported postoperative

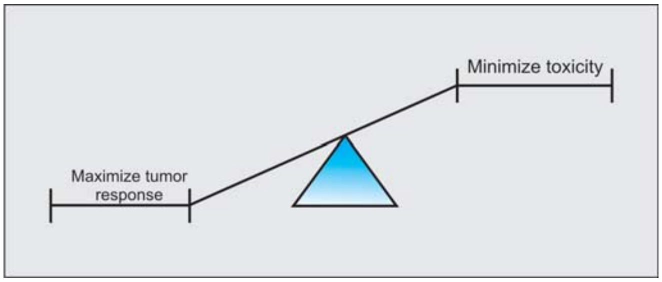

Fig. 114.1: Therapeutic strategy for cancer chemotherapy

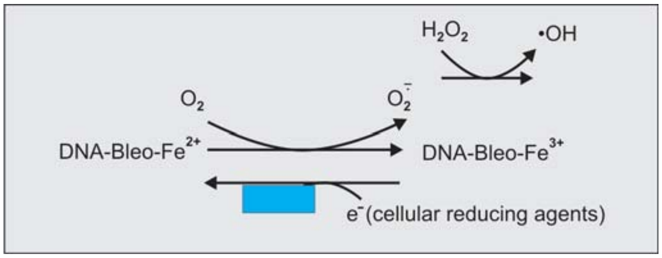

Fig. 114.2: Effect of iron-containing bleomycin on oxygen radical generation

Acute respiratory distress syndrome (ARDS) occurring in patients who have previously received bleomycin.[14,15] Additionally, bleomycin pulmonary toxicity may be associated with an acute inflammatory or immune response in the lung, further comprising lung function. The ability of drugs to cause both direct toxic and indirect inflammatory-mediated lung injury is common to many drugs in the class of cancer chemotherapy agents. Each drug may be unique in how the initial injury occurs and where it occurs in the respiratory system, but the complexity of the mechanisms and the repair responses in the lung often undermine a predictable course for any given patient.

Brief Case Report: A 23-year-old male with a history of embryonal cancer of the testes has received four courses of VP-16, cisplatinum and bleomycin. The patient presented to the emergency room of the hospital with high fevers and abdominal pain. His admission chest X-ray was normal and at laparotomy, he was found to have a bowel infarction. He developed hypoxemia post-operatively that required mechanical ventilation, positive end-expiratory pressure (PEEP) and an increase in the FiO_2 from 0.4 to 0.7. The patient developed diffuse lower lobe infiltrates. There was no evidence of fluid imbalance and a lung biopsy was performed to rule out complicating infection and revealed findings consistent with bleomycin toxicity.

Lessons Learned: Always consider bleomycin toxicity in any individual who develops respiratory distress and has received bleomycin at any time. It is possible that the acute onset of bleomycin toxicity in this patient was precipitated by the surgery and the use of supplemental oxygen postoperatively. Oxygen clearly exacerbates bleomycin toxicity in animal or cellular models, but its impact in human subjects is less clear and it is important to be prudent in patients that have received bleomycin and to avoid any unnecessary supplemental O_2.

Cardiovascular Drugs

Cardiac medications have been implicated as often a rare, but important class of drugs associated with pulmonary toxicity. For example, methyldopa, commonly used to treat hypertension, was one of the first drugs associated with systemic and immunologic findings consistent with drug-induced lupus syndrome.[16] Similarly, procainamide and hydralazine was also recognized for this side effect. Development of a positive immunologic parameter, such as the antinuclear antigen (ANA) may occur with therapy on such drugs, but this is not necessarily that a systemic drug response will occur nor does it mean that therapy should be altered. It occurs commonly with a conversion rate of 40 to 60% of patients on treatment. The drug-induced lupus syndrome, however, can be serious and life threatening.

In the more recent past, the cardiovascular drug amiodarone has become an important cause of pulmonary toxicity with multiple reports and studies documenting the varied clinical presentations and findings.[17-19] Amiodarone is an unusual drug as it is an iodinated benzofuran derivative and its primary metabolite is created by the liver conversion of desethylamiodarone by the removal of an ethyl group from the parent compound. The drug has a very long pharmacologic half-life of approximately 45 days and both, the parent drug and its metabolite, will persist long after the drug is discontinued.[18,19] Amiodarone was used in Europe for decades before approval for use in the USA and the pulmonary toxicity was not recognized until studied in the USA. This may, in part, relate to the higher doses used in the US as it was initially approved for use with only life-threatening rhythm disturbances that typically required higher doses (600 to 800 mg/day). However, since that time, amiodarone pulmonary toxicity has been well recognized to occur with lower doses of the drug (200 to 400 mg/day) throughout the world, although the toxicity is more common with higher dosages. It also appears to typically require several weeks or months of treatment before symptoms or signs of pulmonary toxicity become apparent.

For patients with a history of congestive heart failure and rhythm abnormalities, the onset of dyspnea or cough or signs of new infiltrates on a chest X-ray might easily be attributed to the underlying cardiac condition. Most typically, amiodarone pulmonary toxicity occurs insidiously with cough, dyspnea, weight loss and evidence of progressive interstitial disease. Another form of toxicity may occur acutely with more of an alveolar pattern and can be localized or diffuse. If associated with pleuritic chest pain, the diagnosis can be confused with acute pulmonary embolism, a condition to be suspected in anyone with a diminished cardiac output. Another form of toxicity mimics Bronchiolitis Obliterans with Organizing Pneumonia (BOOP) that may present with a typical unilateral and pleural-based mass-like lesion.

Lung function testing with diffusing capacity for CO (DL_{co}) often reveals restrictive changes and a low DL_{co} in patients with pulmonary toxicity. However, this may not be as helpful as you would think as a screening tool for toxicity. Similar findings of a decrease in the DL_{co} may occur in otherwise asymptomatic patients taking amiodarone and this does not appear to predict risk of toxicity.

Bronchoscopy is often considered in the evaluation of patients with suspected amiodarone pulmonary toxicity. Both Bronchoalveolar Lavage (BAL) and transbronchosopic lung biopsy can be useful to support the diagnosis or perhaps more importantly to help in excluding other diagnostic possibilities, such as infection or cancer. Bronchoalveolar Lavage in almost all subjects, receiving amiodarone, will show the typical findings of "foamy macrophages"[17-19] whereas, this is quite a characteristic of amiodarone use. This is not a diagnostic of toxicity but rather simply a marker of "drug effect". In contrast, a marked lymphocytosis of $CD8^+$ lymphocytes (typically >40% of BAL cells) may indicate a hypersensitivity reaction. Similarly, the lung biopsy is often nondiagnostic, revealing the typical "foamy macrophages" that again provides evidence that the subject is taking amiodarone but does not necessarily indicate that toxicity is present.

Antibiotics/Antimicrobials

Pulmonary toxicity from antibiotic usage is rare, but since antibiotic or antimicrobial use is so common, it becomes one of the most important classes of drugs to consider as a cause of drug induced lung disease (Table 114.3). Nitrofurantoin toxicity is one of the best described and oldest examples of an antibiotic that can cause severe pulmonary-pleural reactions.[20,21] Nitrofurantoin remains a highly effective antibiotic for urinary tract infections and particularly for those with recurrent urinary infections who require chronic suppression or prophylaxis. For subjects who are taking nitrofurantoin for many years, they are often forgetful about reporting it among their list of medications. This is why the diagnosis of chronic nitrofurantoin toxicity is often missed.

TABLE 114.3: Antibiotic agents

- Nitrofurantoin
- Azulfidine
- Sulfonamides
- Gentamicin
- Neomycin
- Polymyxin
- Colistin
- Streptomycin
- INH, PAS
- Minocycline

Nitrofurantoin pulmonary toxicity can also occur acutely even after the first dose and this can appear with sudden onset of cough and dyspnea and a chest X-ray that has diffuse alveolar infiltrates with or without pleural effusions and may mimic the appearance of congestive heart failure. Occasionally, a patient with acute onset may have a high peripheral blood eosinophil count and this can be an important clue to the diagnosis. In some cases, the peripheral blood changes may be normal or with only slightly elevated eosinophil count, but the BAL may show marked eosinophilia (>30% of total cells). If the onset is acute, simply discontinuation of the drug can bring a prompt recovery of the patient with normalization of the chest X-ray or symptoms in just a few days.

In contrast, chronic nitrofurantoin toxicity may mimic the clinical and roentgenographic presentation of Idiopathic Pulmonary Fibrosis (IPF). The concern in this case is that a missed diagnosis of chronic nitrofurantoin toxicity may result in a patient being given the diagnosis of IPF that is essentially a fatal disease over the course of a few years and for which there is no currently effective therapy outside of lung transplantation. Unlike IPF, corticosteroids hasten recovery from the fibrotic like condition of nitrofurantoin toxicity and if instituted early in the course, the patient can expect a full recovery.

Similar to the case of bleomycin above, nitrofurantoin can generate toxic O_2-derived radicals[22] and similarly, the toxicity can be exacerbated in the presence of hyperoxia. Overzealous use of supplemental O_2 can exacerbate the underlying lung injury and convert a mild case of toxicity into a life-threatening event.

There are many other examples of antibiotic-induced lung toxicity but the following case presentation illustrates a typical example and as noted, the antibiotic may not have been given for a serious medical condition or even as the best available treatment for the condition. At times, our comfort with the use of antibiotics as benign therapies in our outpatient clinical practice masks our scrutiny of these therapies as potentially harmful and even life-altering adverse reactions. This is one example.

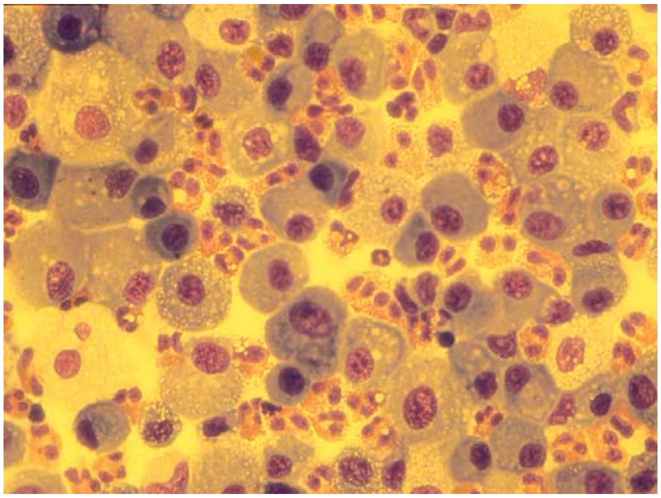

Fig. 114.3: Eosinophilic pneumonia

Brief Case Report: A 17-year-old female athlete (nationally competitive at basketball and running track) presented with a few days of malaise, low-grade fever and light headedness. She developed dyspnea while playing a basketball game and collapsed in the shower after the game. The following day she had dyspnea at rest and a temperature of 39.5°C. A chest X-ray in the emergency room revealed bilateral and peripheral alveolar infiltrates. She was admitted to the hospital and a BAL (Fig. 114.3) and open lung biopsy revealed findings consistent with eosinophilic pneumonia. She was started on oral corticosteroids and tapered over six weeks with modest improvement. She was referred for further evaluation to a pulmonary specialist. Her history revealed that she was started on an antibiotic for "acne and complexion problems," three weeks prior to the onset of her symptoms. On further review, she was found to have taken sulfamethoxazole/trimethoprim, which had not been discontinued despite the hospitalization. Two months after the onset of symptoms, the drug was discontinued and the patient was started on prednisone 60 mg a day for six weeks and with a slow taper of the prednisone dose over six months. Her predicted Forced Vital Capacity (FVC) was 4.65L but when tested at the time of referral was only 2.41L. Six months later, on prednisone 10 mg/ day, her FVC had partially improved to 3.4L. Her chest X-ray had persistent interstitial changes at the bases. She was asymptomatic at rest but was unable to exercise at her prior level of activity and had lost the opportunity to receive an athletic scholarship to a university. Her symptoms and lung functions were unchanged one year later.

Lessons Learned: Always take a complete history on medication use, as any recent medication prior to the onset of a respiratory illness should raise suspicions of a drug-induced respiratory toxicity. Discontinue any medication immediately that is not absolutely necessary if the cause of the respiratory illness is unknown. Eosinophilic pneumonia should always raise the possibility of an environmental source of the pneumonitis, and drug or medication use should be a first consideration. Delays in diagnosis and proper treatment may result in permanent loss of lung function. For a young woman of 17, this was a considerable loss and yet was likely preventable.

Anti-Inflammatory and Miscellaneous Drugs

Several anti-inflammatory agents are associated with respiratory toxicity (Table 114.4). Classically, an overdose with aspirin can result in acute pulmonary edema and marked changes in the acid base balance in the blood, contribute to further respiratory distress.[23] Use of gold salts in rheumatoid arthritis remains a useful therapy for severe diseases and is well recognized as a cause of interstitial lung disease.[24] Clinically, the confusion about the cause of the interstitial changes occurs because rheumatoid disease is also a known cause of interstitial lung disease and it may be difficult to know if the gold or the underlying disease is responsible for the progression of the respiratory disease. Helpful guidelines have been provided to suggest the possibility of a drug reaction, including a fever, skin rash, absence of subcutaneous nodules and more of an alveolar pattern on the chest X-ray.[24] Ofcourse, from a practical perspective, if discontinuation of the gold therapy is possible and results in significant improvement in the symptoms and findings, that would be strongly suggestive that the gold therapy was the source of the respiratory distress.

Penicillamine is another interesting drug that has both chelating and immunosuppressive properties. Its use, primarily as an immunosuppressive agent, in rheumatoid arthritis has been associated with different types of adverse pulmonary reactions, including: (1) Organizing pneumonia, (2) drug-induced lupus syndrome or (3) alveolar hemorrhage.[25] As therapeutic alternatives to penicillamine become increasingly available, it is likely that adverse reactions to this older therapy will become less frequent. However, penicillamine remains an important chelating agent for diseases, such as Wilson's disease and like many therapies; penicillamine may have "second lives" as new indications are found for this therapy from the 1950s.

TABLE 114.4: Anti-inflammatory agents

- Aspirin
- Nonsteroidal
- Gold
- Penicillamine
- Anti-TNF antibodies and other biologics

A variety of miscellaneous drugs not easily put into a single class of drugs or agents also cause lung disease (Table 114.5). For example, there are excellent reviews of how illicit drugs can be a cause of adverse reactions in the respiratory system, including heroin or other narcotic drugs, cocaine and marijuana.[26] In addition, tocolytics, such as oxytocin can induce uterine contractions and thereby prevent postpartum hemorrhage.[27] A diverse number of drugs can cause a drug-induced lupus syndrome, which can mimic systemic lupus erythematosis, including hydralazine, penicillamine, alpha methyldopa, procainamide, various anticonvulsants and more recently anti-tumor necrosis factor (TNF) antibody therapy.[28,29]

TABLE 114.5: Miscellaneous

- Illicit drugs
  - — Cocaine
  - — Heroin
  - — Marijuana
- Drugs inducing SLE
- Tocolytics
- Hydrochlorothiazde
- Diphenylhydyantoin
- Methylsergide
- Sirolimus
- Carbamazine

DIAGNOSIS AND MANAGEMENT OF DRUG-INDUCED RESPIRATORY DISEASE

As noted in the introduction, there is nothing more important in the diagnosis of drug-induced respiratory disease than an accurate history and recognition that a medication or drug might be the cause of the respiratory distress. If that key-step is missed, all the subsequent testing and evaluation may not establish the link and may not make the correct diagnosis in your patient.

The standard diagnostic approach includes everything from a history and exam to a lung biopsy, if necessary (Table 114.6). Obviously, chest imaging with a chest X-ray and chest computerized tomography often

TABLE 114.6: Diagnostic approaches

- History
- Physical examination
- Chest X-ray, Chest CT
- Pulmonary function tests
- Bronchoscopy (biopsy, BAL)
- VATS or open lung biopsy

provide critical information regarding the pattern and extent of the disease and many provide enough information to establish a "working diagnosis" of a drug reaction.[30-32] Pulmonary function tests can be helpful in confirming the typical findings of a restrictive pattern with a decrease in the diffusing capacity, although some drugs may induce obstructive changes whereas others do not affect diffusing capacity. The Pulmonary function tests (PFTs) can also be abnormal prior to the onset of symptoms and do not necessarily indicate clinical disease or clinical progression. Many patients have more than one reasonable explanation for the diagnosis and may require a more invasive approach including a lung biopsy.

Flexible fiberoptic bronchoscopy remains a very useful tool in the assessment of patients with suspected drug-induced respiratory disease. Bronchoalveolar lavage can strongly suggest certain diagnoses, such as eosinophilic pneumonia (Fig. 114.3) or hypersensitivity pneumonitis if there is an exuberant number (>40% of total cells), representing CD8$^+$ (suppressor/cytotoxic) lymphocytes. In addition, bronchoscopy with transbronchoscopic lung biopsy and BAL can help in assessing the presence of other conditions, such as complicating infection, underlying respiratory disease (for which the patient might be receiving the drug) or metastatic cancer.

However, even after completion of all available diagnostic tests, the clinician might remain uncertain if the patients' symptoms reflect a case of drug-induced respiratory disease. Under these circumstances, one can consider all of the information to indicate whether supportive evidence exists or whether careful assessment of the patient's status following drug withdrawal is the best approach (Table 114.7). Many patients respond quickly to the withdrawal of a drug causing the lung reaction but if the symptoms have been present for weeks or months, the response may be slow. Under these circumstances or if the patient is severely ill, many clinicians would favor a course of corticosteroids in addition to the drug withdrawal, as it will hasten recovery and will be reassuring to both the patient and the clinician that the diagnosis was correct.

TABLE 114.7: Verification of diagnosis

- Supportive evidence from lung biopsy or BAL material (also important for exclusion of other diagnosis)
- Improvement in subjective and objective parameters following drug withdrawal
- Rechallenge with drug reproduces findings (rarely indicated)

Even after all of the above, at times the clinician might consider a rechallenge with the drug suspected of causing the reaction, but this is rarely indicated. A rechallenge might only be considered if the drug suspected (but not proven) of causing the lung reaction is the only available therapy for a life-threatening condition. One example in my own experience was a case of suspected amiodarone pulmonary toxicity for a patient with a history of life-threatening ventricular rhythm disturbances. In this case, stopping the drug promptly increase the ventricular rhythm abnormalities. We were uncertain of the diagnosis and elected to rechallenge the patient in the intensive care unit setting. The patient did not show signs of any respiratory distress and resumed full therapy without incident.

There are often no easy answers in the management of patients with suspected drug-induced respiratory disease. One must have the discipline to understand clearly the rationale for each test ordered and what you would do with the information when it is available regarding the management of the patient. Obviously, if the history, exam and chest imaging suffices to establish a "working diagnosis", then drug withdrawal with or without corticosteroids may be the best approach. In some patients, a clear definitive answer is not available even after an open lung biopsy. In such cases, clinical judgment is necessary to determine, if drug withdrawal is best to assess its impact on the patients symptoms and findings. As noted above, the need for a rechallenge with a drug is rarely indicated as almost always, there are alternative therapies available for the patient and there is no justification for a rechallenge, which in itself can be life-threatening. As the dictum in medicine is that "primum non nocere" or "first, do not harm", it is highly unlikely that there will be clinical circumstances that a clinician should seriously consider a rechallenge. There are almost always other therapies available that will provide safe and effective therapy for your patient.

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Section

14

PULMONARY NEOPLASMS

D Behera

115

Epidemiology and Etiopathogenesis of Lung Cancer

Navneet Singh

INTRODUCTION

Lung cancer is the most common malignant neoplasm world over.[1] It accounts for more cancer deaths than any other cancer.[2] Impressive advances have been made in relation to the understanding of the pathogenesis of lung cancer over the past few decades.[3] Tobacco smoke remains the most important risk factor and etiological agent for its development. In addition, several other environmental and occupational carcinogens have been identified. Genetic factors which determine susceptibility to this disease continue to be evaluated. There has also been a steady improvement in the understanding of the pathogenesis of this disease at the molecular level, including progression from normal respiratory epithelium to frank neoplastic cells as well as changes observed after this transition (survival, growth and proliferation of cancerous cells). This has important implications in terms of early detection and chemoprevention of the disease.

EPIDEMIOLOGY

Lung cancer is the most common cancer representing approximately 12% of all new cancers.[1] It is also the most frequent type of cancer in males and remains the most common cause of cancer related mortality in both sexes.[2] Most patients present with an advanced disease.[4]

Distribution of Various Histological Type

The major histological types of lung cancer include Squamous Cell Carcinoma (SqCC), Adenocarcinoma (ADC) and Small Cell Lung Cancer (SCLC).

In the recent past, a relative increase in the incidence of ADC has been witnessed. In most of the developed countries, it has become the dominant histological type of lung cancer.[5,6] It has also overtaken SqCC as the most common form of lung cancer among males in some countries while it has continued to be the commonest type among females.[6] A compilation of population-based lung cancer incidence data from registries contributing to the International Agency for Research on Cancer (IARC) databases revealed that rates of all lung cancer types among women and of ADC among men had risen despite a decline in cigarette use in many Western countries as well as a shift to filtered and low-tar cigarettes.[7]

Incidence rates for SqCC declined by 30% or more among males in North America and some European countries while the decline in those for SCLC was less pronounced. On the other hand, among females, incidence rates for both SqCC and SCLC showed an increase in most of the regions. Importantly, the incidence of ADC increased among both sexes in virtually all areas.

Link between Histology and Smoking

This histological shift (increase in the incidence of ADC) in the developed countries has been linked to changes in the smoking behavior of the population in these regions as well as in the method of manufacturing and composition of cigarettes being marketed therein.[8,9] Use of cigarettes that had filters as well as a lower content of tar and nicotine resulted in a tendency for their smoke to be inhaled more deeply.[10] This led to a higher concentration of carcinogens in the peripheral areas of the

TABLE 115.1: Lack of change in the epidemiological profile of lung cancer in North India (modified and adapted from Singh et al)[13]

Period of data collection	*1977-86*	*2007-09*
Number of cases	1009	250
Mean [±SD] age (years)	54.3 [*]	57.9 [±11.3]
Male: female	4.48 : 1	4.43 : 1
Smokers**: never-smokers	2.68 : 1	2.67 : 1
Major histological types		
• Squamous cell	34.3%	34.8%
• Adenocarcinoma	25.9%	26.0%
• Small cell	20.3%	18.4%

SD = Standard deviation
* SD not mentioned
** Includes both current smokers and ex-smokers

lungs where ADC tends to form.[11] Higher levels of nitrates in the tobacco blends used in cigarette manufacturing have also been linked to the development of ADC.[12]

However, in a recent analysis of temporal trends conducted at the author's institute, no significant change was observed in the epidemiology of lung cancer as compared to that seen three decades ago (Table 115.1).[13] Squamous cell carcinoma was the most common histological type overall as well as among patients who were current/ex-smokers. Adenocarcinoma was the predominant histological type only among never-smokers. Data available from the population based National Cancer Registry Program (NCRP) of India was analyzed to determine the trends in incidence rates of 10 major cancers over a period of almost two decades (1982 to 2000).[14] Here also, no significant changes were observed, during the study period, in relation to lung cancer. However, there was no data about the distribution of different histological types of lung cancer.

One of the likely reasons for the lack of change in the epidemiology of lung cancer in India (and possibly other developing countries) is the fact that the most common smoking product is not cigarette, but *bidi*- the hand rolled form of tobacco wrapped in the dried tendu leaf.[15] In a large Indian multicentric study conducted recently, the ratio of *bidi* to cigarette smoking was 2.6:1 overall and 6.5:1 in the rural areas.[15] The process of *bidi* manufacturing is primarily a cottage industry and has changed little with time unlike that for cigarettes. Moreover, quit rates for smoking continue to be less than 10% in India.[15] Therefore, an absence of change in the smoking pattern of the Indian population may be another reason for the lack of change in the epidemiology of lung cancer. After the recent initiation of vigorous anti-tobacco measures under the national tobacco control program, there is a possibility that, the ratio of smokers to never-smokers as well as the distribution of different types of smoking products may change with time and this may ultimately lead to a change in the clinical-epidemiological profile of lung cancer presentation. However, such a change is likely to occur only after a lag of several years to a few decades, which reflects the time period needed for any intervention related to smoking cessation to have its effect on a disease linked to chronic tobacco consumption.

An important difference in the pathogenesis of the various histological types of lung cancer is in relation to their site and cell of origin. The conducting bronchial airways are the site of origin of almost all cases of SqCC and SCLC. The basal bronchial cell, a candidate stem cell, is believed to be the cell of origin for these histological types.[16] A small proportion of cases of ADC can also arise in this way. However, majority of ADC have their origin in the peripheral compartment of the lung primarily the terminal respiratory unit, respiratory bronchioles and the alveoli. Herein the bronchioloalveolar cell, another putative stem cell, is thought to be the cell of origin. This cell is also believed to give rise to Clara cells and type II pneumocytes.[16]

During the process of development of SqCC, genetic and environmental triggers lead to the changes in the normal bronchial epithelium, often in a stepwise manner, with the formation of hyperplastic, metaplastic and dysplastic lesions. Continuous oncogenic stimuli ultimately lead to the development of carcinoma in situ and frank SqCC. In the case of ADC, a similar mechanism is believed to be operating, since atypical adenomatous hyperplasia (AAH) is a premalignant lesion and often precedes the development of overt ADC.

RISK FACTORS

Risk factors having proven or possible association with lung cancer are elaborated in Table 115.2.

Tobacco Smoking

Tobacco smoking is the most common risk factor for lung cancer. The majority of lung cancers including approximately 85% of Non-Small Cell Lung Cancer (NSCLC) and 98% of SCLC cases arise in smokers. Several carcinogens have been identified in tobacco smoke and strong associations for a few of them [including Polycyclic Aromatic Hydrocarbons (PAH) and nicotine-derived

TABLE 115.2: List of risk factors that have proven or possible associations with lung cancer

Tobacco Smoking (Active)
Environmental tobacco smoke (ETS) exposure
Pulmonary Diseases
- Chronic obstructive pulmonary disease (COPD)
- Idiopathic pulmonary fibrosis (IPF)
- Systemic sclerosis related interstitial lung disease
- Pneumoconiosis

Systemic Diseases
- HIV infection

Air pollution (indoor and outdoor)
- Domestic cooking fuels
- Petroleum product combustion exhaust exposure

Environmental exposures
- Radon
- Arsenic, nickel, chromium
- Asbestos

Dietary factors
- Alcohol consumption
- Intake of vitamins, fruits and vegetables

Hormone therapy
Genetic factors
- Familial (hereditary)
- Specific gene abnormalities (non-hereditary)

nitrosoaminoketone], have been observed with the occurrence of lung cancer. These carcinogens are responsible for the development of genetic mutations through formation of deoxyribonucleic acid (DNA) adducts.

In a case control study conducted at the author's institute, an evaluation of the role of tobacco smoking in relation to the occurrence of lung cancer was undertaken.[17] Ever-smoking was associated with odds ratio (OR) of 5.0 [95% confidence interval (CI) = 3.11-8.04] among men and 2.47 (95% CI = 0.79 to 7.75) among women for occurrence of lung cancer. Among the patients, men were found to smoke a higher average number of cigarette-equivalents per day, for longer duration and started at an earlier age as compared to controls. Interestingly, tobacco smoking in traditional Indian forms (*bidi* and *hookah*) was associated with similar ORs as compared to cigarette smoking implying that tobacco smoking is equally bad in its various forms. In a subsequent study performed at this institute aimed at evaluating the risk factors associated with development of lung cancer among females, it was observed that the odds were highest for active tobacco smoking (OR = 4.87; 95% CI = 1.34-17.76) although majority (74.6%) of the subjects (females) were nonsmokers.[18] Therefore, in the Indian context and possibly elsewhere in the world also wherein a similar socioeconomic profile is present, active tobacco smoking is the principal risk factor responsible for causation of lung cancer among men while several other risk factors besides smoking are important in the case of women.

Lung Cancer in Never-smokers

An estimated 10 to 15% of lung cancer related mortality is related to factors other than active smoking. Moreover, majority of the cases of lung cancer attributable to such factors occur in never-smokers. Lung cancer occurring among never-smokers is believed to be different from that occurring among smokers and this hypothesis is supported by differences in the molecular profile seen in the two groups.[19] Lung cancer among never-smokers (often referred to as nonsmokers) arises in the peripheral compartment, in contrast to smokers where it occurs in the central compartment. Important risk factors for occurrence of lung cancer among never-smokers include Environmental Tobacco Smoke (ETS) exposure as well as exposure to outdoor and indoor air pollutants, several of whom can induce, promote and propagate the process of carcinogenesis. Despite this, in several cases, a clear etiological agent(s) may not be identifiable since the available data on the association of such factors with occurrence of lung cancer is not as strong as it is for active tobacco smoking and several exogenous carcinogens remain poorly defined.

ETS Exposure

A case-control study was conducted previously at the author's institute to assess the relationship between exposure to ETS and occurrence of lung cancer in lifetime never-smokers.[20] Assessment of ETS exposure from different tobacco products during childhood at home and during adulthood at home, at work place and inside vehicles was made. Overall, an increasing risk for lung cancer was found with increasing number of smokers and duration of exposure. A strong association was observed between ETS exposure during childhood and lung cancer [OR = 3.9; 95% CI = 1.9-8.2]. In relation to adult life, the increased risk due to ETS exposure from a smoking spouse was observed only in case of cigarette smoke (OR = 5.1; 95% CI = 1.5 to 17). Exposure to ETS inside vehicles was also detected to be a risk factor (OR = 5.2; 95% CI = 1.9 to 14).

Indoor Pollution

Indoor pollution due to domestic cooking fuels has also been implicated as a causative agent in lung cancer especially among women. In a case control study at the author's institute, information about exposure to various cooking fuels was obtained from women using a questionnaire.[18] Among non-smokers, the risk of development of lung cancer was highest for biomass fuel exposure [OR = 5.33; 95% CI = 1.7-16.7]. This risk persisted (OR = 3.59; 95% CI = 1.07-11.97) even after adjustment for smoking and ETS exposure was made in multivariate logistic regression analysis. Use of mixed fuels was associated with a lesser risk (OR = 3.04; 95% CI = 1.1-8.38).[18] Duration of exposure is an important determinant as was seen in one study wherein cumulative exposure of greater than 45 years to indoor air pollution from use of coal or wood for cooking or heating showed an OR of 1.43 (95% CI = 0.33-6.30) for the development of lung cancer.[17]

It has been demonstrated that wood smoke exposure can produce similar molecular effects on p53 tumor suppressor gene as tobacco and thus be an important risk factor for lung cancer among never-smokers.[21]

Socioeconomic Profile

In a systematic review and meta-analysis of published literature, the association between various socioeconomic indicators and lung cancer incidence was evaluated.[22] On analysis of 64 studies which were eligible for inclusion, an overall increased risk in lung cancer incidence was observed among people with low socioeconomic profile. Two important observations were noted in this article. Firstly, the increased risk persisted even after adjustment for smoking status, a potentially important confounder. Secondly, the increase in lung cancer incidence was observed in three different aspects of socioeconomic profile namely educational, occupational and income-based with the association being strongest for the former and weakest for the latter.[22]

Analyses of a subsample of the European Prospective Investigation into Cancer and Nutrition (EPIC) study was conducted to determine the extent to which occupational exposures could influence the socioeconomic inequalities in lung cancer incidence.[23] In this, exposure to three carcinogens {asbestos, heavy metals and PAH} was analyzed. These occupational exposures could account for 14% of the socioeconomic inequalities remaining after adjustment for tobacco smoking and dietary factors (fruits and vegetables consumption).

Enviromental Exposures to Minerals and Metals

Arsenic has been identified as a lung carcinogen in humans. In a geographically defined cohort study, more than 10,000 subjects residing in arseniasis-endemic areas were followed up for an average period of eight years.[24] After adjustment for cigarette smoking and other risk factors, a significant dose-response trend was observed between level of arsenic in drinking water and lung cancer. The relative risk for the highest arsenic level, as compared with the lowest, was 3.29 (95% CI = 1.60-6.78). Lung cancer was attributable to the joint exposure of ingested arsenic and cigarette smoking in 32 to 55% of cases. A synergistic effect of ingested arsenic and cigarette smoking on occurrence of lung cancer was also noted. Chromium, nickel and asbestos are other important carcinogens.

Radon has been associated with lung cancer among miners working under ground. However, even the general population remains at risk due to exposure to indoor radon and its decay products. The risk of lung cancer from this environmental exposure is in the form of a linear dose-response relationship with no threshold.[25] In certain areas, radon is believed to be the second main causative agent for lung cancer, after tobacco smoking, in the general population without any other form of occupational exposure. This has important implications for disease prevention, since it is important to identify buildings which have high radon concentrations.

Petroleum Product Combustion

The association of petroleum product combustion with lung cancer has also been evaluated. In particular, use of diesel for power generation became very common in the 1950s and till 1990, exhaust from its combustion was 100 fold compared to current levels using newer technology. In a recent review, the possible link between particulate matter in diesel exhaust and lung cancer was assessed.[26] However, majority (24) of the 34 studies had either indeterminate or negative trends while only ten showed a positive trend in exposure-response analyses. Moreover, it could not be ascertained even in the small number of positive studies, whether the association was causal in nature or not.

Alcohol Consumption

Analysis of the Environment and Genetics in Lung Cancer Etiology (EAGLE) Study, a population-based case-control study, was done to investigate the relation between alcohol consumption and lung cancer.[27] Consumption of alcohol during adulthood was assessed in 1,855 cases and 2,065 controls. Interestingly, both non-drinkers [OR = 1.42; 95%; CI = 1.03 to 2.01] and very heavy drinkers ($\geq$60 gm/day; OR = 1.44; 95% CI = 1.01 to 2.07) were at significantly greater risk than very light drinkers (0.1 to 4.9 gm/day). However, the alcohol effect was confounded by smoking behavior since no excess risk was observed among never-smokers on multivariate analysis. This was a hypothesis generating study since it suggested the possibility of an interaction between alcohol consumption and tobacco smoking in relation to occurrence of lung cancer.[27]

Hormone Use

Association between hormone use and lung cancer among women was assessed in a prospective study involving 2,861 women aged 31 to 79 years with a follow- up period of approximately 30 years.[28] Overall, this study did not find any association between hormone use and lung cancer (hazard ratio = 1.13; 95% CI = 0.73-1.73). Even on analysis after stratification by age (55 years being taken as an approximate cut off for menopausal status), the results did not reach statistical significant. However, divergent results were observed with a trend for higher risk among women aged 55 years or above and for a lower risk among women younger than this age.

Structural Lung Disease

Structural lung disease is believed to be a predisposing factor for the development of lung cancer. Idiopathic Pulmonary Fibrosis (IPF) is one of the important disorders in this group. In a retrospective longitudinal cohort analysis, the cumulative incidence of lung cancer after the diagnosis of IPF was assessed.[29] During the observation period, 20.4% patients developed lung cancer. The cumulative incidence rates increased as the duration of follow-up increased being 3.3%, 15.4% and 54.7% at 1, 5 and 10 years respectively. Systemic sclerosis and other causes of interstitial lung disease as well as old scars of pulmonary tuberculosis and other infections have been occasionally implicated to predispose to the development of lung cancer.

Human Immunodeficiency Virus (HIV) Infection

Lung cancer risk is substantially elevated in HIV-infected individuals as compared to the general population. However, there are two important features in relation to HIV related lung cancer. First, the risk is unrelated to HIV-induced immunosuppression.[30] Second, smoking does not account for all of the increase seen in the incidence of lung cancer – the higher risk being present even after adjustment for smoking.[30,31] The other factors responsible for the increased incidence remain poorly identified as of now.

Genetic Factors

Familial aggregation of cases has also been documented in literature. In a case control study conducted at the author's institute, patients with lung cancer were more likely than controls to have relatives with cancers [OR = 1.27; 95% CI = 0.49 to 3.10] both among smokers and non-smokers (OR = 1.31; 95% CI = 0.27 to 6.79 and OR = 1.21; 95% CI = 0.12 to 6.16 respectively).[32] Sisters of cases, in particular, had a higher risk (OR = 8.72; 95% CI = 0.85 to 430.08). This study lends credence to the suggestion that genetic factors perhaps are independent risk factors for the occurrence of lung cancer.

MOLECULAR BIOLOGY

Several genetic alterations, elaborated in Table 115.3[33] have been observed in lung cancer. The main molecular mechanisms observed in its pathogenesis include abnormalities in growth-stimulatory signaling pathways, abnormalities in tumor suppressor gene pathways, evasion of apoptosis and epigenetic changes (Table 115.4).[16] In some cases of NSCLC, a single specific mutated oncogene can act as the primary genetic "driver" responsible for the pathogenesis of cancer. The two most commonly mutated oncogenes in lung cancer

TABLE 115.3: List of genetic alterations observed in lung cancer (modified and adapted from Sato et al)[33]

Gene	*Type of Alteration*
Epidermal growth factor receptor (EGFR)	Mutation, amplification
HER-2	Mutation, amplification
RAS	Mutation
p53	Mutation, deletion
PI3K/AKT/mTOR	Constitutively activated
MEK	Constitutively activated
Vascular Endothelial Growth Factor (VEGF)	Over-expression
Telomerase	Over-expression
BCL-2	Over-expression
c-Kit	Over-expression

are the Epidermal Growth Factor Receptor (EGFR) gene and KRAS gene.

EGFR Expression

The EGFR family of genes encodes widely expressed transmembrane tyrosine kinase molecules. On activation by the ligand, these receptors signal through the RAS-RAF-mitogen activated protein kinase and phosphatidylinositol 3-kinase pathways and play a key role in regulating cell proliferation and survival (Fig. 115.1). Mutation or hyperexpression of these receptors are responsible in lung cancer for their oncogenic activation, favoring proliferation, differentiation, apoptosis and angiogenesis. The most common EGFR mutations observed are exon 19 deletion and exon 21 L858R point mutation. In the latter, leucine at amino acid 858 is replaced by arginine.

KRAS Mutations

The RAS genes encode a family of membrane-bound 21-kd Guanosine Triphosphate (GTP)-binding proteins, which by interacting with multiple effectors, are involved in the regulation of cell growth, differentiation, and apoptosis. KRAS mutations are known to occur in 20 to 30% of NSCLCs.[34] These mutations lead to impaired

TABLE 115.4: Molecular mechanisms of pathogenesis of lung cancer (modified and adapted from Brambilla et al)[16]

Abnormalities in growth-stimulatory signaling pathways

- Epidermal growth factor receptor (EGFR) signaling pathway
  - EGFR deregulation
  - Mutations in other EGFR signaling pathway genes - KRAS
- Anaplastic lymphoma kinase (ALK) fusion proteins
- Thyroid transcription factor 1 (TTF-1)
- Myc family

Abnormalities in tumor suppressor gene pathways

- p53 pathway
- p16INK4/cyclin D1/Rb pathway
- Serine/threonine kinase 11 gene

Evasion of apoptosis

- Altered regulation of mitochondrial apoptosis (Bax/Bcl-2 imbalance)
- Deregulation of death receptor (Fas-FasL) pathway
- Inappropriate telomerase activity

Epigenetic changes

- DNA methylation and hypermethylation
- Epigenetic modifications (change in acetylation and/or methylation status) of histones
- Somatic mitochondrial DNA (mtDNA) mutations
- MicroRNAs–dysregulation and/or specific expression patterns

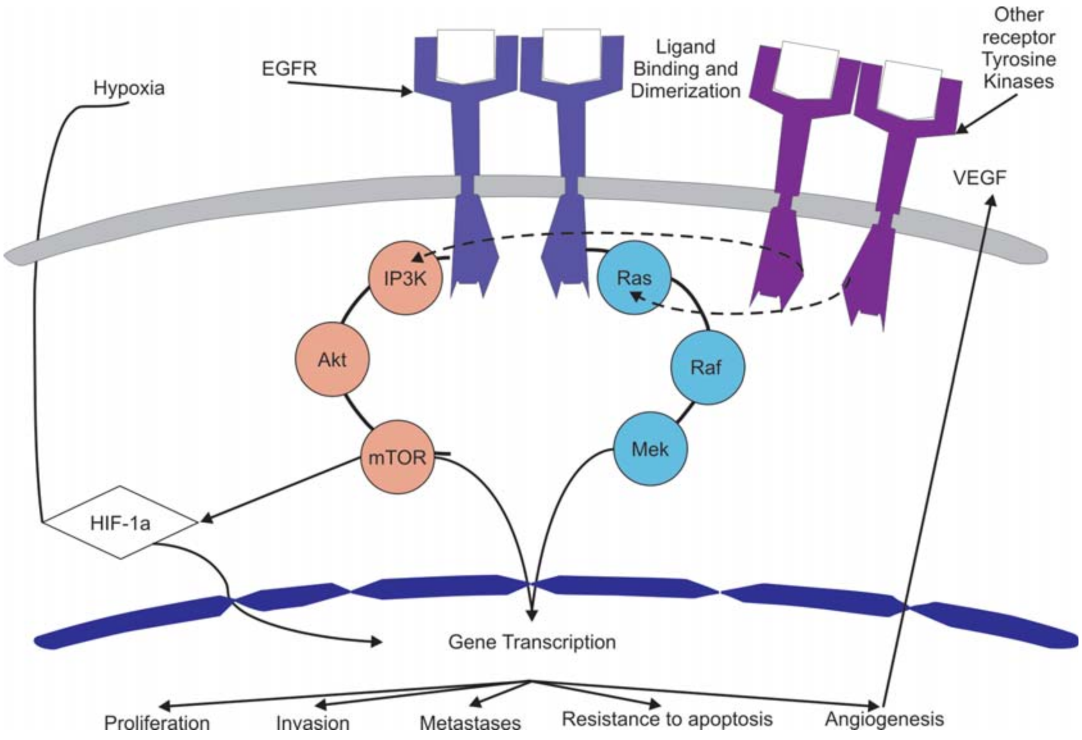

Fig. 115.1: Downstream EGFR signaling pathways through the RAS-RAF mitogen-activated protein kinase pathway and PI3K/AKT pathway

GTPase activity, which is located downstream of EGFR and consequently constitutive activation of RAS signaling.

Comparison of Mutations in EGFR and KRAS Genes

There are several differentiating features between mutations in these two genes. First, EGFR mutations are more commonly found in never-smokers in contrast to KRAS mutations which are commonly present in those with significant tobacco exposure.[35] Second; these mutations determine sensitivity to drugs that target the EGFR signaling pathway. Anti-EGFR molecules like gefitinib and erlotinib are important drugs among the targeted therapies available for treatment of NSCLC and act by blocking EGFR receptor mediated signals which in turn prevent downstream events mediated by RAS and other effector molecules. EGFR receptor blockade ultimately leads to inhibitory effects on tumor cell survival and proliferation.

On the other hand, in the presence of KRAS mutations, as opposed to wild type KRAS gene, KRAS mediated effects are permanently "turned on" and downstream signals occur despite blockade of EGFR allowing the tumor cells to survive and proliferate.[36] Presence of KRAS mutations is therefore an important factor which determines lack of responsiveness to anti-EGFR drugs.[37] Lastly, EGFR and KRAS mutations also serve as prognostic factors with better overall survival being observed in patients having EGFR mutations than those whose with KRAS mutations.[35] Thus, mutations in these two genes are believed to represent subgroups of patients with NSCLC with different natural histories as well as responses to targeted therapy.[36]

Fragile Histidine Triad Gene

The Fragile Histidine Triad (FHIT) gene plays an important role in the pathogenesis of lung cancer. Alterations in the FHIT gene in the form of loss of heterozygosity and complete/partial gene methylation were observed in 100 and 84% of cases.[38] The latter was also observed to be associated with loss of FHIT mRNA expression.

Angiogenesis and Role of Vascular Endothelial Growth Factor (VEGF)

Angiogenesis, the formation of new tumor-feeding blood vessels, from pre-existing vasculature, is critical for the development and growth of tumors and subsequently for invasion and metastasis. Angiogenesis is regulated and determined by the balance between pro-angiogenic and anti-angiogenic factors released by tumor cells and adjacent host cells. However, after a variable period of time, with ongoing growth of tumor cells, the balance shifts in favor of the pro-angiogenic response. This results in endothelial cells growing from nearby blood vessels, crossing the basement membrane and migrating into the tumor mass wherein they undergo proliferation leading to formation of capillaries. However, these are and often leaky. However, neovascularisation is characterized by presence of blood vessels that are qualitatively poor, heterogeneous and leaky. Not only do they contain disorganized and irregularly shaped endothelial cells, the basement membranes are also abnormal.[39]

Proteins encoded by the Vascular Endothelial Growth Factor (VEGF) family of genes are the predominant pro-angiogenic factors. The VEGF family of growth factors is comprised of several structurally related molecules, including VEGF-A, VEGF-B, VEGF-C and VEGF-D. VEGF-A, commonly referred to as just VEGF, is one of the most important in this group. Its binding to the VEGF receptor (VEGFR-2) leads to activation of multiple signaling pathways, as well as up-regulation of genes which promote the proliferation and migration of endothelial cells as well as vascular permeability.[40] Targeting the VEGF pathway has become an important addition to the armamentarium available for the treatment of NSCLC since bevacizumab (a humanized monoclonal antibody directed against VEGF) has been shown to increase overall survival of patients with advanced non-squamous NSCLC when administered in combination with standard platinum based doublet chemotherapy.[41]

Evasion of Apoptosis

The Bcl-2 family of proteins plays a critical role in the regulation of apoptosis and changes in this pathway can lead to altered ratio of pro- and anti-apoptotic molecules and consequently development of lung cancer. Bcl-2 (anti-apoptotic) and Bax (pro-apoptotic) are key regulators of mitochondrial apoptosis. Bcl-2 overexpression has been observed in lung cancer especially SCLC. A positive association of p53 (a tumor suppressor gene) with Bax expression has been demonstrated in bronchial biopsy specimens obtained from patients with locally advanced squamous cell carcinoma of the lung.[42]

Another mechanism for evasion of apoptosis is via the death receptor pathway. The death receptor (Fas) activates a signaling pathway on binding to its ligand (FasL) leading to apoptosis. The Fas receptor and FasL are down-regulated in a majority of cases of NSCLC.

Telomeres are repetitive sequences (TTAGGG repeats) that are located at the end of chromosomes. They protect chromosomes from degradation and loss of essential genes. Under normal circumstances, telomeres shorten after each round of cell division. When critical shortening of telomeres occurs, it leads to induction of apoptosis or cellular senescence. The enzyme telomerase maintains telomeres by elongating telomeric DNA through the process of reverse transcription. Telomerase gene over-expression is another molecular abnormality observed in lung cancer. Telomerase activity in sputum correlates with that observed in bronchial biopsy specimens. Sputum telomerase activity has been shown to have sensitivity, specificity, negative predictive value and positive predictive value of 67.6%, 90%, 71% and 88.46% respectively for the diagnosis of this disease and thus is a candidate non-invasive biomarker.[43]

Other Molecular Abnormalities

Microsatellites of DNA are tandem repeats of 1 to 6 nucleotides that are normally found at different locations in the human genome. Microsatellite Instability (MSI) refers to the phenomenon of expansions and contractions of these tandem repeats that is observed as an early genetic alteration during the process of carcinogenesis. Deletion of one allele of a pair at specific chromosomal loci is known as Loss of Heterozygosity (LOH). Microsatellite instability and LOH correlate with high mutational rates in tumor cells. Both these microsatellite alterations (MSI and LOH) have been observed in DNA extracted from bronchial washings and tumor specimens obtained on bronchoscopy.[44] Detection of these alterations provides better sensitivity than conventional cytology for the diagnosis of lung cancer.

An important understanding has been made in the last decade with the identification of a new mode of gene regulation in the form of non-coding RNAs termed microRNAs (miRNAs or miRs). These molecules are very short (approximately 19 to 22 nucleotide) single stranded RNAs that are involved in the process of gene regulation by either causing induction of mRNA degradation or inhibition of translation.[45] MicroRNAs can regulate several genes simultaneously and thus cellular processes and pathways (like apoptosis, development, proliferation and differentiation). Dysregulation as well as discrete patterns of miRNA expression have been observed in lung cancer in both *in vivo* and *in vitro* studies.

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Pathology of Lung Tumors

Ashim Das

INTRODUCTION

Classification of lung tumor based on histopathological examination has remained debatable. A standardized nomenclature and uniform criteria for diagnosis helps not only in maintaining consistency in diagnosis and treatment but also gives uniformity in epidemiologic and molecular studies. Only morphological aspects by routine light microscopy are taken into account for classification. In addition to H and E stain, a simple mucin stain is only used for this classification of lung tumors. Most of the time, a minimum use of ancillary techniques are used for this purpose.

According to the World Health Organization (WHO) Classification (2004), malignant epithelial lung tumors are divided into five major groups (Table 116.1).[1]

TABLE 116.1: Classification of malignant epithelial tumors of lung

1. Squamous cell carcinoma
2. Adenocarcinoma
3. Small cell carcinoma
4. Large cell carcinoma
5. Carcinoid tumors

MINOR GROUPS

- Sarcomatoid carcinoma and salivary gland tumors
- Adenosquamous carcinoma

Most of the malignant tumors develop through a phase of preinvasive component. The preinvasive lesions are:

1. Squamous dysplasia/carcinoma *in situ*
2. Atypical adenomatous hyperplasia
3. Diffuse idiopathic neuroendocrine cell hyperplasia

These three preinvasive lesions are recognized in WHO classification, as these may progress to invasive neoplasm.

Squamous Dysplasia—Carcinoma *in Situ*

Many small cell carcinomas may arise through this type of alterations. Basal cell hyperplasia, goblet cell hyperplasia and squamous metaplasia are also identified as earlier changes of dysplasia/carcinoma *in situ* changes of squamous epithelium of central airways.

Basal cell hyperplasia is defined as the presence of three or more layers of basal cells without any evidence of keratinization or intercellular bridges but lacking cellular atypia.

Goblet cell hyperplasia is characterized by excessive numbers of mucus secreting goblet cells in the respiratory epithelium.

Squamous metaplasia is recognized by the replacement of full thickness of respiratory epithelium by squamous cells.

In squamous dysplasia/carcinoma *in situ*, four grades are recognized. Macroscopically, these areas could be pale with loss of transparency, vague nodularity or granularity can be seen. The grading of squamous dysplasia depends on the presence of atypia in the different layers of epithelium with increasing severity of cellular and nuclear pleomorphism. Maturation of cells and cellular orientation are also taken into account in categorizing the different grades. Among the nuclear features, nuclear-cytoplasmic ratio with finely granular to thick coarse chromatin pattern along with increase in number of mitotic figures are important for the recognition of different grades of squamous dysplasia/carcinoma *in situ*.

Mild dysplasia; is characterized by minimal architectural and cytological atypia limited to the lower third of lung with absent or rare mitosis. Moderate dysplasia shows cellular crowding in the lower two-thirds of the epithelium with mild pleomorphism and anisocaryosis with mitosis observed in lower third. On the other hand, severe dysplasia is characterized by marked cytological atypia involving even the upper third with mitotic figures observed in the lower two-thirds. However, a progression of maturation from base to surface can be seen.

Carcinoma *in situ* (CIS) does not show any progression of maturation towards the surface and is characterized by cellular crowding of the entire epithelium with widespread atypia along with the presence of mitotic figures in the full thickness of the mucosa.

Atypical Adenomatous Hyperplasia (AAH)

This has been recognized as a putative precursor of invasive adenocarcinoma. It is difficult to localize AAH lesions grossly without being subjected to proper inflation-fixation of lung. Microscopically, it is defined as "localized proliferation of mild to moderately atypical cells lining involved alveoli and sometimes, respiratory bronchioles, resulting in focal lesions in peripheral alveolated lung, usually less than 5 mm in diameter in the absence of interstitial inflammation". Usually, the interstitium is thickened in these areas with prominent alveolar epithelial cells, which could be cuboidal to low columnar to round in shape with admixing of peg cells with apical snouts. The size of AAH (<5 mm as proposed by WHO for the diagnosis of AAH) may be more than 5 mm even some authors have described lesions of AAH more than 5 mm as carcinoma.

AAH should not be diagnosed in the presence of lesions in which there is an injury to pneumocytes to distinguish it from reactive pneumocytic hyperplasia. AAH is usually diagnosed in a background of adjacent normal alveolar lining. It is also not true that the diagnosis of AAH cannot be done in a background of fibrosis and inflammation. In distinguishing AAH from localized non-mucinous bronchioloalveolar carcinoma (BAC), the features taken into account are as follows: A lesion with increased cell stratification and higher cell density with overlapping of nuclei having coarse chromatin with prominent nucleoli should be diagnosed as non-mucinous BAC. These lesions can show true papillae with cricket fence arrangement of cells and the height of the cells can exceed the normal heights of terminal bronchiole.

Diffuse Idiopathic Pulmonary Neuroendocrine Hyperplasia

This extremely rare lesion may develop into peripheral type of spindle cell carcinoid tumors. It is characterized by widespread proliferation of pulmonary neuroendocrine cells, not only as single cell but also in groups. A linear intraepithelial proliferation is also a characteristic feature. The nodules can project into the lumen with intact luminal lining and intact basement membrane.

EVOLUTION OF WHO CLASSIFICATION

One major change which has occurred in the 1999, WHO classification is the revision of the classification of neuroendocrine tumors and re-definition of bronchiolo-alveolar carcinoma. The introduction of preneoplastic process like atypical AAH and diffuse neuroendocrine hyperplasia is also an important feature in this classification.

The 2004 modification retains much of the same nomenclature as the 1999 edition and maintains the same major diagnostic groups with emphasis on morphologic features of diagnosis and the molecular biology of the various lung malignancies is also extensively covered.

Concept of Bronchioloalveolar Carcinoma (BAC)[2]

In the 1999/2004 classification, BAC is defined as an adenocarcinoma showing 'growth of neoplastic cells along pre-existing alveolar structures (lepidic growth) without evidence of stromal, vascular or pleural invasion (Fig. 116.1). Following this definition, resected localized non-mucinous BACs show 100% 5-year survival. Localized non-mucinous BACs probably evolve from foci of atypical AAH. Foci of stromal invasion are taken as a step towards the development of adenocarcinoma. Some authors commented that this could equally "well, or perhaps better, be considered as adenocarcinoma *in situ*". Hence, if there is an invasion, a diagnosis of BAC done solely based on the presence of a lepidic pattern somewhere in the lesion, could no longer be regarded as BAC. Bronchioloalveolar carcinoma, particularly the mucinous variant, may produce diffuse pneumonic

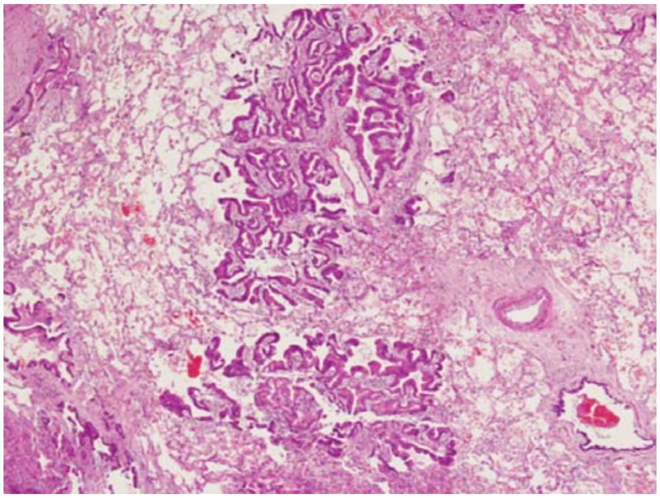


Fig. 116.1: Bronchioloalveolar carcinoma with lepidic pattern of growth, H and E

consolidation. Radiographically, peripheral adenocarcinomas produce a spectrum of ground-glass to solid opacities. The greater the solid component, the greater is the likelihood of an invasive growth component. The radiographic ground-glass component is correlated with the BAC component in pathology specimens.

Challenges Posed by 1999/2004 WHO Classification of Lung Adenocarcinomas[3]

The WHO classification is predicated on the histological examination of the whole of the tumor. The lung adenocarcinoma is a heterogeneous form of lung cancer and most of them are histologically variable, both between cases and within individual tumors. Small biopsy samples which are routinely used may not be representative of the whole tumor and the tumor architecture cannot be appreciated in a small biopsy. Most of the adenocarcinomas are diagnosed on small biopsy or cytology material, using a histological classification that is not really suited to this type of material. Hence, a subtyping of non-small cell carcinomas on small biopsy or cytology samples is not reliable with a relatively poor inter-observer agreement. A mucin stain can improve the figure. The subtype accuracy for adenocarcinoma based on biopsy material is much lower than squamous cell carcinoma. It has been found that most of the cases unclassifiable on small biopsy examination were adenocarcinomas in the surgically resected lung.

Traditionally, the epithelial tumors are divided into *non-small cell and small cell carcinoma* with a view that small cell carcinoma has a different mode of treatment than non-small cell carcinoma. The non-small cell carcinoma includes squamous cell, adenocarcinoma and large cell carcinoma. It is now believed that non-small cell carcinomas are heterogeneous both in molecular biology and also in treatment response.

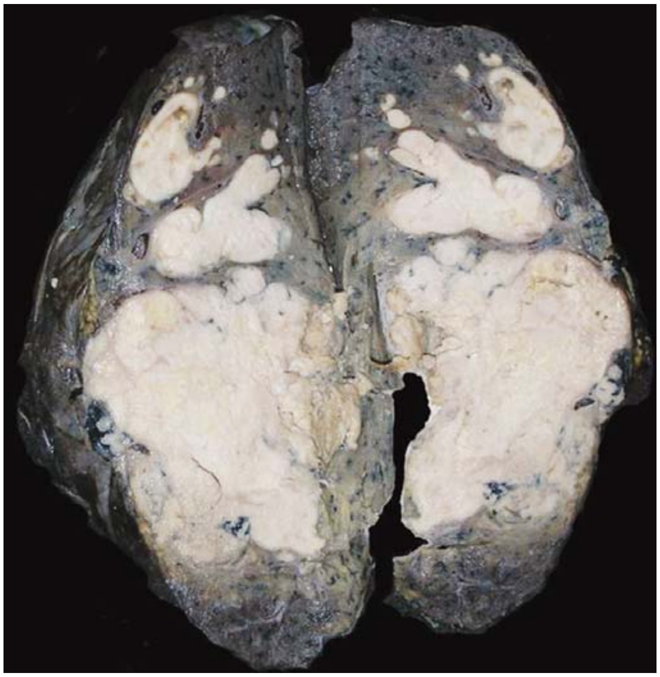


Fig. 116.2: Gross photo of squamous cell carcinoma

Squamous Cell Carcinoma (SCC)

Squamous cell carcinoma typically occurs as a central mass, but approximately 25% are located peripherally and 5% show central cavitation. Histologically, two features are important for diagnosis; keratinization and intercellular bridges (Figs 116.2 and 116.3). The WHO classification recognizes four variants namely; papillary, clear cell, small cell and basaloid. The small cell variant of squamous cell carcinoma is a poorly differentiated variant which contains small tumor cells but retains cellular characteristics of a non-SCC such as coarse chromatin, nucleoli and distinct cell borders.

Adenocarcinoma

The incidence of adenocarcinoma exceeds that of SCC in the developed countries. In our institute, the incidence of adenocarcinoma is increasing but not exceeding. Of a total of 606 cases of lung carcinoma, small cell carcinoma constituted 26.7%. Among the non-SCC (67.7%), SCC

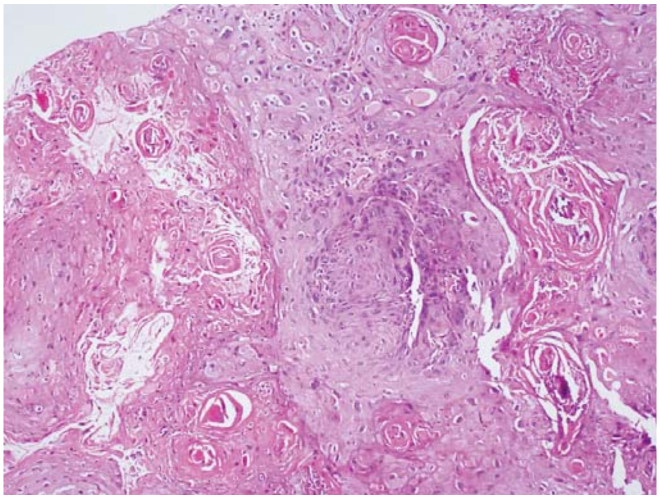


Fig. 116.3: Numerous squamous pearls with tumor cells showing keratinization. (H and E)

represented 71.2% whilst the adenocarcinoma constituted 17.6%. Also, a total of 28 cases were reported as non-small cell carcinoma without any further classification. Adenosquamous (6 cases) and large cell carcinoma (12 cases) constituted smaller groups.

Adenocarcinoma most commonly presents as a peripheral nodule and only rarely shows cavitation (Fig. 116.4). Occasional adenocarcinomas may present as a central or endobronchial tumor. Rare adenocarcinomas may produce a diffuse thickening of the visceral pleura, mimicking a mesothelioma. Histologically, mixtures of patterns are usually seen. These histological patterns may have different biological behavior with potential therapeutic applications for the patients. In fact, 80 to 90% of patients with adenocarcinoma show more than one histological pattern. A simple diagnosis of adenocarcinoma is thus not enough for diagnosis. All possible combinations of the four patterns, acinar (AC), solid (SOL), bronchioloalveolar carcinoma (BAC) and papillary (PAP) tumor can be seen (Figs 116.5 to 116. 7). The most common patterns are acinar and solid tumor. The BAC and solid patterns seemed to be least likely to coexist. The tumors that were predominantly BAC pattern were significantly smaller than those showing predominance of either a papillary or a solid pattern.

Criteria for Diagnosis of Pulmonary Adenocarcinomas

1. Tumor architecture in the form of gland formation in an intact fragment of tumor is essential for the diagnosis of adenocarcinoma.
2. Mucin secretion in two high-power (X400) fields of tumor, each containing at least five tumor cells with intracytoplasmic mucin is recommended for a diagnosis of solid adenocarcinoma with mucin.

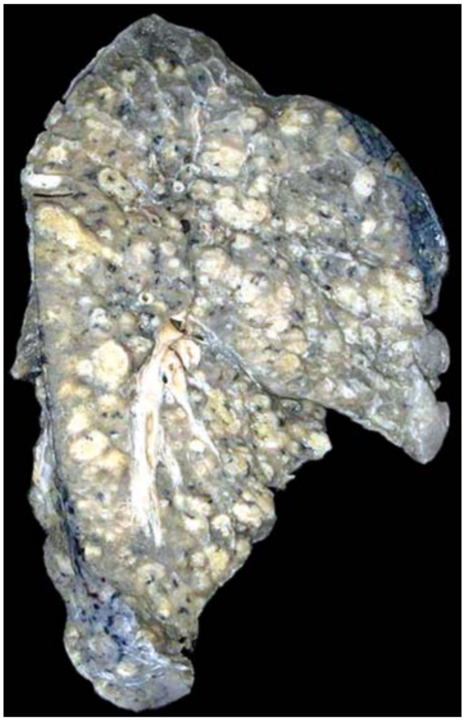
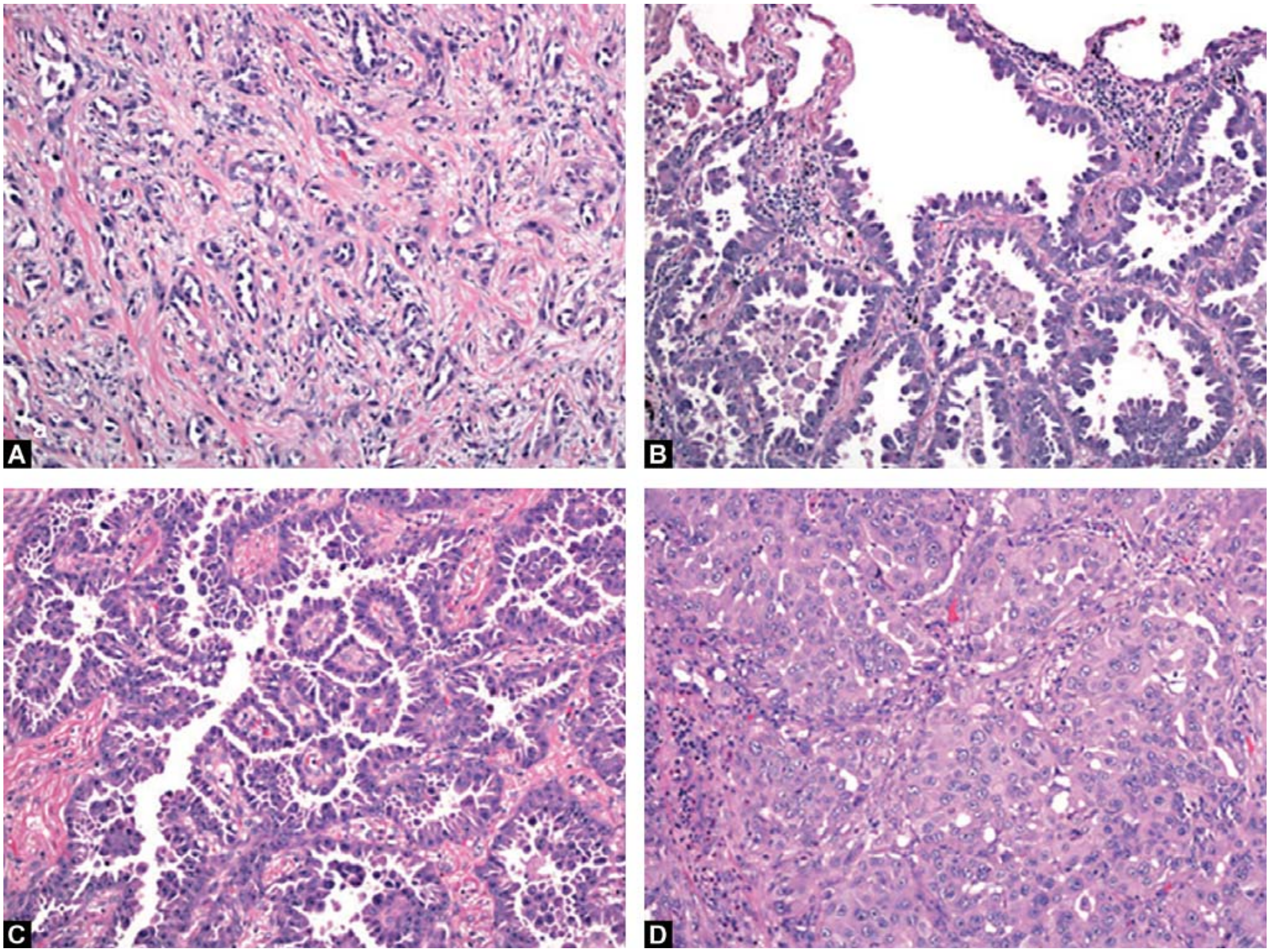


Fig. 116.4: Gross photo of adenocarcinoma with extensive nodular lesions

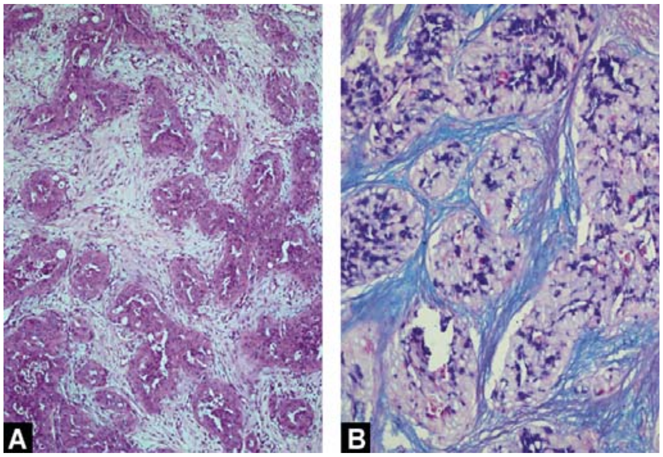
It is important to note that unequivocal squamous cell carcinomas may also show occasional cells containing mucin and there are no unique, reliable individual cytological criteria that allow diagnosis of adenocarcinoma. Immunohistological approaches to refining the separation of squamous cell from adenocarcinoma are potentially valuable, but they need to be measured against cell type classification on resected tumors and against appropriate clinical data and outcomes. Immunohistochemistry should not overwrite the histological classifications of lung tumors.

Small Cell Carcinomas [4,5]

It constitutes approximately 25% of usual lung cancers and it was also known as oat cell carcinoma or small cell neuroendocrine carcinoma. Grossly these tumors are centrally located in the majority of cases. It shows large areas of multifocal necrosis. Microscopically, in the majority of cases the bronchial or transthoracic core biopsy specimens, show an infiltrate of "small" cells with variable crush artefacts and nuclear smearing (Fig. 116.8). The character of the cells should be seen in the better preserved areas. The cells have round or fusiform nuclei



Figs 116.5A to D: Different histological types of adenocarcinoma: A. Acinar pattern, B. Bronchioloalveolar pattern, C. Papillary pattern and D. Solid pattern (H and E)



Figs 116.6A and B: Adenocarcinoma with A. Acinar pattern cells (H and E) showing mucin positivity, B. Alcian blue stain at pH 2.5

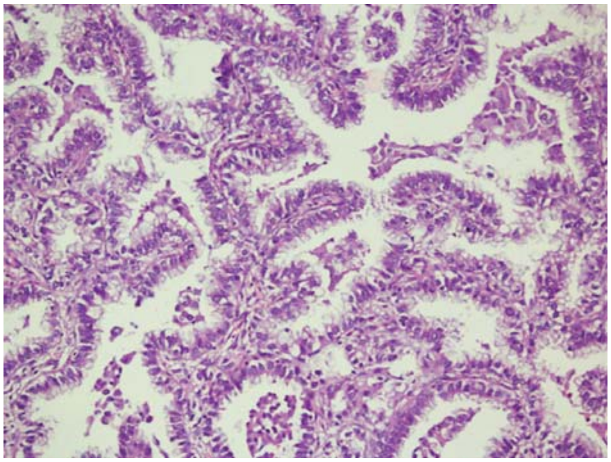


Fig. 116.7: Adenocarcinoma with extensive lepidic pattern of growth by mucinous cells

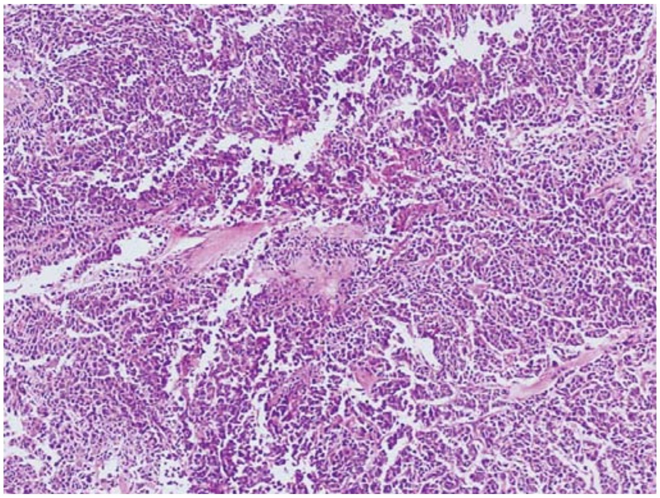


Fig. 116.8: Photomicrograph of small cell carcinoma with single cell infiltration, H and E

with stippled or ground glass chromatin. Only small indistinct nuclei are seen. There can be some larger cells with larger nuclei and occasional nuclei. Abundant cytoplasm may be seen. The0=se are intermediate sized small cell carcinomas according to older WHO classification (WHO 1973).

The small cell carcinoma cells show invariably membrane- bound, dense core neurosecretory granules. Immunohistochemically, cells express low molecular weight cytokeratin expression as perinuclear dot. The cells express neuroendocrine markers like neuron-specific enolase and synaptophysin or chromogranin. The small cell variant of squamous cell carcinoma and non-Hodgkin's lymphomas are the two differential diagnosis of small cell carcinoma. The finding of foci of keratinization will be useful for the diagnosis of basaloid squamous cell carcinoma.

Large Cell Carcinoma

The WHO classifies large cell carcinoma as a tumor of non-small cells with lack of light microscopic or histochemical evidence of glandular or squamous differentiation. This subtype is usually a collection of tumors. *In situ* changes are usually lacking. These tumors are usually peripherally located with pleural and chest wall invasion. Microscopically, the tumor usually shows cohesive clusters of large or intermediate polygonal cells, having abundant eosinophilic cytoplasm with large vesicular nuclei. There is always marked nuclear pleomorphism with numerous mitotic activity. The tumor cells do not show intercellular bridges or keratinizations which are characteristic of squamous cell carcinoma and devoid of any gland formation as seen in adenocarcinoma. A neutrophilic infiltrate is prominent in the stroma. There can be eosinophilic infiltrate (Figs 116.9 to 116.11). A diagnosis of large cell carcinoma hence requires a detailed sampling to exclude poorly differentiated squamous cell carcinoma or adenocarcinoma.

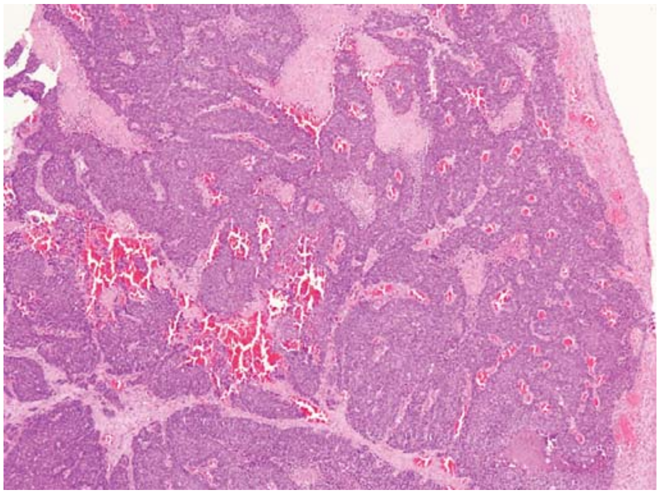


Fig. 116.9: Low power photomicrograph of large cell carcinoma showing large cluster of cells with areas of necrosis (H and E)

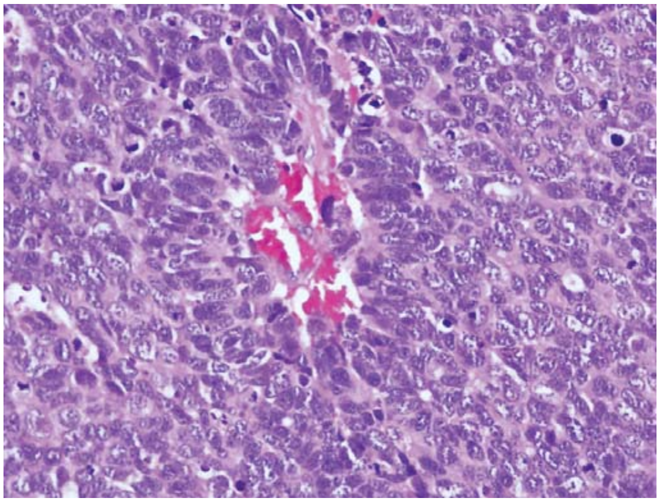


Fig. 116.10: High power photomicrography showing large pleomorphic cells without glandular or squamous differentiation (H and E)

Adenosquamous Carcinoma

The WHO defines a tumor as adenosquamous when both, i.e. adeno and squamous component are present in a same tumor with each occupying at least 10% of total tumorous area. The origin of tumor is mostly from pluripotent cells with dual differentiation. The collision

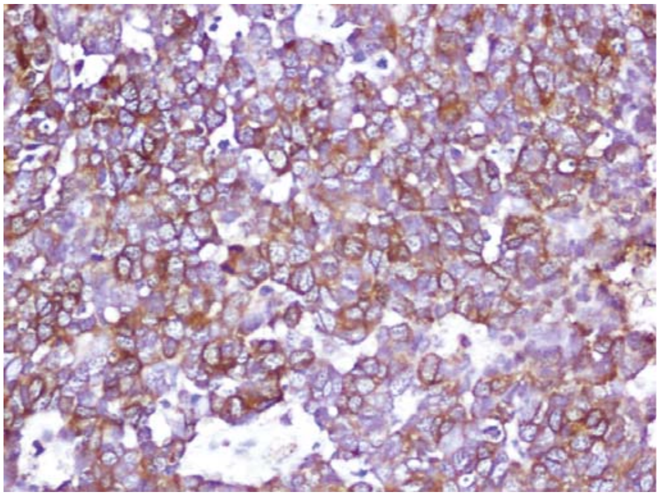


Fig. 116.11: Strong cytokeratin positivity in the neoplastic cells (MNF 116)

theory of adenocarcinoma and squamous cell carcinoma or squamous metaplasia of adenocarcinoma is unlikely.

NEUROENDOCRINE LESIONS OF LUNG[6,7]

A spectrum of neuroendocrine lesions is seen in the lungs:

Neuroendocrine Hyperplasia

- Neuroendocrine cell hyperplasia is seen in association with fibrosis and inflammation. Diffuse hyperplasia can be noticed with or without airway fibrosis or obstruction (Fig. 116.12). The periphery of carcinoid tumor may also show neuroendocrine hyperplasia (Figs 116.13 and 116.14).
- Among the pure neuroendocrine neoplasms, the conditions which are recognized are as follows: Tumorlets, typical carcinoid, atypical carcinoids, large cell neuroendocrine neoplasms and small cell carcinoma.
- A few non-small cell carcinomas can show neuroendocrine differentiation. Many other tumors are also neuroendocrine properties, e.g pulmonary blastoma,

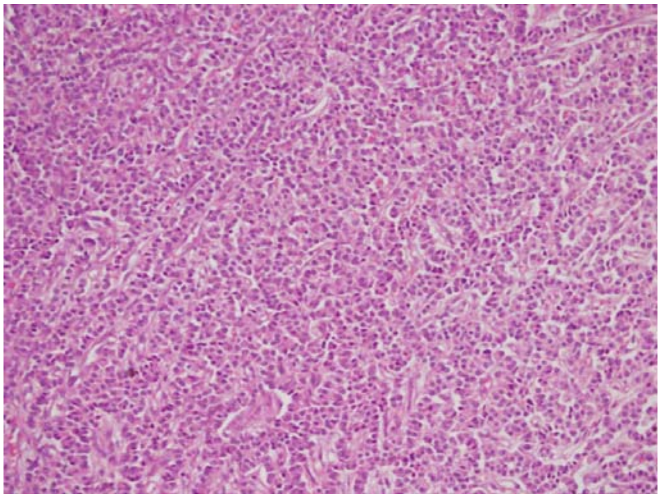


Fig. 116.12: Photomicrograph of carcinoid tumor with cluster of cells separated by thin vascular channels and gyriform pattern of growth (H and E)

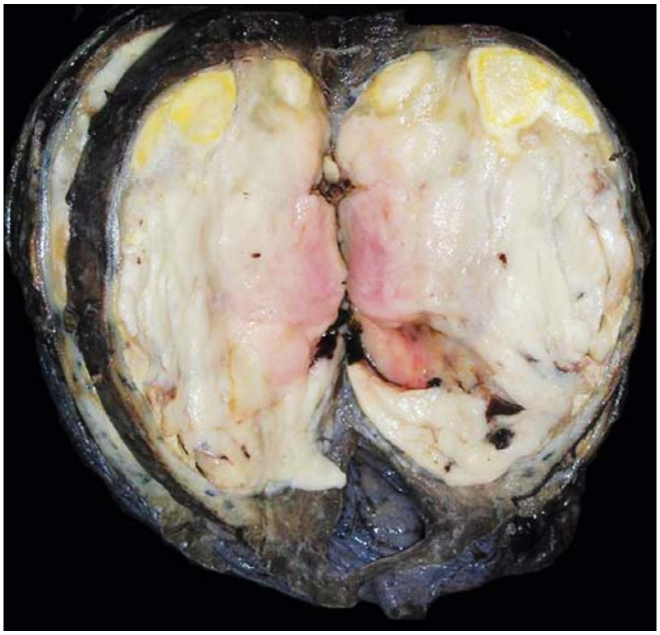


Fig. 116.13: Gross photograph of circumscribed carcinoid tumor

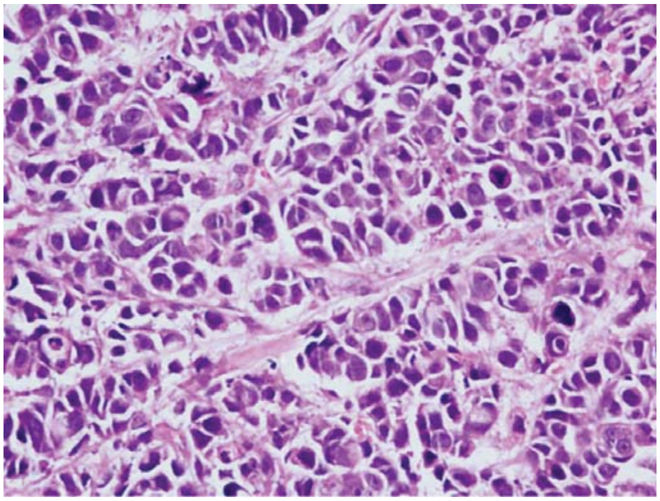


Fig. 116.14: High power photomicrograph showing nuclear molding (H and E)

primitive neuroendocrine tumors, desmoplastic round cell tumors, etc.

Tumorlets

Typical carcinoid tumor is characterized by a large yellow tan lesion in the central bronchus immediately beneath the surface epithelium. It can occur more proximally in the trachea or in the peripheral airways. It measures 0.5 cm or higher. The histological features show organized pattern with trabecular, insular, solid and spindle cell morphology. Other histological pattern like oncocytic, melanocytic pattern is also seen. The cells express neuron-specific enolase, synaptophysin and chromogranin A. The tumor show less than 2/10HPF (per 2 mm^2) mitotic figures without any areas of necrosis.

Atypical Carcinoid Tumor

These lesions are seen in the periphery of the lung in the majority of cases (60%). These are yellow-tan in color. Histologically, the tumor shows organoid pattern with prominent fibrous bands surrounding the groups of cells. The cells show more pleomorphism with increased mitotic figures and areas of necrosis. The mitotic figure is usually 2 to 10 mitoses per mm^2 (per 10 high power field).

Large Cell Neuroendocrine Carcinoma

These tumors are located peripherally and the tumor show cytological features of non-small cell carcinoma having neuroendocrine features like organoid, pallisading, rosettes or trabecular pattern. The cells are larger than three times of the nuclear diameter of resting lymphocytes. The tumors have high nuclear cytoplasmic ratio with increased mitotic rate (>10/10HPF) and areas of necrosis. Neuroendocrine markers, e.g. synaptophysin, chromogranin A and neuron specific enolase are usually positive in these tumors and show neurosecretory granules by electron microscopy.

Small Cell Carcinoma

The previous WHO classification divided this tumor into three types: oat cell type, intermediate cell type and combined oat cell carcinoma with squamous cell and adenocarcinoma. It has been observed that there were biological differences in the different subgroups. In 1999 WHO classification, the small cell carcinomas are dived into two subgroups:

a. Small cell carcinoma replacing the all other terminologies
b. Second group includes mixed small cell-large cell carcinoma and a combination of small cell carcinoma with neoplastic squamous or adenocarcinoma.

Small cell carcinomas are centrally located and the tumors are soft and gray white with areas of multifocal necrosis. The tumors frequently metastasize to different organs. The tumor cells have round to fusiform nuclei with fine strippled chromatin. Some cells are larger with occasional nucleoli. Nuclear material impregnation in the wall of vessels (Azzopardi phenomenon) is frequently seen with areas of necrosis. The tumors show low molecular weight cytokeratin positivity with expressions of neuron-specific enolase, synaptophysin or chromogranin.

Combined Small Cell/Large Cell Carcinoma

It is composed of small undifferentiated cells like small cell carcinoma along with scattered large cells within the small cells. The large cells show variable eosinophilic cytoplasm with distinct cell border and have large vesicular nuclei and prominent nucleoli.

Combined Small Cell/Non-small Cell Carcinoma

It is characterized by a tumor with characteristic small cell morphology combined with a squamous carcinoma, adenocarcinoma or large cell undifferentiated carcinoma component.

STAGING OF LUNG TUMORS[8-10]

An accurate staging of lung tumor is important for various reasons. It helps for collaboration and comparison of cases among various centers. It is extremely useful for treatment planning and evaluating the results of treatment; besides determination of prognosis.

Tumor Size (T Component)

It is an important prognostic indicator in the lung. The tumor diameters of 2 cm, 3 cm, 5 cm and 7 cm are taken into account. T1a is less than or equal to 2 cm but T1b denotes greater than 2 but less than or equal to 3 cm. The T2 is subdivided into T2a which is greater than 3 but less than or equal to 5 cm whilst the T2b is designated as greater than 5 but less than or equal to 7 cm. The T3 tumor is greater than 7 cm.

Two essential features are needed to discuss here:

1. *Measurement of tumor diameter*: The tumor should be measured before fixation. It is essential to subtract the adjacent region of pneumonia and

atelectasis. Regions of central scarring and necrosis should be taken within the measurement of tumor.

2. *Multinodularity of tumor*: In the 6th TNM staging system, the presence of additional nodules in the same lobe was classified as T4 and additional nodules in ipsilateral separate lobes were designated as M1 disease. The International Association for the Study of Lung Cancer (IASLC) recently published the Staging Manual in Thoracic oncology. In this new study, the tumors with multiple nodules (multinodular disease) within the same lobe showed similar survival pattern to T3 tumors, but ipsilateral multinodular disease in separate lobes showed survival pattern to T4 tumors. The histology is important in two areas. The first is to distinguish synchronous primary tumors from intrapulmonary metastases and the second is the changing from stage IV to stage IIIA in node negative disease. This allows the clinician to consider surgery as a primary treatment option even when tumors are considered intrapulmonary metastases.
3. *Differentiation of multiple primary tumors from metastases*[9]: The multiple nodules are usually metastatic. However, if the tumor nodules are histologically different; or when these nodules show a totally different component in different nodules; or these have different cytological or stromal features; or without any mediastinal lymph node metastasis or lymphatic emboli in common lymphatic drainage areas; then only these nodules can be labeled as multiple synchronous primary tumors. In case of multiple primary nodules, the T status should be given maximum with the number of nodules to be mentioned either as M or actual number like T(m) or T(3).
4. *Aspect of pleural invasion*[10]: The pleura is composed of several layers and from outer aspect to inner aspect, it consists of mesothelial layer, loose connective tissues, external elastic lamina, another layer of loose connective tissue and an ill-defined innermost internal elastic lamina. A definite pleural invasion means when a tumor crosses the external elastic layer and it can divided into:
   a. PL1; when it invades the elastic lamina
   b. PL2; when it invades the mesothelial surface
   c. PL3; when it invades the parietal pleura/chest wall. An elastic stain is always indicated for accurate assessment of pleural invasion. When a tumor invades the pleura at the interlobar fissure and it extends into the adjacent lobe, the staging remains T2.

N Component

N1 denotes when there is involvement of ipsilateral peribronchial, hilar and intrapulmonary lymph nodes. N2 is designated when subcarinal and ipsilateral mediastinal lymph nodes are involved. Supraclavicular, scalene and contralateral mediastinal lymph nodes are designated as N3.

M Component

When the tumor was confined to the lung, pleura and pericardium, it is labeled as M1a but with the discontinuous nodules in chest wall, diaphragm or mediastinal structures, it is designated as M1b. The distant metastases (outside of lung or pleura) are also designated as M1b. The ipsilateral separate nodules are down staged to T4 but the contralateral nodules are to be designated as M1a.

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Lung Cancer: Clinical Manifestations

Javaid Ahmad Malik

INTRODUCTION

Lung cancer is usually recognized late in its natural history. In general, of newly presenting patients with lung cancer, 80% are inoperable at presentation and only 20% may proceed to curative resection.[1] The number of potentially resectable tumors at the time of diagnosis is much less in India. Lung cancer produces more symptoms in adults than any other cancer, which includes both respiratory and constitutional symptoms.[2-4] There is no clear demarcation between the clinical pictures of Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), however due to rapid dissemination of the disease, the duration of symptoms of small cell cancer tends to be shorter.

The symptoms and signs of bronchogenic carcinoma may be caused by any of the following: the local tumor itself, invasion of the tumor into the adjacent structures, regional lymph node enlargement, growth at anatomically discontiguous sites after dissemination and effects of tumor products leading to various paraneoplastic syndromes. Accordingly, the spectrum of clinical presentation of lung cancer can be divided into: (1) local manifestations, (2) metastatic manifestations and (3) nonmetastatic systemic manifestations (also called paraneoplastic syndromes). Most of the lung cancer patients in developing countries like India, compared to the patients in the developed countries, have lower mean age and advanced disease at diagnosis with 52% patients having evidence of metastases.[5-7]

LOCAL MANIFESTATIONS

Hemoptysis

Although the cardinal symptom of lung cancer particularly in an elderly smoker, hemoptysis, is neither the most common feature nor diagnostic of cancer. Hemoptysis is one specific symptom that prompts rapid consultation from the physician.[8] It is usually caused by bronchial mucosal ulceration, thus tends to be scanty. However, if the tumor erodes the bronchial artery or the pulmonary artery, as shown in Figure 117.1, hemoptysis

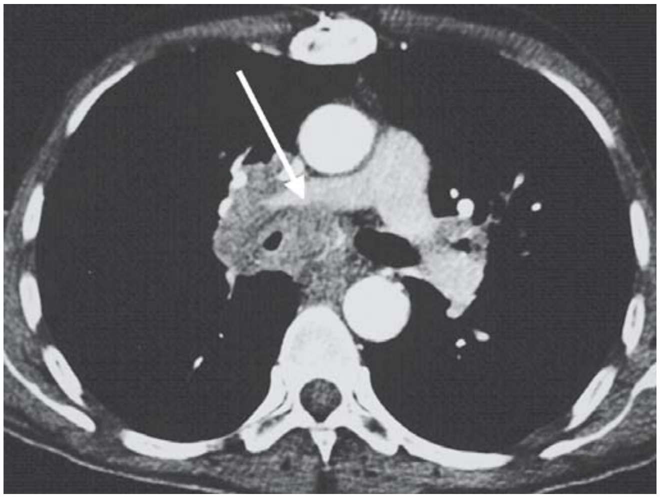


Fig. 117.1: Contrast computed tomography scan showing a large right hilar mass causing invasion and narrowing of the right pulmonary artery (arrow)

may be massive resulting in potentially fatal hemodynamic or airway compromise. Chest radiographs are usually abnormal in patients with hemoptysis, but in a small percentage of patients it may be normal.[9] In the developing countries like India, tuberculosis is always a competing diagnosis at all ages.

Cough

Cough is the most common presenting symptom of lung cancer, but it does not per se alarm the physician to look for malignancy, hence the delay in the diagnosis.[10,11] The development of new cough or a recent increase in the preexisting chronic productive cough in a middle aged smoker raises suspicion of lung cancer.[12] In smokers of more than 35 years of age, any new cough that persists for more than 2 weeks should be taken as suspicious of malignancy and investigated accordingly. Among the initial symptoms of lung cancer, cough is present in more than 65% patients and productive cough in more than 25% of patients and is more likely among patients with tumor originating in the airways.[13] In patients with chronic lung disease, a change in the character of an established cough may actually herald the development of lung cancer. Other conditions that can contribute to cough in these patients include esophageal reflux, coexisting Chronic Obstructive Pulmonary Disease (COPD) or congestive heart failure.[14]

Bronchorrhea, i.e. expectoration of large amounts of mucoid sputum occurs in 10% of patients with bronchioloalveolar carcinoma.[15] Endobronchial tumors cause cough either by airway obstruction and its associated postobstructive pneumonia or by bronchial mucosal ulceration, whereas peripheral tumors cause cough primarily by pleural involvement.

Breathlessness

- Like cough, dyspnea is the most commonly reported symptom in lung cancer, with 15% of patients having dyspnea at diagnosis and 65% at some point during the course of their illness.[16] In bronchogenic carcinoma, breathlessness is more common in men, older patients and those with lower quality of life scores and its incidence is higher when pain and anxiety predominate.[17,18] Various causes of dyspnea in patients with lung cancer includes:
- Direct involvement of the respiratory system by the tumor (major airway obstruction, consolidation, carcinomatous lymphangitis)
- Indirect respiratory complications of lung cancer (postobstructive pneumonia, pleural effusion, phrenic nerve paralysis)
- Treatment related (anemia or radiation and chemotherapy induced lung toxicity) respiratory complications that occur more frequently in these patients (pulmonary embolism and lung infections)
- Comorbid conditions (COPD, asthma, heart failure, prior lung resection, pericardial effusion and malnutrition). Some patients of lung cancer have no obvious cause of breathlessness but may have significant respiratory muscle weakness, due to general weight loss and the muscle deconditioning of advanced illness.[19]

Chest Pain

An ill-defined chest discomfort which is intermittent and aching in quality is common in bronchogenic carcinoma, occurs in up to 50% of patients at diagnosis. Definite pleuritic pain is the result of direct spread of the tumor to the pleural surface and is usually a manifestation of peripheral neoplasms (adenocarcinoma or large-cell carcinoma) because of their tendency to seed pleura. It is the invasion of pain receptors in the parietal pleura by the tumor that produces typical pleuritic pain which frequently disappears with accumulation of pleural fluid. Once the malignancy spreads beyond the pleura into the chest wall, it produces continuous pain that usually interferes with sleep. Shoulder pain that typically radiates along the ulnar distribution of arm may originate from local extension of tumor growing in the apex of the lung involving eighth cervical, and first and second thoracic nerves (Pancoast's or superior sulcus tumor).

METASTATIC MANIFESTATIONS

Intrathoracic Metastasis

Superior Vena Cava Syndrome

The thin vessel wall coupled with low intravascular pressure and surrounding lymph nodes, makes Superior Vena Cava (SVC) vulnerable to extrinsic compression and obstruction by the malignant tumor, leading to increased venous pressure in the head, neck and upper thorax producing a clinically unique entity known as Superior Vena Cava Syndrome (SVCS).[20,21] Bronchogenic carcinoma accounts for 46 to 75% of all cases of SVC obstruction, the most common histologi-cal subtype associated with SVCS is small cell carcinoma.[21-24] At the time of diagnosis, SVC obstruction is present in 10% of patients with SCLC and 1.7% with NSCLC.[25,26] Malignancies other than lung cancer that are responsible

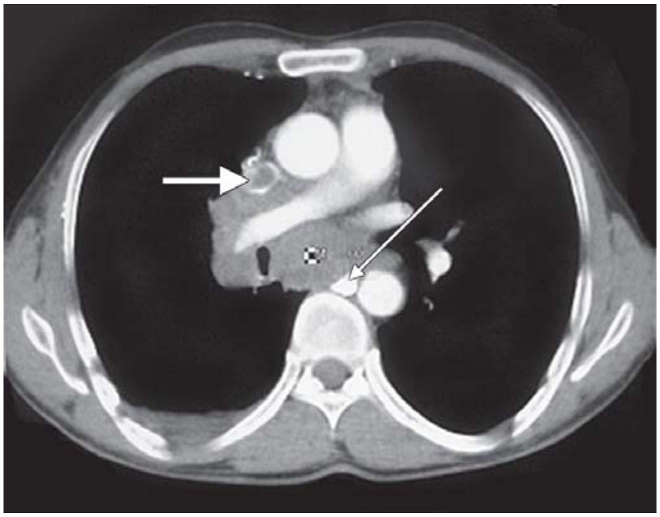


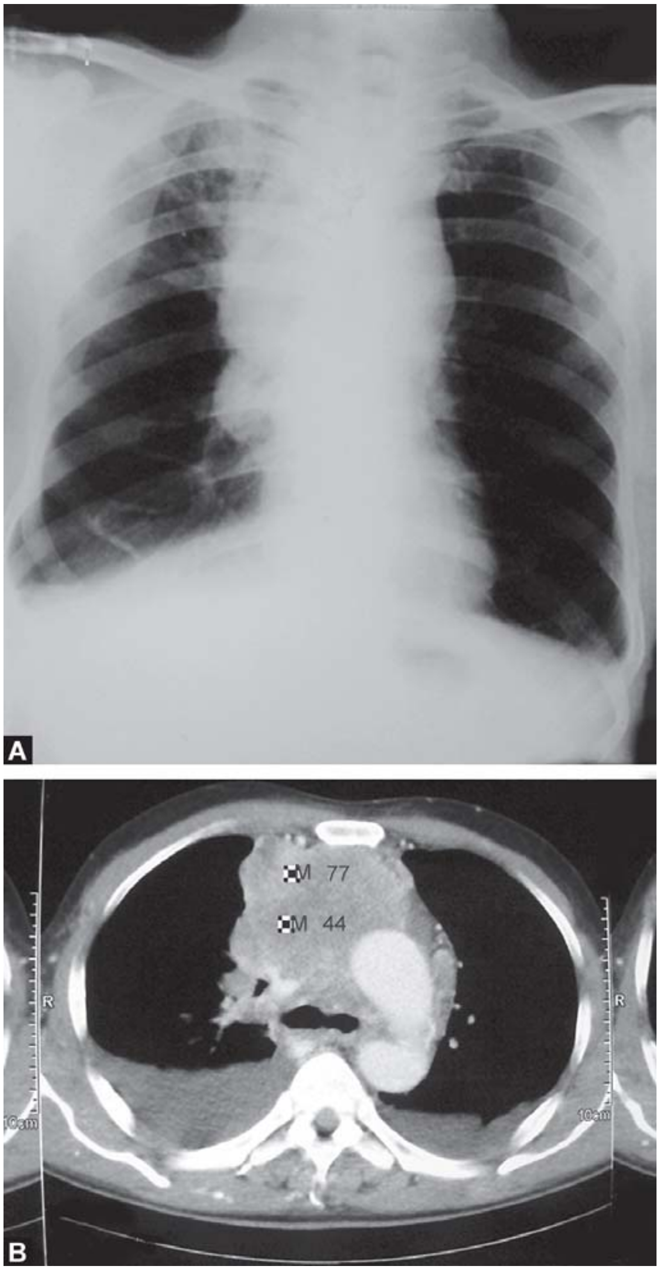
Fig. 117.2: Contrast CT scan chest of a patient of small cell carcinoma showing a thrombus in superior vena cava (short arrow). Enlargement of right hilar, sub-carinal and azygoesophageal recess lymph nodes is also seen. Note pleural effusion on right side and dilated azygos vein (long arrow) due to blood diversion

for obstruction of SVC in 20% of the cases include lymphoma, mesothelioma and metastatic mediastinal lymphadenopathy and the remaining 20% patients can have benign etiologies like granulomatous mediastinitis, mediastinal fibrosis, intrathoracic goiter or aneurysm, placement of pacemakers or thrombosis complicating central venous catheterization.[27-29] Various mechanisms that lead to SVC obstruction include direct compression by the primary tumor, compression by enlarged right paratracheal metastatic lymph nodes or intraluminal thrombosis (Fig. 117.2).

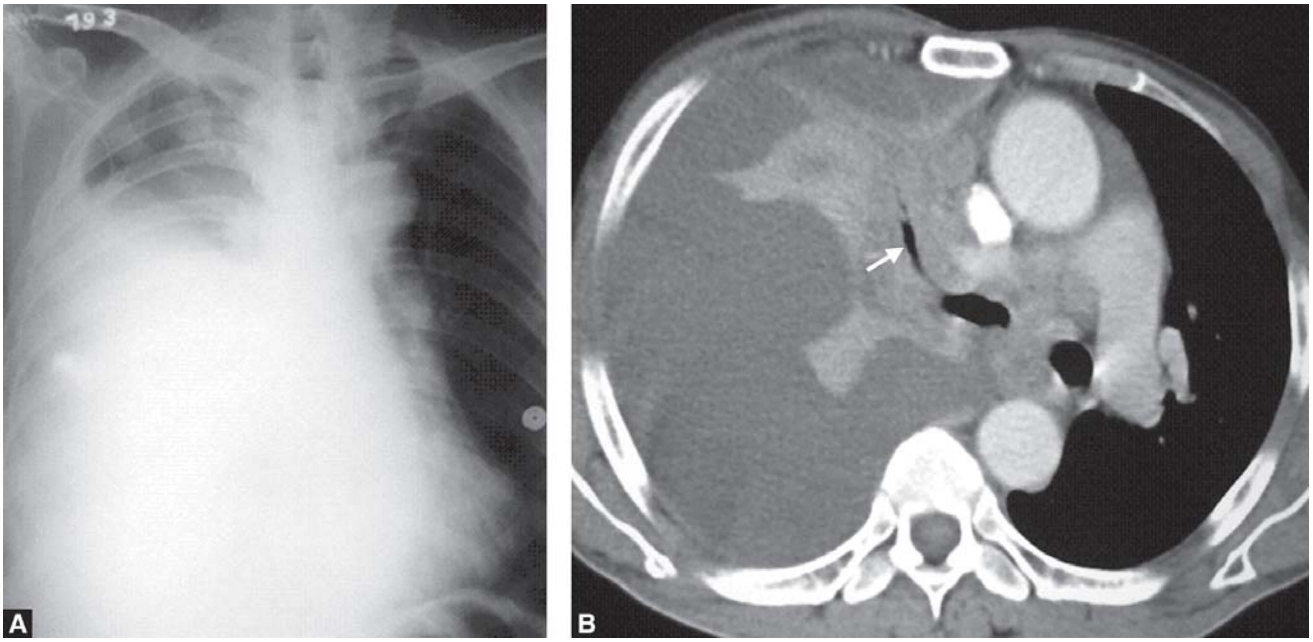
Symptoms of SVCS are often debilitating, tend to get exacerbated in supine position, include progressive swelling of neck, face, eyelids, arms and upper chest, conjunctival congestion, epistaxis, tinnitus, headache, disturbances in vision and sensorium.[20-23,30] Neck veins are distended and nonpulsatile, well developed collaterals are usually obvious on neck and anterior chest wall. SVC obstruction may get complicated with jugular venous and cerebrovascular thrombosis. Although radiograph of chest may show nonspecific mediastinal widening, diagnosis is usually confirmed by contrast CT scan (Figs 117.3A and B) which demonstrates not only the blockage of SVC with collateral formation but also suggests the most likely underlying etiology.

Malignant Pleural Effusion

Pleural effusions that occur due to direct pleural involvement by bronchogenic carcinoma occur in 7 to 15% of lung cancer patients.[31-33] On the other hand, paramalignant effusions are not the direct result of malignant involvement of the pleura but are still related to the primary lung tumor. Paramalignant pleural effusions may be due to postobstructive pneumonia



Figs 117.3A and B: Chest radiograph showing massive mediastinal adenopathy with right pleural effusion in superior vena caval obstruction in a 65-year-old male who presented with rapidly progressive swelling of neck, face and neck vein distension (A). Contrast CT scan showing a huge mediastinal mass causing posterior displacement and invasion of the aortic arch and SVC with bilateral pleural effusion. The diagnosis of small cell carcinoma was confirmed by bronchoscopic biopsy (B)



Figs 117.4A and B: Malignant pleural effusion. Chest X-ray (A) showing massive pleural effusion on right side. Contrast enhanced CT scan chest (B) showing massive pleural effusion causing compression of right upper lobe bronchus (arrow) and collapse of the underlying lung along with displacement of mediastinal structures to the left. Bronchoscopy in this 70-year-old male revealed an endobronchial growth and pleural fluid cytology confirmed metastatic non-small cell lung cancer

complicated by parapneumonic effusion, pulmonary embolism and infarction, chylothorax due to obstruction of the thoracic duct, radiation therapy and chemotherapy.[34,35] Lung cancer patients may also have pleural effusions that are due to concurrent non-malignant disorders like congestive heart failure, renal disease or hypoproteinemia.

Dyspnea, the most common presenting symptom of malignant pleural effusion is reported by more than 50% of patients.[35] Though, the exact mechanism of dyspnea in pleural effusions is unclear, various mechanical factors influencing the chest wall, depression of the ipsilateral diaphragm, mediastinum and its contents, pleural space, and the lung itself, all may contribute to dyspnea.[36-39] Malignant pleural effusion if massive (Figs 117.4A and B), may also produce other symptoms such as orthopnea, cough and chest discomfort.

Recurrent Laryngeal Nerve Palsy

Patients of lung cancer may develop hoarseness of voice because of vocal cord paralysis due to recurrent laryngeal nerve involvement. It produces cough that lacks explosive quality of a normal cough resulting in ineffectual expiratory noise (bovine cough). Recurrent laryngeal nerve palsy occurs in 2 to 18% of lung cancer patients, is associated with poor expectoration of tracheobronchial secretions and an increased risk of aspiration.[40] Left recurrent laryngeal nerve is more commonly involved due to entrapment by the tumor or by the metastatic mediastinal lymph nodes, as it passes over the left main bronchus and loops around the aortic arch. Right recurrent laryngeal nerve loops around right subclavian artery at the root of neck and may be involved by thoracic inlet tumor or metastatic cervical nodes.

Phrenic Nerve Paralysis

Diaphragmatic paralysis may complicate lung cancer due to phrenic nerve entrapment by the tumor in the mediastinum.[40] In unilateral phrenic nerve dysfunction, patient may not have any specific symptom, it may be incidentally discovered on the chest radiograph from the presence of an elevated hemidiaphragm. In bilateral phrenic nerve paralysis, patients are severely symptomatic, have orthopnea and a downhill disease course.

Pancoast's Syndrome

Pancoast tumor (also known as thoracic inlet or superior sulcus tumor) is a complication of local extension of an apical lung cancer. It was first reported in 1924 by Henry Pancoast, a radiologist from the University of Pennsylvania.[41] It is usually associated with squamous cell lung cancer, however any histological type of bronchogenic carcinoma can produce this syndrome. Pancoast tumors are uncommon, comprise fewer than 5% of all lung cancers.[42] The syndrome results from the involvement of lower part of brachial plexus by the tumor producing pain in the lower part of shoulder and inner aspect of arm along C8, T1 and T2 distribution that may be associated with sensory loss, weakness and wasting of the small muscles of hand. Incomplete forms of the Pancoast's syndrome are also seen in clinical practice. Radiologically, in addition to the apical lung mass, Pancoast tumor is often characterized by the destruction of first and second ribs posteriorly and sometimes of transverse process or vertebral body. In anterior superior sulcus tumor, the predominant complaint is chest pain; the imaging studies reveal destruction of anterior ends of first and second ribs and invasion of subclavian vessels. In order to determine the extent of involvement of neurovascular structures, a Magnetic Resonance Imaging (MRI) scan is often required in addition to a CT scan in the evaluation of Pancoast tumor.

Horner's Syndrome

Horner's syndrome is a consequence of invasion by the apical lung cancer of the lower cervical and first thoracic ganglia, which frequently fuse into a single ganglion, the stellate ganglion. It may be observed in 20 to 50% of bronchogenic carcinoma patients at presentation.[43] Its clinical components include ipsilateral ptosis, miosis, enopthalmos and lack of facial sweating (anhidrosis). Application of topical cocaine to the miotic eye fails to cause pupillary dilatation, while appropriate dilatation is noted in the unaffected eye.[44] Horner's syndrome is usually a complication of superior sulcus lung tumor, but may very rarely complicate spontaneous pneumothorax that produces mediastinal shift and consequent mechanical traction of the sympathetic ganglion.[45,46]

Involvement of Heart and Pericardium

Cardiac and pericardial metastases from bronchogenic carcinoma usually occur by direct lymphatic spread. In lung cancer, cardiac involvement is reported in 15% of the cases at autopsy.[47] Pericardium is the most common site of cardiac involvement in lung cancer (Fig. 117.5). Some patients may even develop cardiac tamponade.[48]

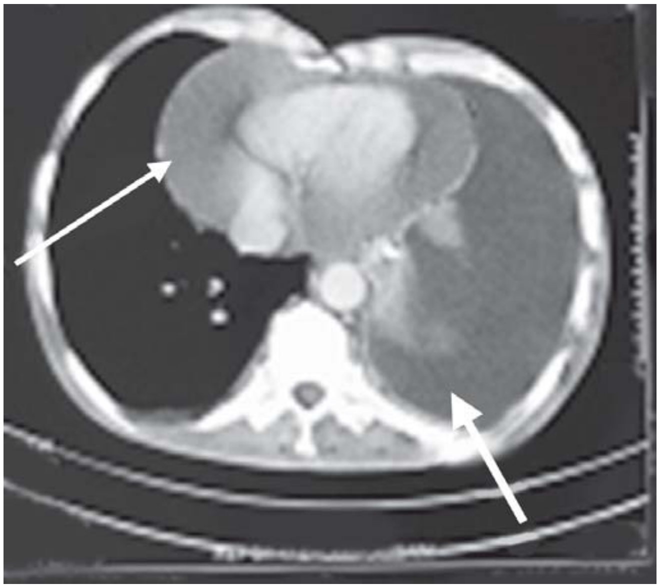


Fig. 117.5: Malignant pericardial effusion. Sixty-five years old male patient had signs of pleural effusion and volume loss on left hemithorax. Contrast CT scan chest showing pericardial effusion (long thin arrow) and volume loss on left side with massive pleural effusion (short thick arrow) on the same side. Bronchoscopy revealed an endobronchial growth that completely occluded the left main bronchus. Patient subsequently developed cardiac tamponade that needed pericardial catheter drainage

Involvement of Esophagus

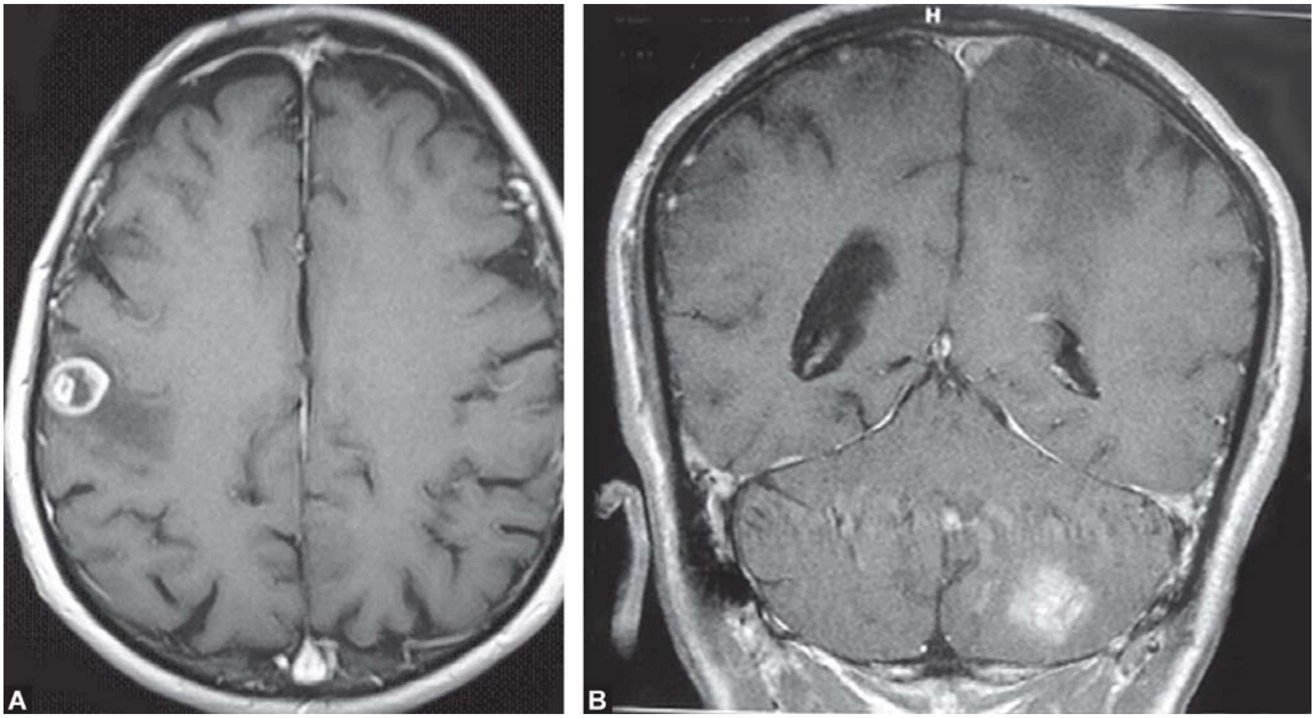
Dysphagia due to esophageal compression by massively enlarged metastatic hilar and mediastinal nodes is an unusual clinical feature of lung cancer and is generally a late symptom.

Extrathoracic Metastasis

Metastases from lung cancer may occur in virtually every organ system but are more commonly in brain, bones, liver, adrenal glands and lymph nodes. Extrathoracic spread of bronchogenic carcinoma makes a patient clearly inoperable. Metastatic disease in general, is more common with small cell than with non-small cell lung cancer.

Brain Metastases

Intracranial metastases constitute the first clinical problem in 10% of SCLC patients the cumulative incidence at 2 years is more than 50%.[49] Likewise, brain metastases from NSCLC occur in 33% of patients.[50] It is more common from lung cancer than from any other primary site, lung being the primary site of 70% of



Figs 117.6A and B: Brain metastasis from bronchogenic carcinoma. (A) Post-Gadolinium T1-W MRI of the brain in a patient of small cell carcinoma lung showing a ring enhancing lesion with a central nodule and thick walls surrounded by vasogenic edema in the right parietal lobe. (B) Coronal Post-Gad MRI in a 55-year-old male patient showing metastatic deposits in the cerebellum with avid enhancement of the lesion (*Courtesy:* Dr Irfan Rubani, Radiologist, SKIMS)

cancers that initially present with symptomatic brain metastases.[51] Squamous cell lung cancer metastasizes to brain less often than adenocarcinoma and large cell carcinomas.[52] Sometimes, brain metastases form the only extrathoracic site of spread of lung cancer.[53]

Intracranial metastatic lung cancer usually presents with headache, nausea and vomiting, rarely with impaired intellectual function or personality changes. Seizures and motor or sensory neurological deficits may occur. Progressive neurological symptoms in cerebral metastases usually complicate the widespread disease. Rarely, brain metastases are detected when primary bronchogenic carcinoma is asymptomatic and radiological examination of the chest is normal. If the patient with brain metastases is not treated, neurologic deterioration occurs quickly.[54,55] Lung cancer can metastasize to any part of the brain (Figs 117.6A and B) and cause devastating neurological complications.

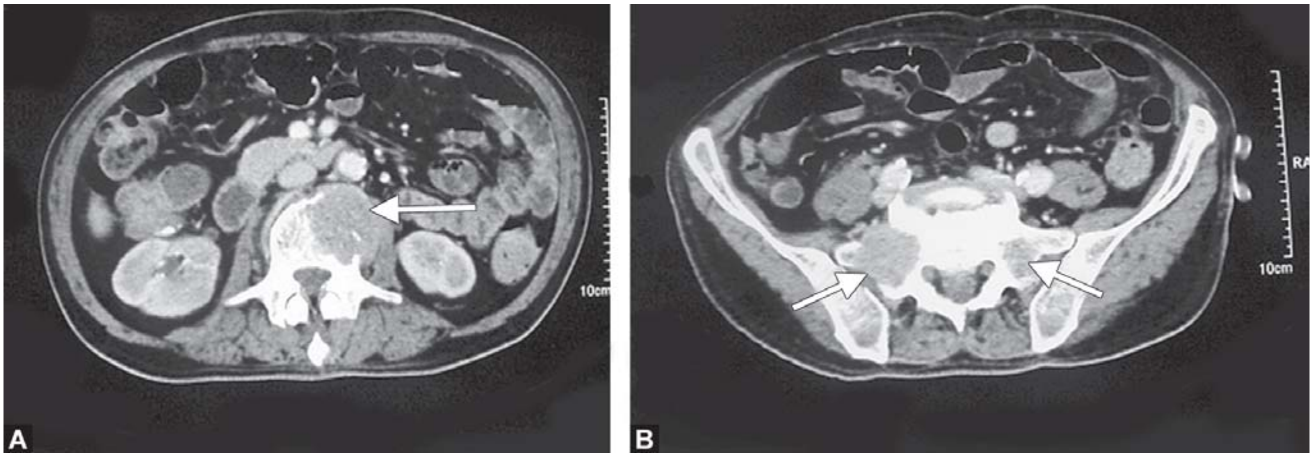
Skeletal Metastases

Bronchogenic carcinoma frequently metastasizes to vertebrae (Figs 117.7A and B) and ribs however, any bone in the body may be involved. Bony metastases usually produce pain which is invariably progressive. If the ribs are involved, pain gets aggravated by coughing and body movement.[56] Skeletal metastases may also lead to pathological fractures. When bone marrow is invaded by metastatic lung cancer, it leads to cytopenias or leukoerythroblastosis.

Radiograph of the affected bone may reveal lytic lesion, but it is not as sensitive as isotope bone scanning in detecting skeletal metastases. Though sensitive, bone scan lacks specificity, up to 50% of the scans may be false-positive, mostly due to benign metabolic bone disorders.[57,58] Bone scan is more useful in small cell carcinoma, because of the higher incidence of skeletal metastases with SCLC than with NSCLC.[59] Rarely, bone biopsy is required to confirm the metastatic spread of bronchial tumor.

Spinal Cord Compression

Due to epidural or vertebral metastases may complicate lung cancer producing an oncologic emergency.[60] Such patients need immediate assessment by a neurologist. Spinal cord metastases are less common and tend to occur in patients with cerebral metastases.



Figs 117.7A and B: Spinal metastasis from bronchogenic carcinoma. CT scan showing lumbar vertebral body deposits (A) and multiple sacral deposits (B) [*Courtesy:* Dr Syed Nisar, SKIMS Hospital]

Adrenal Metastases

Involvement of adrenal glands (Fig. 117.8) by metastatic lung cancer, usually by small cell carcinoma, is common but rarely produces adrenal insufficiency.[40] Solitary adrenal metastasis if resected along with primary lung tumor has a better prognosis with a 3-year survival rate of 38%.[61] Surgical resection for solitary adrenal metastases, in comparison to chemotherapy alone for usual disseminated metastatic disease, prolongs the median survival, resulting in survival rate of 17% at 15 years.[62]

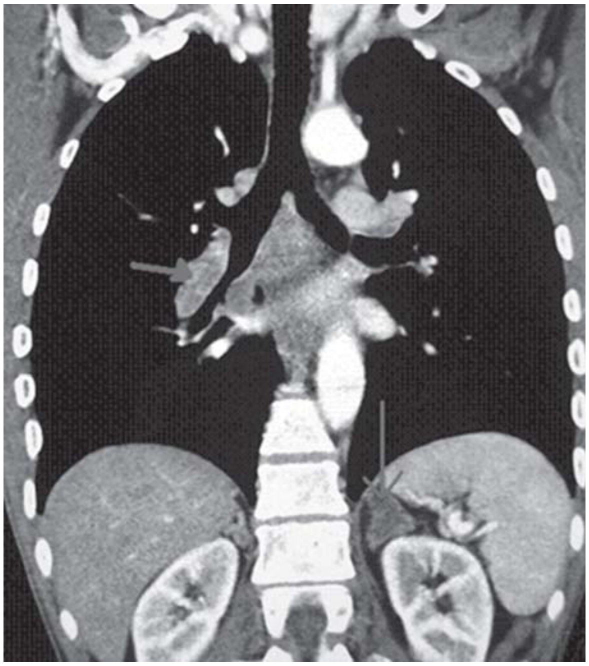


Fig. 117.8: Coronal contrast CT scan revealing a right hilar bronchogenic carcinoma (short thick arrow) with metastasis in the left adrenal gland (long thin arrow)

Lymph Node Metastases

An enlarged lymph node due to metastatic lung cancer is extremely helpful in facilitating both diagnosis and staging. Supraclavicular lymph nodes are the more common sites of palpable lymphadenopathy in lung cancer, involved in 15 to 20% of patients during the course of the disease.[40] Fine needle aspiration of the enlarged lymph node has high sensitivity and little morbidity.[63]

Hepatic Metastases

Liver metastases occur commonly with lung cancer (Fig. 117.9), their presence carries a very poor prognosis.[40] Patient usually complains of fatigue and weight loss; on physical examination the liver is hard and irregularly enlarged. However, liver function test results are seldom abnormal until the metastases are numerous and large. Both ultrasonography and CT scan are equally good in picking up hepatic metastases, a finding that makes the patient inoperable.[64]

Paraneoplastic Syndromes

A group of clinical disorders that are associated with malignant diseases, not directly related to the physical effects of primary or metastatic tumors are known as paraneoplastic syndromes.[65] These syndromes occur in 10% of patients with lung cancer.[66,67] The pathogenetic mechanisms by which paraneoplastic syndromes occur are not fully understood in all cases, but in many it

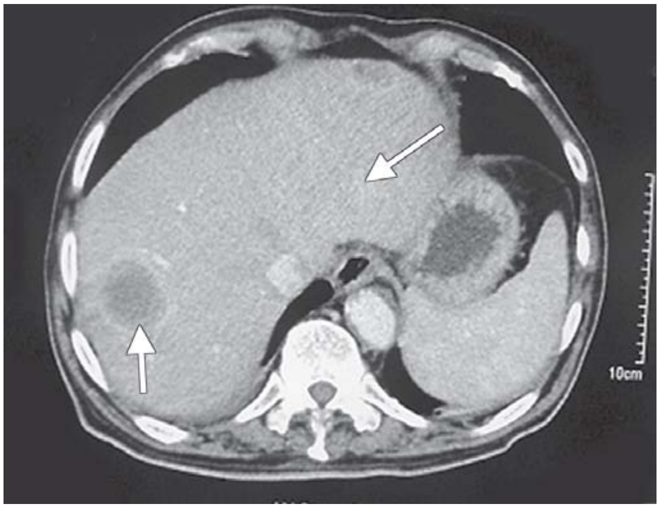


Fig. 117.9: Hepatic metastasis in lung cancer. Contrast CT scan of a 65-year-old male with small cell carcinoma of lung shows multiple ring enhancing lesions in liver (arrows). These lesions on FNAC were found to be metastatic deposits

appears to relate with either the production of biologically active substances by the tumor itself (e.g. polypeptide hormones or cytokines) or in response to the tumor (e.g. antibodies).[68] The size of the primary tumor has no impact on the extent of paraneoplastic symptoms. These paraneoplastic syndromes can precede the diagnosis of malignant disease, may occur late in the course of the illness or herald the first sign of recurrence of lung cancer. The most common tumors producing paraneoplastic syndromes in humans are lung cancers. Paraneoplastic syndromes are more frequently associated with small cell cancers but can be seen with any histological type. These unique clinical entities may antedate the discovery of tumor by months, or even years.[69] Paraneoplastic syndromes may simulate metastatic cancer thereby leading to inappropriate palliation rather than curative treatment of the underlying tumor. With successful treatment of lung cancer, the paraneoplastic phenomena usually resolve.

ENDOCRINE SYNDROMES

Cushing's Syndrome

Lung cancer is the most common source of ectopic secretion of Adrenocorticotropic Hormone (ACTH) among nonpituitary neoplasms. Biologically active ACTH resulting in adrenal gland hyperplasia and hyperfunction is usually produced by small cell carcinoma (85%), uncommonly by carcinoid tumors (10%) and adenocarcinoma (5%) of the lung. Lung cancer cells express precursor gene, Pro-opiomelanocortin (POMC) from which ACTH is derived. Increased serum levels of ACTH may be detectable in up to 50% of patients with bronchogenic carcinoma.[70] Cushing syndrome has been described in 1 to 5% of patients with SCLC.[71,72] Paraneoplastic Cushing's syndrome may rarely be caused by ectopic production of Corticotropin Releasing Hormone (CRH) which leads to excessive ACTH secretion from the pituitary gland.

Because of the short natural history of small cell lung cancer, these patients usually do not develop the classical features of Cushing's syndrome like buffalo hump, moon facies or cutaneous striae, as seen in Cushing's disease due to pituitary adenoma. Diagnosis is usually suggested by features of acute hypercortisolism such as hypertension, hyperglycemia and hypokalemic alkalosis. Muscle weakness associated with hypokalemia, may be profound. Proximal myopathy and edema are commonly found on physical examination.[73] However, full-blown Cushing's syndrome may be caused by certain slow growing cancers like pulmonary carcinoids and tumorlets.[74,75] Clinical course of Cushing's syndrome may be complicated by devastating fungal infections.

Though the biochemical abnormalities of cortisol metabolism including the raised ACTH levels, loss of diurnal variation and failure of cortisol levels to suppress after dexamethasone administration are found in 50% patient's with SCLC, the clinical syndrome is obvious in less than 5%.[68,76,77] Diagnosis is confirmed by demonstration of plasma ACTH level of more than 22 pmol/l, plasma cortisol of more than 600 nmol/l and 24-hour urinary free cortisol of more than 400 nmol/day, which do not suppress after a high-dose dexamethasone.

In addition to the effective treatment of the underlying lung malignancy, hypercortisolism needs to be addressed early to reduce the morbidity. Chemotherapy with or without irradiation for small cell carcinoma and surgical resection for carcinoid tumors should be offered to the patient as early as possible. When the tumor cannot be resected or ectopic ACTH secretion cannot be controlled, bilateral adrenalectomy may be effective in some patients.[78] Ketoconazole, metapyrone, aminoglutethimide or octreotide may be used to induce effective steroid synthesis inhibition.[79] Ectopic ACTH production by small cell carcinoma of lung is associated with aggressive tumor behavior, hence poor prognosis.[76]

Hypercalcemia

Overall, 10% patients of lung cancer have hypercalcemia, which usually complicates squamous cell carcinoma that secretes parathyroid hormone-related peptide (PTH-rP).[80-82] Hypercalcemia may also be seen with adenocarcinoma, but it is extremely rare in patients with small cell carcinoma of lung. Although bone metastases may be found in patients with lung cancer and hypercalcemia most commonly humoral mechanisms account for the hypercalcemia.[83,84] Bronchogenic carcinoma causes hypercalcemia primarily by ectopic production of parathyroid hormone-related peptide (PTH-rP), uncommonly by osteolytic metastatic deposits and very rarely by ectopic secretion of Parathyroid Hormone (PTH).[83-85] PTH-rP and PTH share identical functional activity because the first eight amino acids are homologous in these two peptide hormones. PTH-rP binds to PTH receptors in the bone and the kidney causing enhanced osteoclastic bone resorption and decreased urinary calcium excretion.

The diagnosis of PTH-rP associated paraneoplastic syndrome is considered if serum calcium level exceeds 10.5 mg/dl. Hypercalcemia initially produces nausea, vomiting, constipation, polyuria and nocturia resulting in hypovolemia and renal failure. As serum calcium goes up, patient may become confused, and drowsy and ultimately, coma may supervene misleading the physician towards intracranial metastases. The clinical behavior of PTH-rP associated paraneoplastic syndrome is highly unpredictable, the patient may present with subtle symptoms or as medical emergency. Increased levels of urinary cyclic adenosine monophosphate have been reported in lung cancer patients consistent with increased PTH effect.[86] However, serum immuno-reactive PTH levels are low to undetectable.[87] A protein with PTH-like activity has been purified from lung cancer cell lines.[88,89] Bone scan should be obtained to exclude skeletal metastases. An elevated PTH-rP level confirms the diagnosis in the absence of bone metastases. Other causes of hypercalcemia like sarcoidosis, hyperthyroidism and drugs like thiazides, lithium and vitamin D should also be considered in the differential diagnosis. Primary hyperparathyroidism should be excluded by PTH radioimmunoassay.

PTH-rP associated hypercalcemia usually develops in patients with advanced lung cancer, treatment may not be always required. Control or treatment of underlying lung cancer constitutes the most effective method of managing hypercalcemia. Intravenous saline, usually with furosemide diuresis, is often sufficient in symptomatic mild to moderate hypercalcemia. In severe hypercalcemia, calcitonin is used because of its rapid onset of action. Biphosphonates are used for long-term control of hypercalcemia and may cause dramatic fall in serum calcium.[90] Glucocorticoids though frequently used, have an unreliable calcium lowering effect in this syndrome. Similarly, mithramycin, a cytotoxic antibiotic is rarely used because of its toxicity.

Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

Elevated Antidiuretic Hormone (ADH) levels and impaired water handling are found in 30 to 70% of patients with lung cancer, but the production of excess ADH does not always produce symptoms.[91-93] Only 1 to 5% of lung cancer patients have symptoms that are attributable to the SIADH production. The SIADH production is mainly associated with small cell lung cancer, although other malignant tumors of the lung may rarely be associated with this syndrome.[91,94-96] The excess levels of ADH have been reported to originate from either ectopic production by lung cancer cells or inappropriate peripheral baroreceptor stimulation of ADH release from the hypothalamus.[91,97] Excess of ADH leads to abnormal water retention resulting in hyponatremia and low plasma osmolality. Urinary loss of sodium continues at a level inappropriate for plasma sodium concentration resulting in urinary osmolality twice as high as concomitant plasma osmolality. In a patient of lung carcinoma with euvolemic hypoosmolar hyponatremia, diagnosis of SIADH is made by the measurement of plasma and urinary osmolality.

The exact role of Atrial Natriuretic Peptide (ANP) in hyponatremia of malignancy is not known, though it is also ectopically secreted by the lung tumors. ANP also affects renal salt and water handling. In an individual patient, increased levels of ANP may contribute to hyponatremia by inducing natriuresis.[97] If plasma sodium concentration is marginally low, patient may be asymptomatic or may have confusion, headache, nausea and vomiting. Sodium level of less than 115 mmol/L can produce convulsions, coma and death. However, more often than not, lung cancer associated hyponatremia is only a laboratory abnormality.

Like for any other paraneoplastic phenomenon, the treatment of SIADH consists that of the underlying tumor. The syndrome resolves within 3 weeks after the initiation of combination cytotoxic chemotherapy in 80% of SCLC patients, but commonly recurs with tumor progression.[98] Though the chemotherapy of small cell carcinoma usually results in prompt resolution of SIADH[99] however clinician should keep in mind that some of the drugs like cisplatin, vincristine, melphalan and cyclophosphamide used to treat these cancers can themselves produce SIADH.[100]

Other measures which may be effective to counter hyponatremia while awaiting the effects of chemotherapy include strict fluid restriction (i.e. 500 ml per day), which alone may be sufficient to maintain serum sodium above 128 mEq/L.[101] If patient does not comply with fluid restriction or if it does not prove effective, demeclocycline, which blocks the action of vasopressin in the renal tubule, is used in a daily oral dose of 600 to 1200 mg.[102,103] Severe symptomatic hyponatremia is treated with hypertonic saline (3%) along with intravenous loop diuretic that enhance net free-water clearance. Sodium level should not be raised by more than 2 mEq per hour because it may lead to central pontine myelinolysis, an acute neurologic catastrophe. Unlike ectopic ACTH hormone production, SIADH does not worsen the prognosis of small cell cancer.

Acromegaly

Carcinoid tumor is the most common cause of acromegaly associated with lung malignancy. Small cell carcinoma can also produce this syndrome. Paraneoplastic acromegaly is commonly caused by secretion of Growth Hormone-Releasing Hormone (GHRH) and rarely by Growth Hormone (GH) in to the blood. These patients develop thick leathery skin, prominent skin folds, hypertrophy of face and extremities and sometimes diabetes and hypertension. Increased plasma levels of GHRH and insulin like growth factor-1 (IGF-1) in the presence of a lung tumor, virtually establish the diagnosis. Lung cancer related acromegaly promptly responds to surgical resection as well as to radiotherapy. Patients, who are not eligible for resection or irradiation, should receive octreotide, which inhibits GHRH secretion from the tumor and decreases GH and IGF-1 levels in the serum.

NEUROLOGICAL SYNDROMES

In patients of bronchogenic carcinoma, a variety of poorly understood neurological syndromes including Lambert-Eaton Myasthenic Syndrome (LEMS), limbic encephalopathy, polyneuropathy, cerebellar degeneration, retinopathy, opsoclonus-myoclonus and autonomic neuropathy have been reported.[104-107] Paraneoplastic neurologic syndromes affect 5% of lung cancer patients, associated almost exclusively with small cell carcinoma.[105] The severity of neurologic symptoms is unrelated to the tumor bulk; more often seen in patients with limited disease, in some patients a primary malignant lesion may be undetected before death despite the disabling symptoms.[106,108-110] The syndromes develop through autoimmune mechanisms as nearly all are associated with the presence of type 1 antineuronal nuclear antibodies (also known as anti-Hu antibodies).[111] Upto 20% of patients with small cell lung cancer have detectable circulating levels of anti-Hu antibodies but paraneoplastic neurologic syndromes may not develop in all of these patients.[106,112]

The diagnosis of a neurologic syndrome should be made only after other causes such as electrolyte imbalance, metastatic disease, cerebral and spinal vascular disease, infections and treatment toxicity are carefully excluded. These neurological phenomena progress rapidly and cause significant disability. The response of the neurologic syndrome to an effective chemotherapy in patients with small cell cancer is variable.[73,113-115] Sustained improvements particularly in patients with motor or sensory neuropathies have been reported. The overall prognosis is more favorable in SCLC patients with LEMS than in those without it.[116, 117]

Eaton-Lambert Syndrome

Eaton-Lambert myasthenic syndrome affects up to 5% of patients with small cell lung cancer uncommonly complicates non-small cell lung cancer. It is caused by the formation of IgG autoantibodies directed at voltage-gated P/Q calcium channels involved in the release of acetylcholine at nerve terminals thereby producing a functional blockade at neuromuscular junction.[73,118]

These patients usually present with fatigue, dysphagia, dysarthria, visual blurring, muscle aches and weakness of pelvic girdle muscles. Unlike in myasthenia gravis, muscle weakness in LEMS improves with exercise and not with anticholinestrases. The syndrome is worse in the morning and improves during the day. Although, extraocular muscle involvement is uncommon ptosis is often seen.[119] There is increased muscle action potential with repeated nerve stimulation on electromyography. Demonstration of IgG autoantibodies in the serum of patients with small cell lung cancer confirms the diagnosis of Eaton-Lambert syndrome.

Eaton-Lambert syndrome usually resolves with chemotherapy of small cell carcinoma. If treatment of lung tumor does not improve neuromuscular weakness, remission may be induced with azathioprine, intravenous gamma globulin, diaminopyridine or plasma exchange.

Encephalomyelitis and Sensory Neuropathy

This syndrome is associated with small cell lung cancer and the neuronal damage is mediated by IgG anti-Hu antibody, also known as Anti-Neuronal Nuclear Antibody (ANNA-1).[120] The anti-Hu antibody, present in the blood of these patients, reacts with proteins on small cell carcinoma cells and also with neuronal nuclear antigens in the brainstem, cerebellum, cerebral cortex, spinal cord and dorsal root ganglia.[121]

These patients may present with progressive sensory loss in hands and feet, myelopathy, brainstem involvement or features of limbic encephalopathy including behavioral changes, memory loss or convulsions. Autonomic neuropathy resulting in postural hypotension or gastrointestinal motility disturbances may also occur.[122] Diagnosis of encephalomyelitis is suggested by the MRI images which show increased T2 signal in the affected areas of the brain and is confirmed by demonstration of anti-Hu antibody in the serum.

Removal of culprit IgG by plasmapheresis and corticosteroids administration is effective in only 15% of these patients.

Paraneoplastic Cerebellar Degeneration

Some patients of small cell lung cancer develop cerebellar degeneration leading to nystagmus, impaired coordination and ataxia.[123] These patients have anti-Hu antibodies in serum and frequently tend to develop encephalitis or sensory neuropathy.

Cancer Associated Retinopathy

It is a rare paraneoplastic syndrome that occurs as the first sign of occult small cell carcinoma of lung. Ganglion cells of retina are characteristically damaged by binding of auto-antibodies to recoverin, a photoreceptor-specific protein. Clinically, these patients have photosensitivity, rapid loss of vision, night blindness, visual field defects and arteriolar narrowing. In a given clinical setting, demonstration of anti-recoverin antibody establishes the diagnosis of cancer associated retinopathy. Cancer associated retinopathy responds to systemic steroids but not to the chemotherapy for primary tumor.

Opsoclonus and Myoclonus

This rare paraneoplastic syndrome is associated with both small cell and non-small cell lung cancers. The patient shows rapid involuntary conjugate eye movements in both the horizontal and the vertical directions. Some SCLC patients with this syndrome have anti-Hu antibody in serum.

HEMATOLOGICAL SYNDROMES

Granulocytosis

Granulocytosis with absolute white cell count of 10,000 to 25,000 occurs in 20% patients of non-small cell lung cancer. The specific ectopic hormone responsible for paraneoplastic granulocytosis has not been characterized, although some non-small cell tumors may produce various cytokines like Interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF) or granulocyte-monocyte colony-stimulating factor (GM-CSF). The increase in total white cell count may also be associated with neutrophilia and eosinophilia.[124,125] Bone marrow biopsy is usually normal. Diagnosis is made on exclusion, granulocytosis per se does not produce any symptom in these patients.

Thrombocytosis

Paraneoplastic thrombocytosis is a common phenomenon observed in 40% patients of both small cell and non-small cell carcinomas. The exact pathogenetic mechanism of lung cancer associated thrombocytosis is not known, it is most likely linked to a megakaryocyte cytokine, i.e. IL-6. Like granulocytosis, lung cancer associated thrombocytosis is asymptomatic, diagnosed if bone marrow biopsy is normal and platelet count exceeds 500,000/mm.[2]

Thromboembolism

The pathogenetic basis of lung cancer associated venous thromboembolism is not known, no proteins or cytokines have been linked to it. It can complicate both non-small cell and small cell cancers of lung. Trousseau's syndrome or recurrent migratory venous thrombophlebitis is more commonly associated with bronchogenic carcinoma than pancreatic or other gastrointestinal cancers. Isolated venous thrombosis is treated with oral warfarin, but long term heparin is more effective than warfarin in recurrent thrombosis (Trousseau's syndrome).[126]

SKELETAL

Digital Clubbing and Hypertrophic Osteoarthropathy

Digital clubbing (Fig. 117.10) which is, more common among wowen than man (40 vs 19%), is observed in more than 30% patients and Hypertrophic Pulmonary Osteoarthropathy (HPOA) in up to 10% patients of non-small cell lung cancer, more common among women than men (40% vs 19%).[127,128] Quantitative indexes of the nail profile angle, hyponychial angle and phalangeal depth ratio can be determined to assist in identifying clubbing.[129] Hypertrophic pulmonary osteoarthropathy may be present in up to 5% of patients with non-small cell lung cancer (especially with squamous and adenocarcinomas) and 1% patients with small cell carcinoma.[130] HPOA is a systemic disorder, which involves both; a painful symmetrical arthropathy, usually of the ankles, wrists and knees, and periosteal new bone formation in the distal long bones of the limbs.[131]

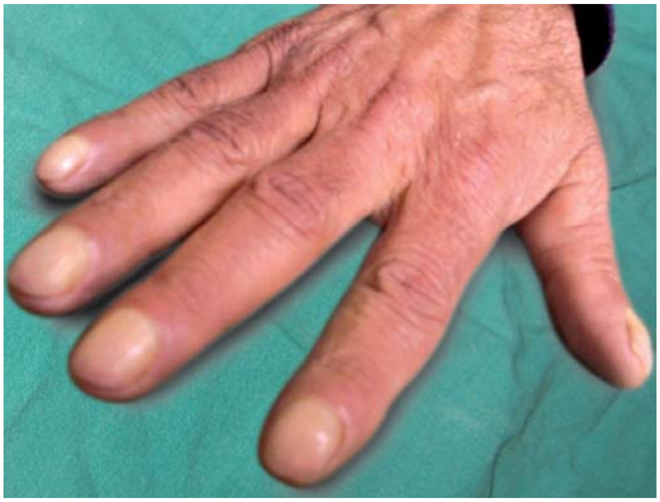


Fig. 117.10: Digital clubbing in a 56-year-old patient of squamous cell carcinoma of lung

The exact mechanism responsible for the development of clubbing and HPOA is not known. The past explanations included neurogenic, hormonal and vascular mechanisms.[132-134] Overexpression of Vascular Endothelial Growth Factor (VEGF) has been implicated in the pathogenesis. Bone scans show active deposition of new bone along the inner aspect of periostium. Clinically, HPOA responds well to surgical resection of the primary lung tumor. In unresectable tumors, corticosteroids and nonsteroidal anti-inflammatory drugs are used for symptomatic relief. For symptom relief, vagotomy can also be done, if thoracotomy is undertaken with an attempt to cure.[135]

MISCELLANEOUS SYNDROMES

There are various other unusual paraneoplastic syndromes known to be associated with bronchogenic carcinoma: renal (glomerulonephritis, nephrotic syndrome), vasculitic (systemic lupus erythematosus), systemic (fever, anorexia, cachexia) and metabolic (hypouricemia, lactic acidosis).[1,136] Several other endocrinal, neurological and hematological syndromes, in addition to those listed earlier can rarely occur.

Cutaneous manifestations of lung cancer are rare, include dermatomyositis-polymyositis, scleroderma, acanthosis nigricans, papillary dermatosis, erythema gyratum repens, erythema multiforme, exfoliative dermatitis, Sweet syndrome, pruritus and urticaria.[137] Adenocarcinoma and large cell bronchogenic carcinoma are known to be associated with gynecomastia due to tumor cell production of human chorionic gonadotropin, which results in overproduction of testicular estrogen.[138]

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Diagnosis and Staging of Lung Cancer

Ajmal Khan, Navneet Singh

INTRODUCTION

The concept of staging in malignant disease originated from the historical observation that survival rates were better for patients with a localized tumor compared to those with advanced disease (widespread progression beyond the area of the primary tumor). The lung cancer staging system is aimed at providing a common basis for categorization of the extent of disease, plan of treatment, estimation of prognosis and ultimately for a comparison of the results of different treatment modalities on overall survival. Thus, accurate staging lays a foundation for grouping patients with similar prognosis and treatment plan and most importantly, identifies patients most likely to benefit from surgery. The optimal strategy for staging should be simple, accurate, noninvasive and cost-effective.

The goal of the initial diagnostic work-up is to both establish a diagnosis and provide sufficient additional information such that a definitive treatment plan can be developed in the most cost-effective manner. The staging should proceed in a sequential fashion with the aim of identifying patients who can be treated with curative intent as quickly and efficiently as possible, while minimizing expensive and invasive testing.[1,2] Similarly, the initial evaluation also needs to identify patients with advanced disease who have incurable disease and therefore minimize the risk of exposing them to the morbidity of surgery or combined-modality approaches.

Delay in the initial diagnostic workup can affect the stage, therefore reducing this delay could increase the detection of potentially resectable tumors and ultimately patient survival.[3]

DIAGNOSIS OF LUNG CANCER

Clinical Assessment (Also See Chapter 117)

The clinical evaluation remains the most important starting point in the work-up of a patient with suspected lung cancer. The initial evaluation, consisting of a thorough history and physical evaluation, is often used to establish a presumptive diagnosis and stage. However, it should also be followed by tissue diagnosis and the information obtained on initial clinical evaluation is utilized to guide further testing.

Majority of the patients with lung cancer present with symptoms like cough, hemoptysis, dyspnea, chest pain, hoarseness and wheezing, that are related to the primary tumor or intrathoracic spread of disease. Cough is probably the most common symptom of lung cancer at presentation, but one specific symptom that has been described to prompt more rapid evaluation is the hemoptysis.[4] Additionally, symptoms related to distant metastasis, paraneoplastic syndromes (Table 118.1) and/or nonspecific systemic symptoms such as fatigue, weight loss and generalized weakness may be present. Less than 10% of lung cancer patients are asymptomatic at presentation.[5,6]

Paraneoplastic syndromes are not directly related to the size or physical effects of primary or metastatic tumors. These occur in up to 10% of patients with lung cancer due to the production of biologically active substances such as polypeptide hormones, antibodies or cytokines. Occasionally one or more of these may precede the diagnosis of malignant disease, and at other times may occur later during the course of illness or may even herald the first sign of recurrence.

TABLE 118.1: Partial list of paraneoplastic syndromes associated with lung cancer[12]

Endocrine disorder
- Syndrome of Inappropriate secretion of Anti-diuretic Hormone (SIADH)
- Non-metastatic hypercalcemia
- Cushing syndrome
- Gynecomastia
- Hypercalcitonemia
- Hypoglycemia
- Hyperthyroidism
- Carcinoid syndrome

Neurologic syndromes
- Subacute sensory neuropathy
- Mononeuritis multiplex
- Intestinal pseudo-obstruction
- Lambert-Eaton myasthenic syndrome (LEMS)
- Encephalomyelitis
- Necrotizing myelopathy
- Cancer associated retinopathy

Skeletal disorders
- Hypertrophic osteoarthropathy
- Clubbing

Systemic syndromes
- Anorexia and cachexia
- Fever

Cutaneous
- Acquired hypertrichosis languinosa
- Erythema gyratum repens
- Erythema multiforme
- Tylosis
- Erythroderma
- Exfoliative dermatitis
- Acanthosis nigricans
- Pruritus and urticaria

Lung cancer is responsible for 46 to 75% of all cases of Superior Vena Cava Obstruction (SVCO) with Small Cell Lung Cancer (SCLC) being the most common histological subtype associated with SVCO.[7-9] SVCO is generally caused by the direct invasion of the tumor into the mediastinum or by lymphatic spread leading to enlarged right paratracheal lymph nodes. Mediastinal involvement and invasion to other vascular structures can also occur by direct extension. In lung cancer, pericardium is the commonest site of cardiac involvement leading to effusion or supraventricular arrhythmias.[10]

In lung cancer, distant metastasis occurs commonly to the brain, liver, bones and adrenal glands, but can also involve other body organs like spinal cord, lymph nodes and skin. Almost 30% of patients with lung cancer develop brain metastases and almost 10% of patients have intracranial metastasis at presentation.[11,12] Lung cancer is the most common primary site among all cancers metastasizing to the brain. Spinal cord metastases are less common and tend to occur in patients with cerebral metastases.

Radiological Assessment

Initial chest radiograph plays a pivotal role in the recognition of lung cancer that may present as a straightforward spiculated mass but its presence may also be inferred from other appearances such as an unresolving pneumonia or lobar collapse. However, the nonresolving radiographic appearance may be quite variable. In general, lung cancers present slightly more often on the right than the left side, and in the upper than in the lower lobes.[13-15] About 40% of the chest radiographic appearances of lung cancer are related to the central tumors causing airway obstruction with secondary atelectasis and consolidation.[16,17]

Once a pulmonary lesion is encountered, an important next step is comparison with old radiographs. Benign lesions typically have a prolonged doubling time of greater than 16 months. Doubling times of malignant nodules have been reported to vary from 40 to 360 days.[18] Conventionally, growth stability over a two-year interval is considered a reliable indicator for the presence of benign disease. Characteristics of the nodule on chest radiography may also be valuable. The presence of a spiculated margin, often termed as corona radiata, indicates a high likelihood of a malignant lesion, although a benign process such as a round pneumonia or scar may also manifest this sign.

Approximately two-thirds of squamous cell carcinoma occur centrally with involvement of a mainstem, lobar or segmental bronchus and associated with bronchial obstruction and obstructive pneumonia. Cavitation is seen more frequently in squamous cell carcinoma than in the other histological types.[19,20] Adenocarcinoma representing approximately 30% of all lung cancers is typically peripherally located with cavitation occurring in about 4% and mediastinal or hilar involvement in half of the cases.[21-23] Small cell lung cancer often presents with bulky hila and mediastinal lymph node metastasis with noncontiguous parenchymal mass and is rarely associated with cavitation.[22,24,25]

Establishing a Diagnosis

The decision to pursue a tissue diagnosis of the lung cancer depends on the initial presentation and clinical impression of the lesion, including the likelihood that it represents a primary lung cancer. For the lesions with lower likelihood of malignancy, a tissue diagnosis can be pursued best with sputum cytology or bronchoscopy if the lesion is located centrally, and a Transthoracic Needle Aspiration (TTNA) if the lesion is peripheral.[26] In the Duke University Center for Clinical Health Policy Research comprehensive review of the published literature, the average sensitivity and specificity of sputum cytology were 66% and 99%, respectively. In the same study, the overall sensitivity of flexible bronchoscopy for central tumors was 88%, compared with 69% for peripheral tumors. Among the bronchoscopic techniques, endobronchial biopsies were associated with the highest sensitivity (74%), followed by brushings (59%) and washings (48%). Similarly, for peripheral lesions larger than 2 cm, TTNA had a sensitivity of 62% as compared to 33% for the lesions that were smaller than 2 cm.[26] In a meta-analysis, the pooled sensitivity for differentiating between malignant versus all other categories by TTNA was 86.1% (range 83.8–88.45%) with a specificity of 98.8% (98.4 to 99.2%). However, the procedure was associated with very high incidence of pneumothorax [24.5% (range 3.1 to 41.7%)].[27]

A positive result from sputum cytology, bronchoscopy, or TTNA should be considered reliable because false-positive results typically have been reported to be less than 2%.[26,27] Although these modalities are useful in confirming the diagnosis, the false-negative rate for all three has not been well defined, or remains too high to rule out the diagnosis effectively. Therefore, if the clinical suspicion for a lung cancer diagnosis remains high, additional evaluation is usually required after a negative test result. In such cases for early diagnosis, special attention can be given to modern techniques like, Autofluorescence Bronchoscopy (AFB) and electromagnetic navigation.

In patients with simultaneous pleural effusion, diagnostic thoracentesis should be considered. The sensitivity of pleural fluid cytology is only 60%, which increases to 80% with three separate fluid specimens and therefore a minimum of three samples should be evaluated by an experienced cytologist.[28-31]

Once the tissue diagnosis has been achieved the final component of the diagnostic assessment is a functional evaluation of the patient including overall evaluation using performance status scales and evaluation for specific pulmonary status.

STAGING OF NON-SMALL CELL LUNG CANCER

If the diagnosis of Non-Small Cell Lung Cancer (NSCLC) is suspected based on the clinical presentation or has been confirmed by a tissue diagnosis, the new TNM system (Tables 118.2A and B) serves as the basis for the staging evaluation.[32-35] In this system, the major determinant chosen for development of subgroups of T, N, and M descriptors as well as the stage groupings was the overall survival, based on the best stage (pathologic, if available; otherwise clinical).[36,37] Overall, 40% of patients with NSCLC present with distant metastatic disease at presentation, 30% present with locally-advanced disease (stage IIIA/IIIB), while only the remaining 24% to 30% present in either stage I or stage II.[38] Two main methods of lung cancer staging are the clinical staging and the pathologic staging. Information provided by noninvasive or minimally invasive techniques, such as physical examination, radiologic examination, endoscopic ultrasound, bronchoscopy, mediastinoscopy and thoracoscopy prior to any treatment, are utilized for clinical staging. In pathologic staging, information obtained from clinical staging is combined with findings from both the invasive surgical procedure and the pathologic evaluation of the excised tissue.[39] Clinical staging helps to determine the next appropriate step in therapy, such as the decision to proceed with pathologic staging.

Mediastinal Staging

After a tissue diagnosis of lung cancer is established and surgical resection is the option, consideration must be given toward the determination of the extent of disease, or stage because this will impact directly the management and the prognosis. Mediastinal involvement is the threshold, at present, at which curative therapy may be implemented (IIIA is potentially curable while IIIB is not).[40] Thus, the status of regional lymph nodes is a major factor for staging, assigning treatment, and evaluating treatment efficacy in patients with lung cancer (Tables 118.3A and B).[41,42] Approximately 30 to 40% of patients with lung cancer already have mediastinal metastases at the time of initial diagnosis that necessitates histological or cytological evaluation of metastases to the mediastinal nodes.[43] Mediastinal lymph node staging can be divided into non-invasive (imaging) and invasive (sampling) procedures.

TABLE 118.2A: TNM System of staging NSCLC[35]

Descriptor	*Definition*	*Subgroups*
Primary tumor (T)		
T_0	No primary tumor	
T1	Tumor ≤3 cm, in the greatest dimension surrounded by lung or visceral pleura, not more proximal than the lobar bronchus	
T1a	Tumor ≤2 cm in the greatest dimension	T1a
T1b	Tumor >2 but ≤3 cm in the greatest dimension	T1b
T2	Tumor ≥3 but >7 cm in the greatest dimension or tumor with any of the following: Invades visceral pleura, involves main bronchus ≥2 cm distal to the carina, atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung; T2 tumors with these features are classified as T2a if ≤5 cm	
T2a	Tumor >3 but ≤5 cm in the greatest dimension	T2a
T2b	Tumor >5 but ≤7 cm in the greatest dimension	T2b
T3	Tumor >7 cm	$T3_{>7}$
	or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura,	$T3_{inv}$
	or parietal pericardium	
	or tumor in the main bronchus <2 cm distal to the carina	$T3_{Centr}$
	or atelectasis/obstructive pneumonitis of entire lung	$T3_{Centr}$
	or separate tumor nodules in the same lobe	$T3_{Satell}$
T4	Tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body,	$T4_{Inv}$
	or carina	$T4_{Ipsi\ Nod}$
	or separate tumor nodules in a different ipsilateral lobe	
Regional lymph nodes (N)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral peribronchial and/or perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes	
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes	
Distant metastasis (M)		
M0	No distant metastasis	
M1a	Separate tumor nodules in a contralateral lobe	$M1a_{Contr\ Nod}$
	or tumor with pleural nodules or malignant pleural dissemination	$M1a_{Pl\ Dissem}$
M1b	Distant metastasis	M_{1b}
Special situations		
TX, NX, MX	T, N, or M status not able to be assessed	
Tis	Focus of *in situ* cancer	T_{is}
T1	Superficial spreading tumor of any size but confined to the wall of the trachea or mainstem bronchus	$T1_{SS}$

TABLE 118.2B: Stage groups according to TNM descriptor and subgroups[35]

T/M	*Subgroup*	*N0*	*N1*	*N2*	*N3*
T1	T1a	IA	IIA	IIIA	IIIB
	T1b	IA	IIA	IIIA	IIIB
T2	T2a	IB	IIA	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	$T3_{>7}$	IIB	IIIA	IIIA	IIIB
	$T3_{Inv}$	IIB	IIIA	IIIA	IIIB
	$T3_{Satell}$	IIB	IIIA	IIIA	IIIB
T4	$T4_{Inv}$	IIIA	IIIA	IIIB	IIIB
	$T4_{Plpsi\ Nod}$	IIIA	IIIA	IIIB	IIIB
M1	$M1a_{Contr\ Nod}$	IV	IV	IV	IV
	$M1a_{Pl\ Disem}$	IV	IV	IV	IV
	M1b	IV	IV	IV	IV

Noninvasive Mediastinal Staging

The clinical staging of lung cancer is usually directed by noninvasive imaging tests that guide the likelihood of the presence or absence of metastatic involvement in the regional lymph nodes.

a. *Chest radiography:* At initial presentation of patients with lung cancer, majority of cancers are first detected or suspected on a plain chest radiograph. In selected patients, the chest radiograph may itself define spread of tumor to the mediastinum; however, in general this is an insensitive measure to detect mediastinal lymph node involvement and warrants further tissue confirmation as well as noninvasive and/or invasive assessment is required.

b. *Computed tomography (CT) of the chest:* A CT scan is relatively inexpensive, essentially performed as a preliminary step in order to define the nature of a pulmonary abnormality and to arrive at a clinical diagnosis of suspected lung cancer. CT scanning overall remains the best modality to study the anatomy of the thorax that guides the choice of nodes for selective node biopsy by invasive techniques. Computed tomography is the primary means of anatomic staging involving evaluation of the primary lesion, mediastinal lymphadenopathy and distant metastasis. It is also used adjunctively in the evaluation of local extension of central tumors into the mediastinum, into the chest wall, or invasion of superior sulcus tumors into the brachial plexus. The major limitations of anatomic imaging are the use of size criteria to define benign versus malignant lymph nodes, failure to distinguish tumor from atelectasis, and the nonspecific appearance of metastatic disease in general, which makes pathologic confirmation generally necessary.

The most widely used criterion to define the malignant involvement of mediastinal lymph nodes is a short-axis lymph node diameter of greater than or equal to 1 cm on a transverse CT scan. However, other criteria have also been used: A long-axis diameter of ≥1 cm, a short-axis diameter of greater than/equal to 1.5 cm, a short-axis diameter ≥ 1 cm plus evidence of central necrosis or disruption of the capsule and a short-axis diameter of ≥2 cm regardless of nodal morphology. The varied sensitivity and specificity for identifying malignant involvement in various studies is because of the use of these different criteria in the assessment of individual nodal stations.[44,45]

In a systematic review of 43 peer reviewed studies involving 5111 evaluable patients, the median prevalence of mediastinal metastasis was 28% (range, 18 to 56%) when presence of one or more lymph nodes measuring greater than 1 cm on the short-axis diameter was used as a cut-off to define a positive test. Additionally, in the same study, the pooled sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were 51 [95% Confidence Interval (CI), 47 to 54%] and 86% (95% CI, 84 to 88%), respectively. The corresponding positive and negative likelihood ratios were 3.4 and 0.6, respectively.[40] These data show that CT scanning

TABLE 118.3A: Mountain and Dresler regional lymph node classification for lung cancer staging[41]

Lymph Nodes	*Stations*	*Anatomic Landmarks*
Superior Mediastinal Nodes		N2 nodes: All N2 nodes lie within the mediastinal pleural envelope
• Highest mediastinal	1	Nodes lying above a horizontal line at the upper rim of the bracheocephalic (left innominate) vein where it ascends to the left, crossing in front of the trachea at its midline
• Upper paratracheal	2	Nodes lying above a horizontal line drawn tangential to the upper margin of the aortic arch and below the inferior boundary of No. 1 nodes
• Prevascular and retrotracheal	3	Prevascular and retrotracheal nodes may be designated 3A and 3P; midline nodes are considered to be ipsilateral
• Lower paratracheal (including azygos nodes)	4	The lower paratracheal nodes on the right lie to the right of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the right main bronchus at the upper margin of the upper lobe bronchus, and contained within the mediastinal pleural envelope The lower paratracheal nodes on the left lie to the left of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the left main bronchus at the level of the upper margin of the left upper lobe bronchus, medial to the ligamentum arteriosum and contained within the mediastinal pleural envelope
Aortic Nodes		
• Subaortic (A-P window)	5	Subaortic nodes are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope
• Para-aortic (ascending aorta/phrenic)	6	Nodes lying anterior and lateral to the ascending aorta and the aortic arch or the innominate artery, beneath a line tangential to the upper margin of the aortic arch
Inferior Mediastinal Nodes		
• Subcarinal	7	Nodes lying caudal to the carina of the trachea, but not associated with lower lobe bronchi or arteries within the lung
• Para-esophageal (below carina)	8	Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes
• Pulmonary ligament	9	Nodes lying within pulmonary ligament, including those in the posterior wall and lower part of the inferior pulmonary vein
N1 Nodes		N1 nodes: All N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura
• Hilar	10	Proximal lobar nodes, distal to the mediastinal pleural reflection and the nodes adjacent to the bronchus intermedius on the right; radiogically, the hilar shadow may be created by enlargement of both hilar and interlobar nodes
• Interlobar	11	Nodes lying between the lobar bronchi
• Lobar	12	Nodes adjacent to the distal lobar bronchi
• Segmental	13	Nodes adjacent to the segmental bronchi
• Subsegmental	14	Nodes around the subsegmental bronchi

TABLE 118.3B: The IASLC lymph node map, including grouping of lymph node stations into“zones”[42]

Stations	Lymph Nodes
1	*Supraclavicular Zone*
	Low cervical, supraclavicular and sternal notch
Superior Mediastinal Nodes	
	Upper Zone
2R	Upper paratracheal (right)
2L	Upper paratracheal (left)
3A	Prevascular
3P	Retrotracheal
4R	Lower paratracheal (right)
4L	Lower paratracheal (left)
Aortic Nodes	
	Aortopulmonary Zone
5	Subaortic
6	Para-aortic (ascending aorta or phrenic)
Inferior Mediastinal Nodes	
	Subcarinal Zone
7	Subcarinal
	Lower Zone
8	Paresophageal (below carina)
9	Pulmonary ligament
N1 Nodes	
	Hilar/Interlobar Zone
10	Hilar
11	Interlobar
	Peripheral Zone
12	Lobar
13	Segmental
14	Subsegmental

has a limited ability to confirm or exclude mediastinal metastasis in patients with lung cancer. In two earlier meta-analyses, the median sensitivity and specificity of CT scanning for identifying malignant mediastinal nodes was reported to be 61% and 79%, and 64% and 74%, respectively.[46,47]

The major limitation of CT scanning is that approximately 60% of the nodes identified as malignant turn out to be benign and similarly, approximately 20% of all nodes identified as benign by CT criteria are actually malignant.[40,48] Thus CT scan tends to both understage and overstage status of mediastinal lymph nodes. Moreover, even if the CT criteria are met for malignant nodes, there is still a need to prove by biopsy or resection that the nodes are malignant.

c. *Positron emission tomography (PET) scanning: PET imaging with [18F]-fluoro-2-deoxy-D-glucose* (FDG)-PET is widely used to stage lung cancers and to assess therapeutic response and determine prognosis.[49-54] FDG, a glucose analog, is taken up via glucose transporter membrane proteins present in both normal and tumor cells. Intracellular FDG is then converted to FDG-6-phosphate by hexokinase, but unlike glucose does not enter further metabolism and remains trapped in cells.[55] The combination of increased uptake of ^{18}F-FDG and a decreased rate of dephosphorylation by glucose-6-phosphatase in malignant cells results in an accumulation of ^{18}F-FDG-6-phosphate in these cells.[56,57] The disintegration of positrons from ^{18}F emit high energy gamma rays at 180° which can then be detected, localized and imaged as areas of higher metabolic activity. The relative activity in a given structure as related to background physiologic activity is termed Standardized Uptake value (SUV). In order to calculate the SUV accurately, information of body weight and serum glucose are necessary. An SUV greater than 2.5 is generally considered suspicious for neoplasm. Importantly PET scanning is primarily a metabolic examination and has limited anatomic resolution. The integration of PET and CT fusion provides, precise localization of the lesions on the FDG PET scans within the anatomic reference frame provided by Computed Tomography (CT). This increases the specificity of the imaging modality.

Overall, in the setting of an undiagnosed pulmonary nodule of greater than 1 cm, ^{18}F-FDG PET has a sensitivity of 96.8% and specificity of 77.8% in the detection of malignancy.[58] Recently, in a systematic review of 44 studies, a pooled estimates of sensitivity and specificity for identifying mediastinal metastasis were 74% (95% CI, 69% to 79%) and 85% (95% CI, 82 to 88%), respectively. Corresponding positive and negative likelihood ratios for mediastinal staging with PET scanning were 4.9 and 0.3, respectively.[40] An additional benefit of PET scanning is its ability to provide information about the primary site in the chest along with the intrathoracic and extrathoracic metastases with a single study. The exception is in the evaluation for brain metastases; generally, PET is considered to be less accurate than CT or Magnetic Resonance Imaging (MRI) scanning, with a reported sensitivity of only 60%.[59] These findings demonstrate that PET scanning has both higher sensitivity and higher specificity than CT scanning for the evaluation of mediastinal lymph nodes as well as metastatic disease.

Infection, granulomatous disease, and sarcoidosis all may have increased metabolic activity and limit the specificity of PET. False negative results may occur with well differentiated adenocarcinomas, bronchioalveolar cell carcinoma, carcinoid tumors and lesions less than 1 cm.[60-62]

Integrated ^{18}F-FDG PET/CT imaging outperforms CT alone, ^{18}F-FDG PET alone, conventional visual correlation or superimposition of CT and ^{18}F-FDG PET acquired individually.[63-67] The diagnostic advantages include more precise demarcation of primary tumor, improved diagnosis of tumor invasion, demarcation of tumor within atelectasis or infection, more precise localization of mediastinal lymph nodes greater than 8 mm in size, as well as the precise localization of extrathoracic lesions.[68] Most notably, integrated systems allow more accurate staging impacting treatment decisions in up to 20% of patients.[63]

In interpreting PET-CT results, particular attention is needed for false-negative and false-positive results, identifying them and confirming by additional imaging studies, even biopsy is necessary for key management decisions.[69,70] A PET-CT finding that is discordant with the pretest probability of neoplastic involvement is a key clue to a false-negative or a false-positive PET-CT result. Hence, due to the limited diagnostic specificity for identifying mediastinal metastases, tissue proof of PET positive lesions are recommended to prove that the lesions are truly malignant before denying surgical resection.[71] In summary, PET scanning is the most accurate noninvasive imaging modality available to evaluate the mediastinum in patients with lung cancer.

Invasive Mediastinal Staging

Once the presumptive clinical stage with respect to the mediastinum is obtained by initial clinical evaluation and noninvasive testing, in many clinical situations confirmation of the status of these nodes by an invasive test is necessary. Imaging studies are not sufficiently reliable in many situations that makes these invasive tests an important part of appropriate staging. Several invasive tests with differing performance characteristics are available to stage the mediastinum. These include mediastinoscopy, the Chamberlain procedure (also known as an anterior mediastinotomy), Transthoracic Needle Aspiration (TTNA) of the mediastinum, Transbronchial Needle Aspiration (TBNA), Endobronchial Ultrasound (EBUS) with Needle Aspiration (NA), Esophageal Endoscopic Ultrasound (EUS) with NA, and Video-Assisted Thoracic Surgery (VATS).

The invasive procedures are required to more accurately confirm the presumptive mediastinal stage but in selected cases used simply to confirm the diagnosis of malignancy. When it is used for diagnosis only, the choice of the test is driven primarily by the patient-specific issues rather than the test-specific performance characteristics. In contrast when it is used to confirm the mediastinal stage, the choice of procedure is governed by how reliably the test will define the absence or presence of nodal involvement

a. *Mediastinoscopy:* Mediastinoscopy is performed under general or local anesthesia in an operating room as an outpatient procedure.[72-74] It involves an incision just above the suprasternal notch and biopsy of the mediastinal nodes after insertion of a mediastinoscope alongside the trachea. Nodes that are accessible via this approach are right and left high and low paratracheal nodes (stations 2R, 2L, 4R, and 4L), pretracheal nodes (stations 1 and 3), and anterior subcarinal nodes (station 7). While posterior subcarinal nodes (station 7), inferior mediastinal nodes (stations 8 and 9), Aortopulmonary Window (APW) nodes (station 5), and anterior mediastinal nodes (station 6) node groups cannot be biopsied with this technique. Ideally, five nodal stations (stations 2R, 4R, 7, 4L, and 2L) should routinely be examined, with at least one node sampled from each station unless none are present after actual dissection in the region of a particular node station.

   To detect mediastinal node involvement from cancer, average sensitivity and False Negative (FN) rate of mediastinoscopy is about 80% and 10% while the specificity and False Positive (FP) rate is 100% and 0%, respectively.[75-84] Among the false negative cases approximately 42 to 57% are due to nodes that were not accessible by the mediastinoscope.[85-87] Mediastinoscopy is associated with a complication rate of 2 to 3% and a surgical mortality rate of around 0.1%.[88-90]

b. *Chamberlain procedure (anterior mediastinotomy):* It involves an incision in the second or third intercostal space just to the left of the sternum to assess the node in the Aortopulmonary Window (APW) (station 5). Cancers in the Left Upper Lobe (LUL) have a predilection for involvement of the nodes in the APW. These mediastinal nodes represent the most important group of N2 nodes that are not accessible by standard cervical mediastinoscopy. When Chamberlain procedure is combined with standard cervical mediastinoscopy in patients with LUL tumors, the sensitivity and FN rate is approximately 87% and 10%, respectively.[84,91]

Extended cervical mediastinoscopy where a mediastinoscope is inserted through the suprasternal notch and is directed lateral to the aortic arch, offers an alternative method for the invasive assessment of APW nodes.[91,92] In two large series of extended mediastinoscopy in patients with LUL cancers, the sensitivity and FN rates ranged from 69 to 81% and 9 to 11% respectively. Thoracoscopy and EUS-NA provides an alternative method of sampling APW nodes

c. *Esophageal endoscopic ultrasound with needle aspiration (EUS-NA):* EUS-NA through the wall of the esophagus is particularly useful for inferior pulmonary ligament, esophageal, subcarinal, and APW nodes (stations 9, 8, 7, and 5). In various studies that assessed the use of EUS-NA in the mediastinal staging of 973 evaluable lung cancer patients, the overall sensitivity, specificity, FN and FP rate, was 84%, 99.5%, 19% (range, 0 to 61%) and 0.4%, respectively.[93-98] Similarly in a meta-analysis of 18 studies assessing the diagnostic accuracy of EUS-FNA, it was found that the pooled sensitivity and specificity of EUS-FNA were 83% and 97%, respectively. The sensitivity increased to 90% when the analysis was limited to patients who had abnormal mediastinal lymph nodes seen on CT scans, however, the specificity remained the same.[99] The performance characteristics of EUS-NA apply broadly to patients with cN0-cN1 tumors, because the technical issues are probably governed by the size of the nodes.

EUS-FNA is also capable of detecting metastatic disease to subdiaphragmatic sites such as the left adrenal gland, celiac lymph nodes and the liver. Similarly, evaluation for the presence of direct tumor invasion into the mediastinum can also be performed by EUS-FNA. Although EUS can be helpful in determining the T stage in less cost than the surgical procedure, its usefulness for treatment decisions is limited by the high FP rate.

The major limitation of EUS-FNA in lung cancer staging is the inability to assess nodes in the anterior mediastinum, resulting in an imperfect sensitivity. This is due to the fact that ultrasound cannot penetrate air-filled structures, so, nodes immediately anterior to the trachea (i.e. levels 2R, 4R, 3, and 6) are not well visualized.

d. *Transbronchial needle aspiration (TBNA):* Sampling technique of minimally invasive TBNA through the bronchoscope, originally described by Wang and Terry in 1983, has been shown to be an effective and safe technique in the diagnosis and staging of lung cancers.[100,101] TBNA is feasible for obtaining adequate specimens in approximately 80 to 90% of cases in lung cancer.[102-104] In a meta-analysis of 13 studies, Holty *et al.* using a random effects model, found that the pooled sensitivity and specificity of TBNA in mediastinal staging was 39% (95% CI 17 to 61) and 99% (95% CI 96 to 100), respectively. They concluded that when properly performed, TBNA is highly specific for identifying mediastinal metastasis in patients with NSCLC and the sensitivity depends critically on the prevalence of mediastinal metastasis.[101] Similarly in a recent systemic review of mediastinal staging with TBNA that included 17 studies, the sensitivity, specificity, FN and FP rates were 78% (14 to 100%), 100%, 28% (0 to 66%) and 0% respectively.[105]

The high FN rate of TBNA in the mediastinal staging and dependence of sensitivity on the prevalence of mediastinal metastasis makes this test less useful for staging of the mediastinum in patients with normal-sized nodes. Thus, negative TBNA results, however, cannot sufficiently exclude mediastinal nodal involvement, and additional staging procedures are required.

e. *Endobronchial ultrasound with needle aspiration (EBUS-NA):* Introduction of EBUS as a tool for NSCLC staging has led to a shift from systematic nodal sampling to targeted nodal sampling. With EBUS-TBNA the paratracheal (stations 2 and 4), subcarinal (station 7), hilar and intrapulmonary nodes (stations 10 and 11) can be reached. Compared with mediastinoscopy, EBUS-TBNA has the advantage of routinely accessing posterior mediastinal (level 7) and hilar lymph nodes (levels 10 and 11). The main blind spots for EBUS-TBNA are the lymph nodes in the aortopulmonary window, para-aortic station, paraoesophageal stations and the inferior pulmonary ligament. By localizing the lymph nodes with EBUS, the sensitivity of TBNA can be greatly increased up to the tune of 85%.[106]

In a comparative study, Yasufuku *et al.* found that as compared to CT and PET, EBUS-TBNA has a high sensitivity as well as specificity for mediastinal and hilar lymph node staging in patients with lung cancer.[107] The overall sensitivity reported for EBUS-TBNA was 90%, with values ranging from 79 to 95%. The average FN rate in general was 24% (range, 1 to 37%).[105] Similarly, a recent meta-analysis that included 10 studies found pooled sensitivity of specificity of 88% (95% CI 0.79 to 0.94) and 100% (95%

CI 0.92 to 1.00), respectively.[108] Because of the real-time imaging of nodes with EBUS and the immediate proximity of nodes to the airway, EBUS holds a great deal of promise for this staging method, even in small nodes.

f. *Transthoracic needle aspiration (TTNA):* The ability to perform TTNA for the diagnosis and staging of cancer in the mediastinum has generally been reported to be high (>90%), with a sensitivity of 90%, although approximately 10% ultimately land up with pneumothorax requiring tube placement.[109-113] Because of quite extensive mediastinal involvement in the patients included in the studies, the purpose of the procedure was probably to confirm the diagnosis and less likely to confirm the stage.

g. *Video-assisted thoracic surgery (VATS*): Video-assisted thoracic surgery done under general anesthesia can be used to access mediastinal nodes but its usefulness is limited to an assessment of only one side of the mediastinum. There is a wide variation in the sensitivity from 37 to 100% reported in various studies. An added advantage of VATS is the detection of unsuspected malignant pleural effusion and pleural studding in patients undergoing this procedure.

In conclusion, because of the absence of a striking difference in the sensitivity of various invasive mediastinal staging procedures, several issues must be considered before deciding the optimal investigation to be chosen in a given patient. These issues include:

- Availability and expertise of different procedures at a given centre/institution
- Location of the lymph nodes to be assessed for histopathological/cytological examination
- Patient's general medical condition including performance status and co-morbidities
- Morbidity and mortality of invasive procedures.

STAGING OF SMALL CELL LUNG CANCER

Traditionally, Small Cell Lung Cancer (SCLC) has been staged as either Limited Disease (LD) or Extensive Disease (ED).[114] This was chosen since the former denoted disease restricted to one hemithorax, with or without regional lymph node metastases and/or ipsilateral pleural effusion and thus could be encompassed within one radiation port. Lately it has been shown that use of the 7th edition of the TNM staging can prognosticate patients more accurately than the traditional system.[115] However, for management purposes, the role of surgical resection is limited in case of SCLC. Hence, invasive procedures of the mediastinum, if performed, are more for diagnostic purposes than for staging.

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Approach to Management of Lung Tumors

Navneet Singh, Digambar Behera

INTRODUCTION

Lung tumors are an important group of pulmonary disorders that include both benign and malignant neoplasms. The most important disease entity in this group is lung cancer. Lung cancer is the most common cancer worldwide representing approximately 12% of all new cancers.[1] It is also the most common type of cancer in males and the most common cause of cancer related mortality in both sexes.[1,2] Lung cancer accounts for 17.6% of the total cancer related deaths which is far more than for any other type of cancer.[2] Furthermore, lung cancer mostly presents as an advanced disease.[3] Approximately 80% of cases are of Non-Small Cell Lung Cancer (NSCLC) type.[3] Overall, the prognosis for lung cancer remains dismal, the 5-year survival rates are at best around 15% despite available advances in treatment options.[4] This chapter focuses primarily on specific issues related to lung cancer in the Indian context.

DIAGNOSTIC WORK-UP

Details about the investigations needed to establish a correct diagnosis as well as for staging are given in other chapters. However, it is necessary to emphasize here that in any patient suspected to have a thoracic neoplasm, a contrast enhanced Computed Tomography (CT) scan of the thorax and upper abdomen (including liver and adrenals) is essential for better delineation of the anatomical extent of the tumor as well as for detailed structural assessment. In case of lung cancer, this is also necessary for ensuring that the patient is staged appropriately prior to initiation of treatment. Other imaging modalities are less useful but may be done for specific indications like Magnetic Resonance Imaging (MRI) scan for determining the extent of neural involvement in cases of superior sulcus tumors and Positron Emission Tomography (PET) scan for the functional (metabolic) assessment of a pulmonary/extrapulmonary lesion.[5]

The PET-CT scan which combines the metabolic assessment of PET scan with the structural/anatomical assessment of CT scan is more accurate for staging purposes than either of the two alone.[6] However, this facility is not routinely available in developing countries and is also more expensive than a normal CT scan. Hence, it is prudent that its use is restricted to patients in whom it can potentially lead to changes in management. For example, in a patient of NSCLC with obvious evidence of liver metastases on CT, a PET scan is unlikely to alter the management significantly. However, in a patient with potentially resectable (early stage) NSCLC on initial imaging, a PET-CT is necessary to rule out metastatic disease that may otherwise be inapparent radiologically and therefore to avoid an unnecessary thoracotomy.

It is also necessary to know that no imaging modality by itself can confirm the diagnosis of a lung tumor, which can be provided only by cytological and/or histopathological examination of a representative tissue/fluid specimen. The site and type of tissue/fluid obtained can vary depending upon the anatomical involvement and extent of the tumor. Commonly endobronchial biopsy and bronchial washings for endobronchial tumors, image guided fine needle aspiration and biopsy for peripherally located tumors, pleural fluid analysis and biopsy for tumors associated with pleural effusion and lymph node aspiration and biopsy for peripherally accessible lymph nodes are performed.

TREATMENT PLANNING

Conventionally, as is true for other cancers, the most important treatment modalities for lung cancer have been chemotherapy, surgical resection and radiation therapy. Management of lung cancer is traditionally discussed separately for NSCLC and small cell lung cancer (SCLC) since the surgery holds a very limited role in case of the latter due to its propensity for early dissemination/distant metastases. An algorithmic approach to the management of NSCLC and SCLC is depicted in Figures 119.1 and 119.2 respectively. In the recent past especially in the last couple of decades, targeted therapies have also emerged as a useful addition to the conventional armamentarium for the treatment of NSCLC. Platinum-based chemotherapy (conventionally in association with

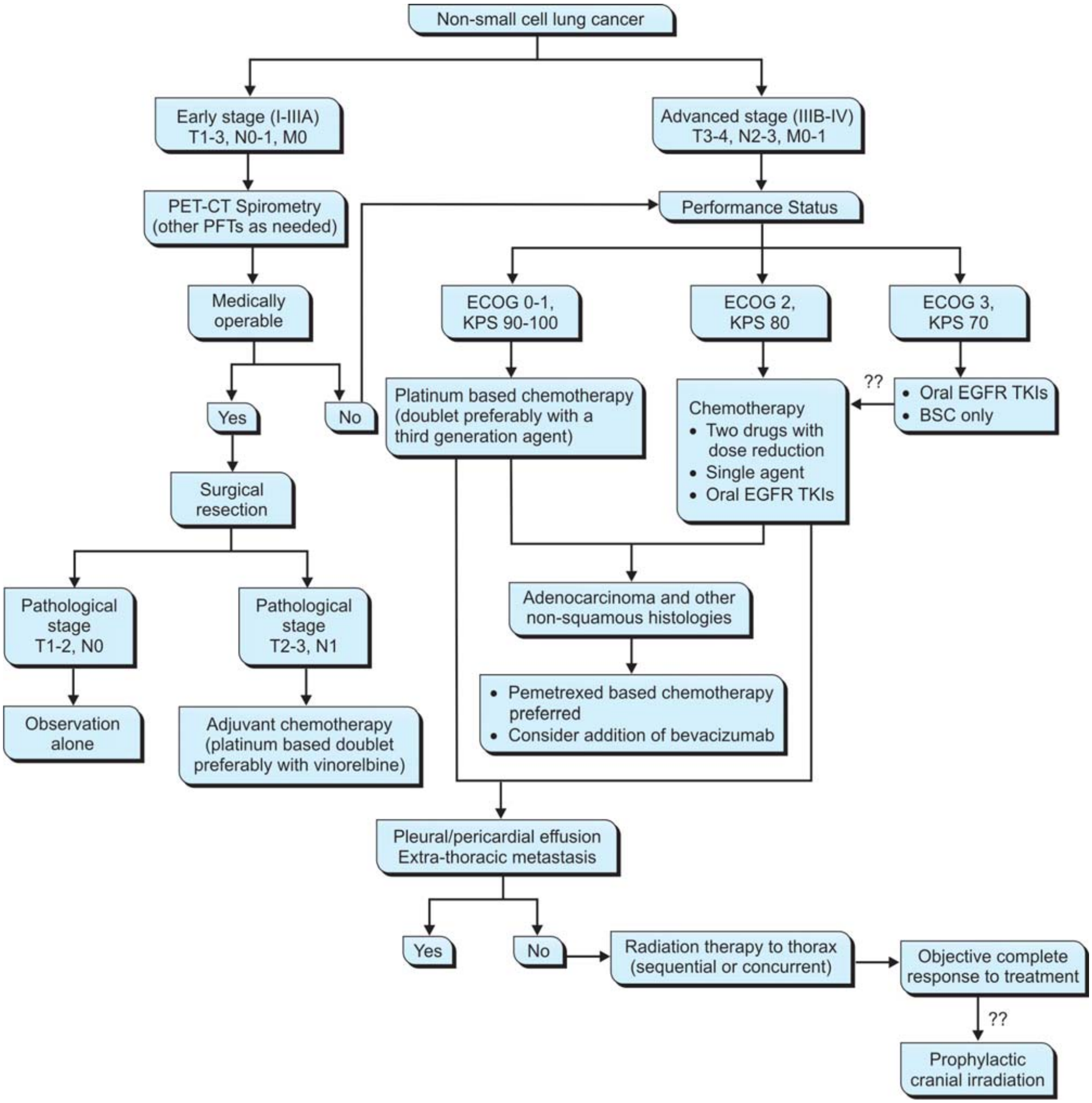
Non-small cell lung cancer
Early stage (I-IIIA) T1-3, N0-1, M0
Advanced stage (IIIB-IV) T3-4, N2-3, M0-1
PET-CT Spirometry (other PFTs as needed)
Performance Status
Medically operable
ECOG 0-1, KPS 90-100
ECOG 2, KPS 80
ECOG 3, KPS 70
Yes
No
Platinum based chemotherapy (doublet preferably with a third generation agent)
Chemotherapy
• Two drugs with dose reduction
• Single agent
• Oral EGFR TKIs
??
• Oral EGFR TKIs
• BSC only
Surgical resection
Pathological stage T1-2, N0
Pathological stage T2-3, N1
Adenocarcinoma and other non-squamous histologies
Observation alone
Adjuvant chemotherapy (platinum based doublet preferably with vinorelbine)
• Pemetrexed based chemotherapy preferred
• Consider addition of bevacizumab
Pleural/pericardial effusion Extra-thoracic metastasis
Yes
No
Radiation therapy to thorax (sequential or concurrent)
Objective complete response to treatment
??
Prophylactic cranial irradiation

Fig. 119.1: Algorithmic approach to a patient with non-small cell lung cancer

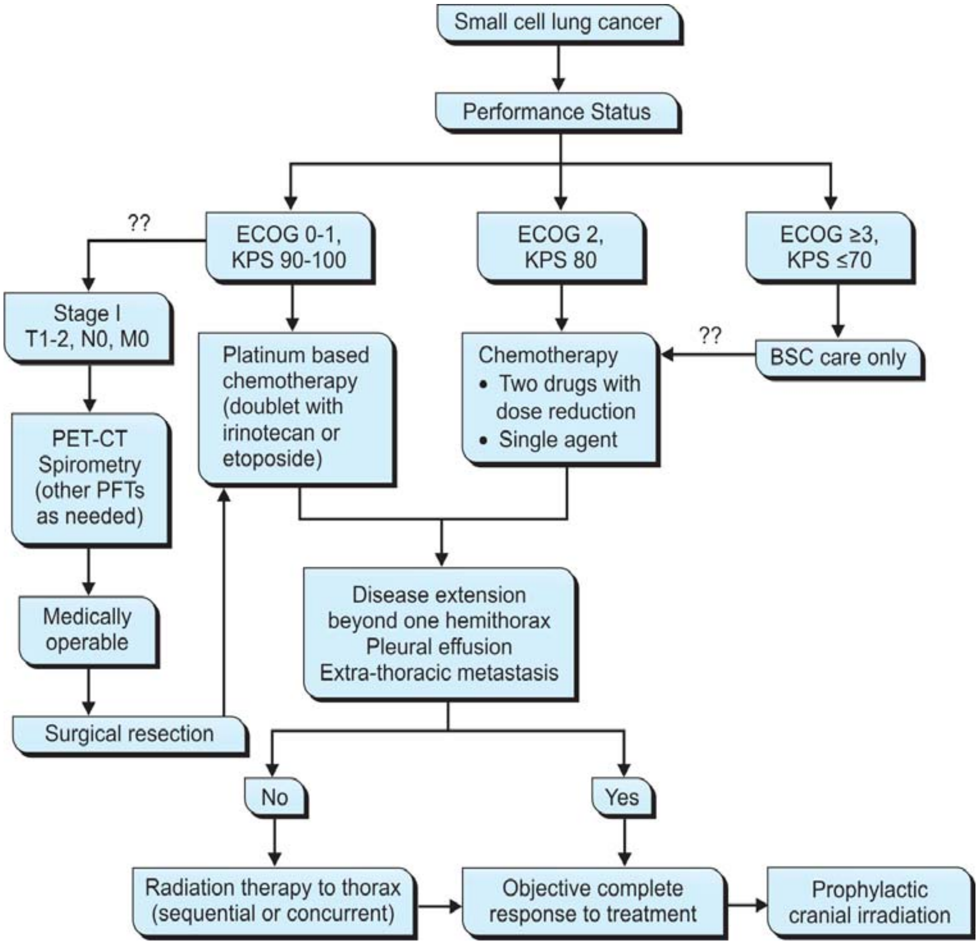
Small cell lung cancer
Performance Status
??
ECOG 0-1,
KPS 90-100
ECOG 2,
KPS 80
ECOG ≥3,
KPS ≤70
Stage I
T1-2, N0, M0
Platinum based
chemotherapy
(doublet with
irinotecan or
etoposide)
Chemotherapy
• Two drugs with
dose reduction
• Single agent
??
BSC care only
PET-CT
Spirometry
(other PFTs
as needed)
Medically
operable
Surgical resection
Disease extension
beyond one hemithorax
Pleural effusion
Extra-thoracic metastasis
No
Yes
Radiation therapy to thorax
(sequential or concurrent)
Objective complete
response to treatment
Prophylactic
cranial irradiation

Fig. 119.2: Algorithmic approach to a patient with small cell lung cancer

a third generation chemotherapeutic agent) remains an important component of the management protocol for almost all patients with NSCLC-early, locally advanced and metastatic.[7,8] The role of surgical resection and radiation therapy in NSCLC is predominantly for patients presenting with stages I-IIIA and IIIA-IIIB respectively (Table 119.1). For advanced/metastatic NSCLC, the current standard of care is chemotherapy alone. The greatest evidence is for the use of a platinum based doublet.[8] A detailed description of the different techniques and modalities available for surgical resection as well as technical aspects related to administration of radiation therapy remains beyond the scope of this chapter. The medical management is however discussed in further detail below.

There have been significant changes in the regimens used for treatment of this disease over the past few decades. Earlier, agents like vincristine, vinblastine, cyclophosphamide, ifosfamide, methotrexate, adriamycin and mitomycin-C were being used for treatment of NSCLC.[9-11] However, currently because of a more favorable toxicity profile, third generation agents (taxanes, gemcitabine, pemetrexed and vinorelbine) are the preferred drugs that are used in combination with a platinum agent. Chemotherapy along with Best Supportive Care (BSC) has been shown to be better than BSC alone in improving survival.[12-14] In addition to this quantitative effect, the benefit of chemotherapy over BSC alone has also been observed in terms of improvement in quality of life (QOL).[15-17]

In an attempt to practice personalized medicine, there are several considerations which the treating physician has to look into. The important ones are listed below:

1. **Choice of Platinum Agent:** The two commonly used platinum agents are cisplatin and carboplatin. An individual patient data meta-analysis involving 2968 patients from nine RCTs compared the efficacy of cisplatin versus carboplatin when used in first line chemotherapy for advanced NSCLC.[18] The objective response rate was observed to be higher with cisplatin

TABLE 119.1: Role of the traditional treatment modalities in different stages of non-small cell lung cancer

*Stage**	*Surgery*	*Chemotherapy*	*Radiotherapy*
IA	Yes	No	Only if medically inoperable
IB	Yes	? Yes (adjuvant)	Only if medically inoperable
IIA & IIB	Yes	Yes (adjuvant)	Only if medically inoperable
IIIA (non-bulky)	Yes	Yes (adjuvant or neoadjuvant)	Yes (post-operative)
IIIA (bulky)	Not routinely	Yes	Yes (sequential or concurrent)
IIIB (without pleural effusion)	No	Yes	Yes (sequential or concurrent)
IIIB (with pleural effusion)† and IV	No	Yes	Only for palliation

*Stage description based upon 6th edition of TNM staging system
† In 7th edition of TNM staging system, presence of a malignant pleural effusion is put in stage IV

than with carboplatin [30% vs 24% respectively, Odds Ratio (OR) = 1.37]. Carboplatin-based chemotherapy was associated with a statistically significant increase in mortality among patients with non-squamous histology [Hazards Ratio (HR) = 1.12] as well as those treated with third-generation chemotherapeutic agents (HR = 1.11).[18] Although cisplatin-based chemotherapy is associated with more severe nausea-vomiting and nephrotoxicity, carboplatin-based chemotherapy is associated with more severe thrombocytopenia.[19] Thus, cisplatin being slightly superior to carboplatin both for response rates as well as Overall Survival (OS), remains the standard drug for formulating a chemotherapy regimen while carboplatin is preferred for patients in whom there are relative contraindications to the use of cisplatin.

2. **Role of Histology:** There is a growing body of evidence to suggest that NSCLC is a heterogeneous disease although, as of now, all the different histological types continue to be clumped as one disease entity. It has been shown in both prospective and retrospective studies that squamous histology remains a favorable prognostic factor for patients undergoing lung resectional surgery.[20-23]Infact, in the JBR.10 trial, presence of squamous histology was the only factor other than administration of chemotherapy that was associated with both an improvement in OS as well as in recurrence-free survival among patients with completely resected early-stage NSCLC.[20] The converse has however been observed for patients with unresectable disease.[24,25] In addition to being a prognostic factor, histological type remains an important predictive factor also for different therapeutic modalities in NSCLC.[26] Differences in treatment responses based on histology have indeed been observed in recently published Randomized Clinical Trials (RCTs).[27,28] Results of recently published phase III RCTs involving the use of pemetrexed (an anti-folate drug that inhibits multiple enzymes involved in purine and pyrimidine synthesis) suggest that patients of NSCLC with different histological patterns may respond differently to commonly used chemotherapeutic agents.[29-31] In one study, pemetrexed was compared with gemcitabine in previously untreated patients with advanced NSCLC.[30] Both the chemotherapy regimens were platinum based doublets. Among patients with adenocarcinoma, OS was statistically superior for those who received pemetrexed compared to gemcitabine (12.6 vs 10.9 months; HR = 0.84) while the reverse was seen in patients with squamous cell histology (9.4 vs 10.8 months; HR = 1.23). Patients with large cell and non-squamous histology (as a group) had results similar to those seen with adenocarcinoma.

Even in the second line/maintenance therapy setting, pemetrexed has been demonstrated to result in superior median OS for patients with adenocarcinoma and non-squamous histology, in two phase III RCTs.[29,31] In the RCT comparing pemetrexed to docetaxel as second line therapy for advanced NSCLC, among subgroup with squamous histology, patients treated with pemetrexed had statistically worse OS than those receiving docetaxel.[29,32] In the other trial wherein pemetrexed was used as maintenance therapy after initial treatment with a platinum based doublet, the drug fared no better than placebo, in terms of its effect on OS among the subgroup of patients with squamous histology.[31] In addition, pemetrexed has a superior tolerance and lesser toxicity profile than the other agents with which it has been compared in the above mentioned RCTs.

Histology plays a very important role in decision making. Currently adenocarcinoma and non-squamous NSCLC histologies are preferably treated with pemetrexed. However, it needs to be mentioned that pemetrexed is the most expensive of all the third generation agents which are available. Even if a generic brand is used, the cost can sometimes reach up to 50,000 Indian Rupees (INR). Even if a patient is otherwise a candidate for pemetrexed treatment (non-squamous NSCLC histology), he/she may not always able to afford the drug due to a significant difference in the cost of the regimen compared to the other available agents. The issue of cost versus the benefits must be clearly discussed with the patient/family. Not infrequently, the benefit may in fact be too small compared to a significant different in the cost.

3. Choice of Third Generation Agent to be Used with Platinum Compound: Both the commonly used platinum compounds are quite cheap compared to any of the third generation agents which form the two drug regimen. This is one of the reasons why non-platinum regimens are infrequently used even in the case of intolerance or contraindications to use of plantinum compounds. Most of the third generation agents like paclitaxel, docetaxel, gemcitabine and vinorelbine are similar in efficacy (Table 119.2).[33] At our center, paclitaxel-cisplatin is the cheapest regimen among all the above. This is in part due to use of a lower dose [175 mg/m^2 Body Surface Area (BSA) given on day 1 of a three weekly cycle] as compared to relatively higher doses (200 to 225 mg/m^2 BSA) being used at other centers in the developed countries.[34] Gemcitabine and vinorelbine both share the same disadvantage, that two visits are required for a given cycle, since these drugs are generally given on two days (day one and day eight of a three weekly cycle). The taxanes (paclitaxel, docetaxel) on the other hand are given on day one only. For a center where majority of the patients come from distant areas, the frequency of visits to be made for a given cycle often holds a great importance.

4. Number of Cycles: As regards to the optimal duration of chemotherapy, it is recommended that the initial chemotherapy regimen should be administered for a maximum of four to six cycles.[8] What we follow, as is done by several centers in North America and Europe, is to continue the initial regimen for four cycles (in the absence of obvious disease progression). An assessment of the response to therapy is done most commonly by repeat contrast enhanced CT scan of the thorax and upper abdomen (to include liver and adrenal glands). Response assessment can be done by using either the RECIST or WHO criteria.[35,36] An addition of two cycles can be considered for patients who show a response (partial/complete). There is little benefit in giving the same regimen in the presence of stable disease after four cycles, while second line therapy is warranted if there is evidence of disease progression at any point during the initial treatment. Even for responding patients, no more than six cycles should be given.[37]

TABLE 119.2: Comparison of efficacy of four chemotherapeutic regimens (modified and adapted from reference 33)

Regimen	*Paclitaxel + Cisplatin*	*Gemcitabine + Cisplatin*	*Docetaxel + Cisplatin*	*Paclitaxel + Carboplatin*
Schedule	135 mg/m^2 (over 24 hours) on day 1 + 75 mg/m^2 on day 2 every 3 weeks	1000 mg/m^2 on days 1,8,15 + 100 mg/m^2 on day 1 every 4 weeks	75 mg/m^2 each on day 1 every 3 weeks	225 mg/m^2 (over 3 hours) + AUC* 6 on day 1 every 3 weeks
Response rates†				
• PR	21%	21%	17%	16%
• SD	18%	18%	25%	23%
• PD	49%	40%	42%	49%
Overall survival§	7.8 (7.0–8.9) months	8.1 (7.2–9.4) months	7.4 (6.6–8.8) months	8.1 (7.0–9.5) months
TTP§	3.4 (2.8–3.9) months	4.2 (3.7–4.8) months	3.7 (2.9–4.2) months	3.1 (2.8–3.9) months

*AUC = Area under curve

† For each group, complete response was ≤1%

§ Data is presented as median (95% confidence intervals)

PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; TTP: Time to progression

5. **Dose Intensity:** Dose Intensity (DI) is defined as the dose of a particular chemotherapeutic drug administered per unit time, expressed as milligrams per metre square of body surface area per week ($mg/m^2/week$).[38] Dose intensity is used to indicate both the actual DI used as well as the relative DI. The latter is the ratio of DI of an experimental versus a standard regimen or of the delivered versus planned DI of a given regimen. This is a very important consideration in countries like India where there are constraints related to the availability of health care resources and where a majority of the population is not covered by medical insurance.

The treating physician is faced with the challenge of optimizing treatment efficacy and at the same time, avoiding complications related to chemotherapy. Moreover, DI can be increased either by increasing the dosage per session of chemotherapy and keeping the inter-session interval constant, or by reducing the inter-session interval and keeping the dosage constant.[38] The former can be associated with a higher degree of intolerance/acute toxicity while the latter requires an increased frequency of visits by the patient during a given time period. It is also important to differentiate DI from high dose therapy.[39]

6. **EGFR Targeted Therapy in the First Line Setting:** Targeted therapies have been tried as an alternative to, in conjunction with or following failure of standard chemotherapy regimens. Of the targeted therapies, the most extensive research has been conducted on the oral Tyrosine Kinase Inhibitors (TKIs) of the Epidermal Growth Factor Receptor (EGFR). The latter is frequently, although variably, expressed in tumor cells of patients with NSCLC. Gefitinib and erlotinib are the two EGFR-TKIs that are currently marketed and are available for use in routine clinical practice. Four large RCTs (INTACT-1, INTACT-2, TALENT, TRIBUTE) have failed to show any additional clinical benefit of adding an EGFR-TKI to chemotherapy in the first-line therapy of advanced NSCLC.[40-43] These drugs can however, be considered as an alternative to conventional chemotherapy for patients with poor Performance Status (PS).[44-47] However, the best predictors for response to this class of drugs is the presence of specific mutations in the EGFR gene.[48] Such testing is not commonly available in developing countries and even if available, may not be affordable by a large section of the patient population.[49]

In contrast, the role of EGFR targeted monoclonal antibody (cetuximab) in the first line setting has been somewhat different. EGFR gene copy number as determined by Fluorescent In Situ Hybridization (FISH) has been shown to be helpful in predicting outcome among patients treated with cetuximab.[50] In a large phase III RCT, this drug when combined with chemotherapy was shown to significantly improve OS as compared to chemotherapy alone when used as front line therapy for EGFR-FISH positive advanced NSCLC patients.[51] However, for a drug with no generic substitutes being available till date, the cost of this additional therapy is prohibitory for most Indian patients with no access to medical insurance or reimbursement of medical expenses.

7. **Single Agent:** Patients with sub-optimal PS (generally ECOG PS of 2 or less and Karnofsky PS of 80 or less) can be considered for single agent chemotherapy.[52] Non-platinum agents like docetaxel, gemcitabine and vinorelbine have been shown to be a good treatment option for such patients as well as for patients in whom there is intolerance to or contraindications for combination therapy with platinum agents.[45]

8. **Addition of Bevacizumab to Chemotherapy:** For selected subgroup of patients (non-squamous histology, peripheral tumors, absence of hemoptysis or CNS metastasis), addition of bevacizumab (a vascular endothelial growth factor [VEGF] monoclonal antibody) is associated with improved response rates and even overall survival.[53] The commonly used doses are 7.5 mg/kg body weight and 15 mg/kg body weight.[53,54] The greatest hindrance to its use is not medical but the cost of the therapy. For an average adult weighing 60 kg, the cost of this drug (for which no generic substitutes are available till date) is in excess of 100,000 Indian Rupees (INR) even at the lowest dose used clinically, namely 7.5 mg/kg. This exceeds the cost of chemotherapy by a factor of two or more. Furthermore, its use is recommended till disease progression which differs from that for chemotherapy for which a maximum of four to six cycles are recommended.

The expected life span and severity of symptoms are other additional factors that influence the choice and sequence of treatment for a given patient (Table 119.3). The optimum treatment protocol is also determined by tumor histology (Table 119.4). In the second line setting also, considerations for treatment are similar to those for the first line therapy and generally a drug other than the one used in the first line setting is chosen.[55]

The basic principles of chemotherapy for treatment of SCLC are the same as for NSCLC. As in the case of NSCLC, regimens containing drugs like vincristine,

TABLE 119.3: Factors determining choice of treatment modality for a given patient with lung cancer

Characteristic	*Importance in decision making*
Disease related	
Age	++
Gender	+
Histology	++
Stage	+++
Performance Status	+++
Unrelated to disease	
Comorbid illnesses	+
Socio-economic background/financial constraints	+++
Medical reimbursement/insurance issues	+++
Wishes of patient/family members	++
Frequency of hospital visits	++

cyclophosphamide, ifosfamide and lomustine were used frequently in the past for treatment of SCLC.[56,57] Currently, a platinum based doublet remains the preferred regimen: The agents used in the platinum doublet are either etoposide or irinotecan. The important differentiating feature from NSCLC is that there are limited therapeutic options both in first and second line settings since none of the targeted agents has shown significant clinical benefit till date as to warrant approval for use in routine practice. Most of the standard schedules currently practiced in India, employ a 3-week cycle frequency for both NSCLC and SCLC (Table 119.5).

PALLIATION

A high percentage of lung cancer patients have locally advanced/metastatic disease (stages IIIB/IV) at presentation or relapse after initial treatment. This group of patients often has significant symptoms related to disease. In such cases, the primary aim of management is to achieve symptom relief and improve the QOL. As is true for all patients with advanced cancers, attempting treatment with a curative intent is generally not possible. However, these patients remain candidates for palliative treatment which is not only necessary but also justifiable.[58]

Palliation is an important aspect of management of lung tumors especially advanced lung cancer (Table 119.6).

1. Treatment of locally advanced (especially endobronchial) disease for troublesome symptoms of cough, dyspnea and hemoptysis, is an important part of palliative care of lung cancer. Interventional bronchoscopy, wherever available, is helpful in alleviation of these symptoms since several procedures to relieve endobronchial obstruction can be performed.[59,60] Wherever available, intra lesion brachytherapy is another useful option for this purpose.[61]
2. Treatment of advanced mediastinal disease depends upon the structure that is being involved by the disease process.
    a. Relief of Superior Vena Cava (SVC) compression is commonly achieved by administration of radiotherapy in case of NSCLC and chemotherapy in SCLC.[62] Stenting of the SVC, in institutes which

TABLE 119.4: Optimal first line chemotherapy regimen according to histological type

Histology	*Chemotherapy*	*Preferred drug to be combined with platinum compound*	*Targeted agent in combination with chemotherapy*	
			Cetuximab	*Bevacizumab*
NSCLC	Platinum based doublet*	3rd generation drug†		
• Squamous cell		All except pemetrexed	Yes[§]	No
• Adenocarcinoma		Pemetrexed	Yes[§]	Yes
• Large cell		Pemetrexed	Yes[§]	Yes
• Undifferentiated		All except pemetrexed	Yes[§]	Yes
SCLC	Platinum based doublet*	Etoposide or irinotecan	No	No
Malignant carcinoid	Platinum based doublet*	Etoposide or irinotecan	No	No

* Platinum based doublet consists of a platinum agent (commonly cisplatin or carboplatin) with another drug

†Commonly used third-generation chemotherapeutic agents include gemcitabine, docetaxel, paclitaxel, pemetrexed and vinorelbine

[§] Patients with high epidermal growth factor receptor gene copy number determined by florescent in-situ hybridization testing

NSCLC: Non-small cell lung cancer, SCLC = Small cell lung cancer

TABLE 119.5: Standard dosage of chemotherapeutic drugs used at the authors' institute

	Dose per scheduled visit	*Day(s) of cycle on which drug administered*	*Cycle frequency*
Non-small cell lung cancer			
Platinum compound			
• Cisplatin	60 mg/m^2	Day 1	Every 3 weeks
• Carboplatin	AUC* 5	Day 1	Every 3 weeks
Non-Platinum compound			
• Docetaxel	75 mg/m^2	Day 1	Every 3 weeks
• Paclitaxel	175 mg/m^2	Day 1	Every 3 weeks
• Pemetrexed	500 mg/m^2	Day 1	Every 3 weeks
• Gemcitabine	1000 mg/m^2	Day 1-8	Every 3 weeks
Small cell lung cancer			
Platinum compound			
• Cisplatin	30 mg/m^2	Day 1-8	Every 3 weeks
• Carboplatin	AUC* 5	Day 1	Every 3 weeks
Non-Platinum compound			
• Irinotecan	65 mg/m^2	Day 1-8	Every 3 weeks
• Etoposide	80 mg/m^2	Days 1-3	Every 3 weeks

*AUC: Area under curve

have the facilities for a the same, is a good alternative/adjunct to the above measures.[63]

b. Tracheo-esophageal fistula often requires assessment from both a gastroenterologist and a pulmonologist in order to decide about the best possible intervention that can help in alleviating the symptoms attributable to the fistula. Stenting of the esophagus, trachea or both can prove to be useful in achieving relief.[64-67]

3. Treatment of metastatic disease

a. Malignant pleural and pericardial effusion. Malignant pleural effusion is discussed in another chapter. Malignant pericardial effusion is not infrequently seen in advanced lung cancer, especially among patients who have a malignant pleural effusion. Patients with malignant pericardial effusion can present with insidious onset progressive dyspnea or sometimes with features of cardiac tamponade. Prompt drainage of the effusion is necessary to achieve symptom relief and remove the tamponade. Creation of a pericardial window and intrapericardial sclerosis (by injection of a sclerosing agent into the pericardial space) are more definitive measures. The latter has been shown to be as effective and more cost-effective than open surgical drainage in several studies.[68-70] Unlike benign causes of pericardial effusion where intrapericardial sclerosis is a relative contraindication, the expected life span for a patient with malignant pericardial effusion is generally less than the time taken for a potential complication like pericardial constriction to develop from the procedure.

b. Bone: Bone metastases is a common but under-diagnosed entity among patients with lung cancer.[71] Bisphosphonates are recommended for use in patients with proven osteoskeletal metastasis.[72] Zoledronate is the most widely used drug for this purpose. It has been shown to reduce skeletal complications especially the incidence of Skeletal Related Events (SREs) like pathological fractures in patients with established bony metastasis.[73] The aim of using this drug is to both prevent and delay the occurrence of further bone metastases and SREs as well as to achieve pain relief. It is recommended that this treatment should continue for as long as it is practically feasible in the absence of any significant adverse effects.[72] In addition, local radiotherapy to the affected site helps in more rapid relief of symptoms.

c. Brain and Spinal Cord: Here again, radiation therapy has an important role in providing

TABLE 119.6: Important components of palliation during management of lung tumors

- **Relief of symptoms**
  - **Disease related**
    - Endobronchial disease
      - Hemoptysis
      - Postobstructive collapse
      - Postobstructive pneumonia
      - Stridor related to involvement of trachea/major bronchi
    - Compression/involvement of important mediastinal structures
      - Superior vena caval obstruction
      - Tracheoesophageal fistula
      - Malignant pericardial effusion associated with cardiac tamponade
      - Stridor related to compression of trachea/major bronchi
    - Extrapulmonary metastases
      - Neurological symptoms due to brain or vertebral/spinal cord involvement
      - Bony metastases associated with pain or pathological fractures
    - Paraneoplastic syndromes
      - Pulmonary thromboembolism
      - Cancer related cachexia
      - Hypercalcemia
    - Complications of treatment
      - Peripheral neuropathy
  - **Unrelated to disease**
    - Comorbid illnesses
      - Chronic obstructive pulmonary disease
      - Ischemic heart disease
      - Depression

symptomatic relief. Corticosteroids are used for the same purpose although there is a ceiling to both the dose used as well as the duration for which they provide clinical benefit.[74]

4. Treatment of non-metastatic disease
   a. Anemia: This is more frequently encountered than the other cytopenias during chemotherapy of lung cancer patients in our setting.[34] Oral hematinics and blood transfusion for a greater severity of anemia, remain the most cost-effective method of correcting anemia. Erythropoietin stimulating agents are not only expensive but their usage is also associated with increased incidence of thromboembolic events. Hence they should be used only during the period of chemotherapy and not before or afterwards.[75,76]

   b. Cachexia: Cancer associated cachexia is not uncommonly seen in patients with advanced lung cancer. This symptom complex includes weight loss, anorexia, fatigue and generalized wasting. It is difficult to reverse cachexia in the absence of any definitive therapy for the disease. Patients who receive and respond to chemotherapy or targeted therapy show improvement. Progestins (especially megestrol acetate) have been tried for this paraneoplastic syndrome with variable success.[77]

   c. Deep Venous Thrombosis (DVT) and Pulmonary Thromboembolism (PTE): Both are known to occur more frequently among cancer patients than in the general population since cancer is one of the hyper-coagulable states. However, routine DVT prophylaxis in ambulatory cancer patients is not recommended.[78] Treatment is also similar to that seen in other situations.

5. Treatment of complications of chemotherapy:
   a. Infection: Both pulmonary and extrapulmonary infections may occur among patients with lung tumors. Postobstructive pneumonia is a frequent occurrence among patients with central tumors arising from and occluding a major or lobar bronchus. Typical features of postobstructive pneumonia include recurrent episodes involving the same anatomical area, paucity of expectoration

(unless the obstruction is incomplete) and lack of complete response to antimicrobial therapy. Postobstructive pneumonia is more likely to occur in an untreated patient.

Pulmonary infections are more common after definitive treatment especially with systemic cytotoxic chemotherapy and/or radiation therapy. Pulmonary infections can often present with and be treated in a similar way as they occur in immunocompetent individuals. The treating physician has to be vigilant about the presence of unusual etiological organisms and of unusual clinical features and in such cases, a more aggressive management strategy may be warranted. Extrapulmonary infections are more likely to occur among patients who have received systemic therapy as mentioned above. Presence of neutropenia may be associated with an increase in the incidence, severity and poorer outcomes.

   b. Peripheral Neuropathy: Generally, a complication of chemotherapy with taxanes and platinum agents, it can also occur as a paraneoplastic manifestation. Anticonvulsants and tricyclic antidepressants are used for the treatment of neuropathic pain.[74]

6. Treatment of co-morbid illnesses
   a. COPD: Smoking is an important risk factor for the development of both chronic Obstructive Pulmonary Disease (COPD) and lung cancer. Undiagnosed or inadequately treated airflow obstruction due to COPD can have an adverse effect on the QOL of patients with lung cancer.[58] Spirometric evaluation is a simple and effective measure to detect coexistent COPD. Smoking cessation is the most important intervention to retard progression of COPD. Patients should be assessed for the 5 'A' strategy if they have not quit smoking at the time of initial evaluation.[79] Bronchodilators (inhaled and oral) are important pharmacological measures for providing symptomatic relief.
   b. Depression: It is not uncommon to see depressive symptoms subsequent to the diagnosis and treatment of lung cancer.[80] Some patients may actually fulfill the criteria for major depression. There are even suggestions that addition of a specific intervention for its treatment to the usual standard of care for lung cancer, may actually influence the efficacy of the latter.[81]

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120A

Solitary Pulmonary Nodule

Alladi Mohan, B Vijayalakshmi Devi, Abha Chandra

INTRODUCTION

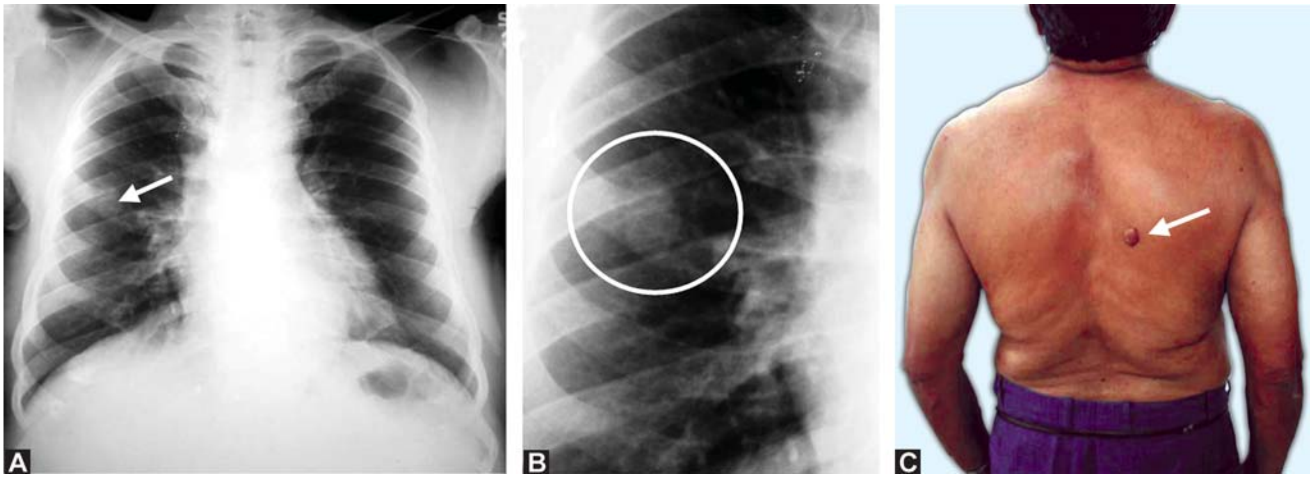
Solitary Pulmonary Nodules (SPNs) are small, focal, radiographic opacities that may be caused by a variety of benign and malignant disorders and constitute a unique diagnostic problem faced by pulmonologists, radiologists and thoracic surgeons.[1-4] In the earlier days of conventional radiography, these lesions used to be most commonly encountered as incidental findings on a chest radiograph. In the present era, widespread use of Computed Tomography (CT) has resulted in a significant increase in the detection of these lesions.[5,6] Many patients with early-stage lung cancer can present with an SPN. The overall 5-year survival rate in patients with lung cancer is poor ($\leq$15%); in comparison, long-term survival in stage IA lesions that can be resected may be as high as 80%.[1,7,8] Therefore, it is important to distinguish whether the lesion is benign or malignant so that early intervention is possible in patients with lung cancer and unnecessary surgery can be avoided in patients with benign SPNs.

Advances in CT technology, such as Multidetector-Row CT (MDCT) for the evaluation of lung and cardiovascular disease, Computer-Aided Diagnosis (CAD), 18F-Labeled 2-Deoxy-D-Glucose Positron Emission Tomography (FDG-PET), have markedly influenced the diagnostic work-up of a patient presenting with an SPN.[5,6] Comprehensive evaluation of an SPN requires careful consideration of a variety of patient-related variables, imaging findings appropriate use of invasive sampling and logistics related to a meticulous follow-up schedule.

TERMINOLOGY

The term "coin lesion" should not be used to describe SPNs because coin lesion implies a flat two-dimensional structure.[7-9] The SPN is defined as a single, spherical, well-circumscribed, radiographic opacity that measures less than or equal to 3 cm in diameter that is surrounded completely by aerated lung and is not associated with atelectasis, parenchymal infiltrates, hilar or mediastinal lymphadenopathy, or pleural effusion.[7-9] Focal pulmonary lesions that are greater than 3 cm in diameter are called "lung masses" and are commonly the manifestations of bronchogenic carcinoma. The lung nodules that measure less than 8 to 10 mm in diameter are called "subcentimeter" nodules, and are much less likely to be malignant. They are difficult to accurately characterize by imaging modalities, and are often difficult to approach by needle biopsy.[7-9] Thus, for practical purposes, the term SPN is used in the context of lung nodules that are at least 8 to 10 mm, but less than or equal to 3 cm in diameter.

The SPN has to be distinguished from multiple pulmonary nodules because the diagnostic significance and the algorithm for work-up of such lesions are different. Furthermore, up to 20% of SPNs observed on chest radiographs may in fact be nonpulmonary in origin when investigated by other methods and may represent nipple shadow, skin lesions (Figs 120A.1A to C), rib fracture, end-on-view of blood vessels, composite shadows or monitor leads.[10]



Figs 120A.1A to C: Chest radiograph (posteroanterior view) of a patient referred for further evaluation showing an SPN in the right mid-zone (arrow) (A); close-up view (open circle) of the SPN (B); Clinical examination revealed that the lesion was a cutaneous papilloma mimicking an SPN (C)

EPIDEMIOLOGY

World Scenario

In an early study[11] SPN was found in 1 of 500 (0.2%) chest radiographs that were obtained in community settings. More recently, about 7% of healthy volunteers (n=1000) in New York who participated in the Early Lung Cancer Action Project (ELCAP)[12] were found to have between one and three nodules on baseline screening chest radiograph; in a majority of them (76%), the largest nodule measured less than 1 cm. Overall, the estimated prevalence of SPN in published literature ranges from 8 to 51%.[13-15]

India

Though there have been occasional case reports on this topic, reliable epidemiological data on the true incidence of SPN are lacking from India. Pulmonary tuberculosis has occasionally been documented to present as an SPN in some studies from India.[16,17] At the Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, during the period 1996 to 2000, 23 patients with SPN underwent thoracotomy for the confirmation of diagnosis. On histopathological examination, etiological diagnosis in a majority of them was tuberculosis (n=15; 65%) and bronchogenic carcinoma (n=5; 22%).[18]

ETIOLOGY

Various etiological causes that manifest as an SPN are listed in Table 120A.1. The etiological spectrum varies depending on the age group, geographical location of the patient, prevalence of risk factors for lung cancer, among others. Common benign causes of SPN include active granulomatous infection (e.g. tuberculosis), hamartoma, lung abscess, round pneumonia, round atelectasis, bronchogenic cyst, hydatid cyst, healed pulmonary infarcts, focal hemorrhage, hemangiomas, and arteriovenous malformations, among others. Most common causes of malignant SPN are adenocarcinoma (47%), squamous cell carcinoma (22%), solitary metastasis (8%), undifferentiated Non-Small Cell Lung Carcinoma (NSCLC) (7%), Small Cell Lung Cancer (SCLC) and bronchioloalveolar cell carcinoma (4% each).[7]

CLINICAL EVALUATION

Majority of the patients presenting with an SPN are asymptomatic with the lesion being picked up incidentally in a chest radiograph or CT carried out for some other purpose. Clinical evaluation of a patient with SPN begins with obtaining a detailed history, and conducting a thorough physical examination (Table 120A.2). This is followed by appropriate imaging investigations and interventions for procuring tissue for cytopathological or histopathological diagnosis.

Age of the patient is an important clue and one of the independent factors predictive of malignancy in an SPN.[1,7,19] Malignancy is rarely a cause of SPN in patients under 30 years of age; older the patient, higher is the likelihood that the SPN is caused by a malignancy. A history of current or remote malignancy (especially lung cancer or head and neck cancer), significantly increases

TABLE 120A.1: Etiological causes of a solitary pulmonary nodule

Developmental
- Bronchogenic cyst
- Bronchial atresia with mucoid impaction
- Sequestration

Infections
- Tuberculosis
- Fungal infections (e.g. coccidioidomycosis, histoplasmosis, cryptococcosis and aspergillosis)
- Organizing pneumonia
- Lung abscess
- Septic embolus
- Round pneumonia
- Fungal infection (*Aspergillus*)

Neoplastic
- ***Benign***
  - Hamartoma
  - Chondroma
  - Teratoma
  - Leiomyoma
  - Endometriosis
- ***Malignant***
  - Carcinoma
  - Metastasis
  - Carcinoid tumor

Vascular
- Arteriovenous malformation
- Pulmonary infarction
- Hematoma
- Pulmonary artery aneurysm

Lymphatic
- Intrapulmonary lymph node
- Lymphoma

Inflammatory
- Rheumatoid nodule
- Wegener's granulomatosis
- Sarcoidosis

Airway
- Mucus impaction (e.g. bronchiectasis)

Others
- Rounded atelectasis
- Amyloidosis

TABLE 120A.2: Parameters to be considered in the evaluation of a patient presenting with an incidentally detected solitary pulmonary nodule

Clinical
- Age
- Smoking history
- Presence of other risk factors for lung cancer
- Current or remote history of malignancy

Radiological
- Size of the lesion
- Site where it is located in the lung
- Presence of calcification
- Growth rate
- Edge characteristics (smooth, spiculated, lobulated)
- Internal characteristics*
- Contrast enhancement

* include the attenuation, satellite nodules, presence of air bronchogram, halo sign, reverse halo sign, growth rate, wall thickness in cavitary nodules

Based on references 1,7,8

the probability of a malignant SPN.[19-21] However, the probability of the SPN being a metastatic lesion in the absence of a known prior malignancy is low.

History of tobacco smoking and other established exposures associated with an increased risk of lung cancer, such as, silica, air pollution, arsenic, cadmium, chromium and radiation (e.g. radon, X-rays and gamma rays) should be obtained. Other important clinical factors in the evaluation of the etiology of SPN include a history of hemoptysis, fever, constitutional symptoms (tuberculosis), and travel history (fungal, parasitic diseases); Human Immunodeficiency Virus (HIV) infection, among others. Meticulous physical examination is helpful in identifying mimics of an SPN, such as nipple shadow, skin lesions or monitor leads.

Some workers have developed models for predicting a malignant etiology in a patient with SPN. Herder and associates[22] using multiple logistic regression analysis described older age, current or past tobacco smoking history, and history of extrathoracic cancer more than 5 years before nodule detection as the independent predictors of malignancy. Gould and colleagues,[23] using multivariate analysis found current or former smoking status, increasing age, increasing nodule diameter, and decreasing interval since smoking cessation to be the predictors of a malignant SPN. There have also been other attempts at predicting malignancy using the likelihood ratio form of Bayes' theorem[24] and neural networks.[25,26]

IMAGING STUDIES

Chest Radiograph

The evaluation of an SPN usually begins with a review of the chest radiograph. Use of nipple markers or apical lordotic projections may help to distinguish normal anatomic structures from lesions causing an SPN. However, SPNs are often missed on the chest radiograph even by experienced chest radiologists, especially if they are located below the diaphragm or behind the clavicle, rib or heart. Availability of dual-energy subtraction digital chest radiograph systems is expected to improve the pick-up rate of SPNs in chest radiographs. Sometimes, characteristic radiological patterns of calcification, are suggestive of a presumptive diagnosis. Presence of diffuse, central, laminated and popcorn patterns of calcification are considered to be of benign etiology. But, stippled and eccentric patterns of calcification should prompt further work-up to rule out malignant etiology.[3,5]

When available, the current chest radiograph should be compared with a previous chest film. This will also facilitate the estimation of the growth rate (doubling time) of the SPN.

Computed Tomography

The CT is the primary imaging modality in the evaluation of a patient with an SPN. The CT by identifying whether the lesion is single or multiple (Fig. 120A.2) and by detecting other lesions, such as atelectasis, other parenchymal infiltrates, hilar or mediastinal lymphadenopathy or pleural effusion, helps in characterizing the lesion as a true SPN. The current multidetector-row CT scanners that use 16 to 128 detector channels facilitate thin-section (0.6–2.0 mm) analysis of an SPN.[3,5]

Location of the nodule: Some studies have suggested that the location of the lesion in the lung is an independent predictor of the lesion being a malignant SPN. While malignant lesions are more likely to be located in the right lung and in the upper lobes, benign lesions are equally distributed throughout the lung fields.[1,3,5,7] This predilection for the upper lobes, is probably related to the higher concentration of inhaled carcinogens that result from tobacco smoking in the upper lobes.

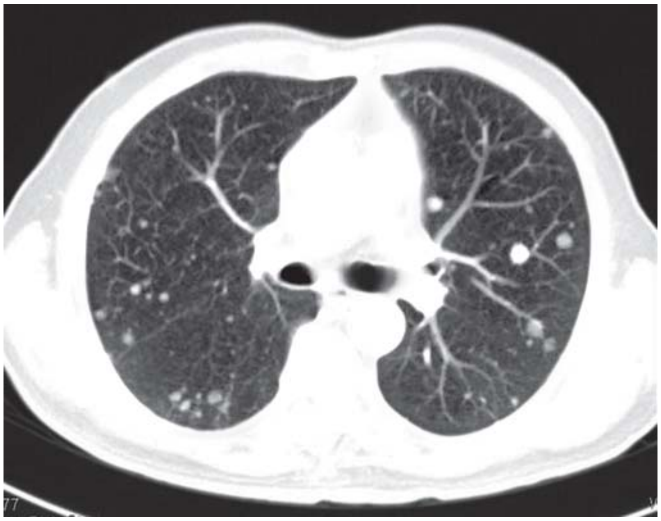


Fig. 120A.2: CT of the chest (lung window) showing bilateral multiple nodules. Further work-up confirmed metastatic malignancy

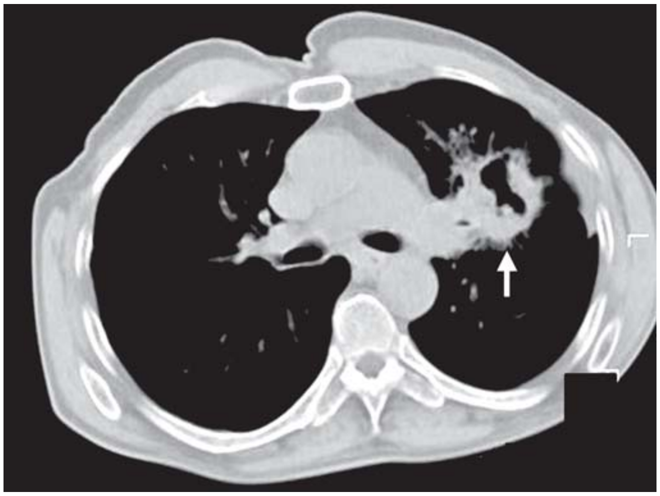


Fig. 120A.3: Non-contrast enhanced CT of the chest (mediastinal window) showing a nodule measuring 41 mm suggestive of a mass lesion. Image-guided biopsy confirmed squamous cell carcinoma of the lung

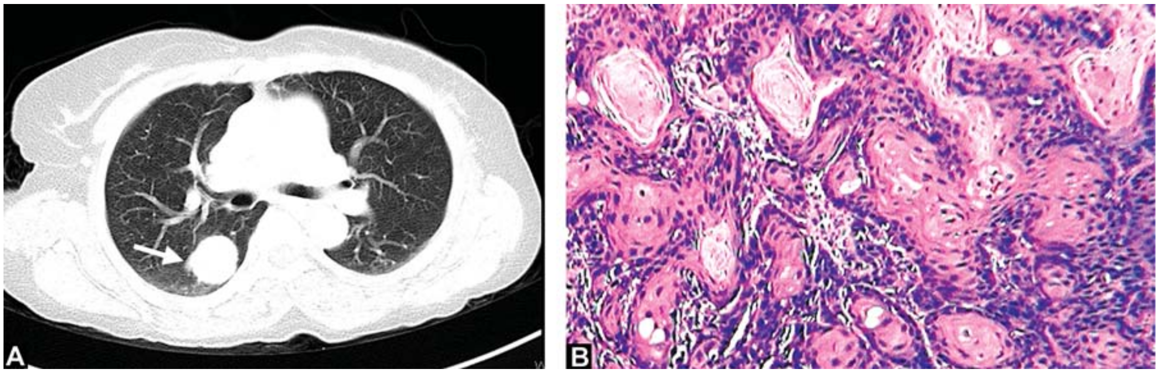
Size: Larger the SPN, higher is the likelihood of malignancy; lesions greater than 3 cm in diameter should be considered malignant until proven otherwise (Fig. 120A.3). The likelihood ratio of malignancy in relation to the size of the SPN as described by Gurney[20] is shown in Table 120A.3.

Shape and margins: Assessment of the shape and margins of the SPN, even though not specific, provides useful clues for categorizing the lesion as benign or malignant.[1,3,5,7] In general, benign SPNs are round in shape and have smooth margins. However, malignant SPNs may rarely present with smooth margins, as in the case of lung cancer (Figs 120A.4A and B), solitary hematogenous metastases

TABLE 120A.3: The likelihood ratio of malignancy in lesions

Size (cm)	*Likelihood ratio*
<1.0	0.52
1.1–2.0	0.74
2.1–3.0	3.7
>3.0	5.2

Data from reference 20



Figs 120A.4A and B: CT of the chest (lung window) showing an SPN with smooth rounded margins (arrow) (A); Photomicrograph of the image guided FNAC was suggestive of squamous cell carcinoma (Papanicolou stain; X 400) (B). (*Courtesy:* Dr KV Sreedhar Babu, Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati)
SPN = solitary pulmonary nodule; FNAC = fine needle aspiration cytology

from colorectal, renal cell or breast cancer, and peripheral carcinoid tumors. Presence of irregular spiculated margins (corona radiata) is highly suggestive of malignancy. Rarely, irregular margins can be observed even in benign lesions, as in the case of the focal areas of organizing or resolving pneumonia. A lobulated margin is most often seen in hamartomas, but can be observed in malignant conditions, like peripheral carcinoid tumors and adenocarcinomas. Presence of satellite lesions surrounding a larger central nodule is suggestive of a granulomatous disease (e.g. tuberculosis). In pulmonary arteriovenous malformations presenting as an SPN, a feeding and draining pulmonary vessel extending from the hilum of the lung can be evident.

The *comet tail sign* is typically seen in rounded atelactasis and indicates a bundle of curvilinear bronchi and vessels extending into the hilar aspect of a peripherally located SPN that lies adjacent to pleural thickening.[3,5]

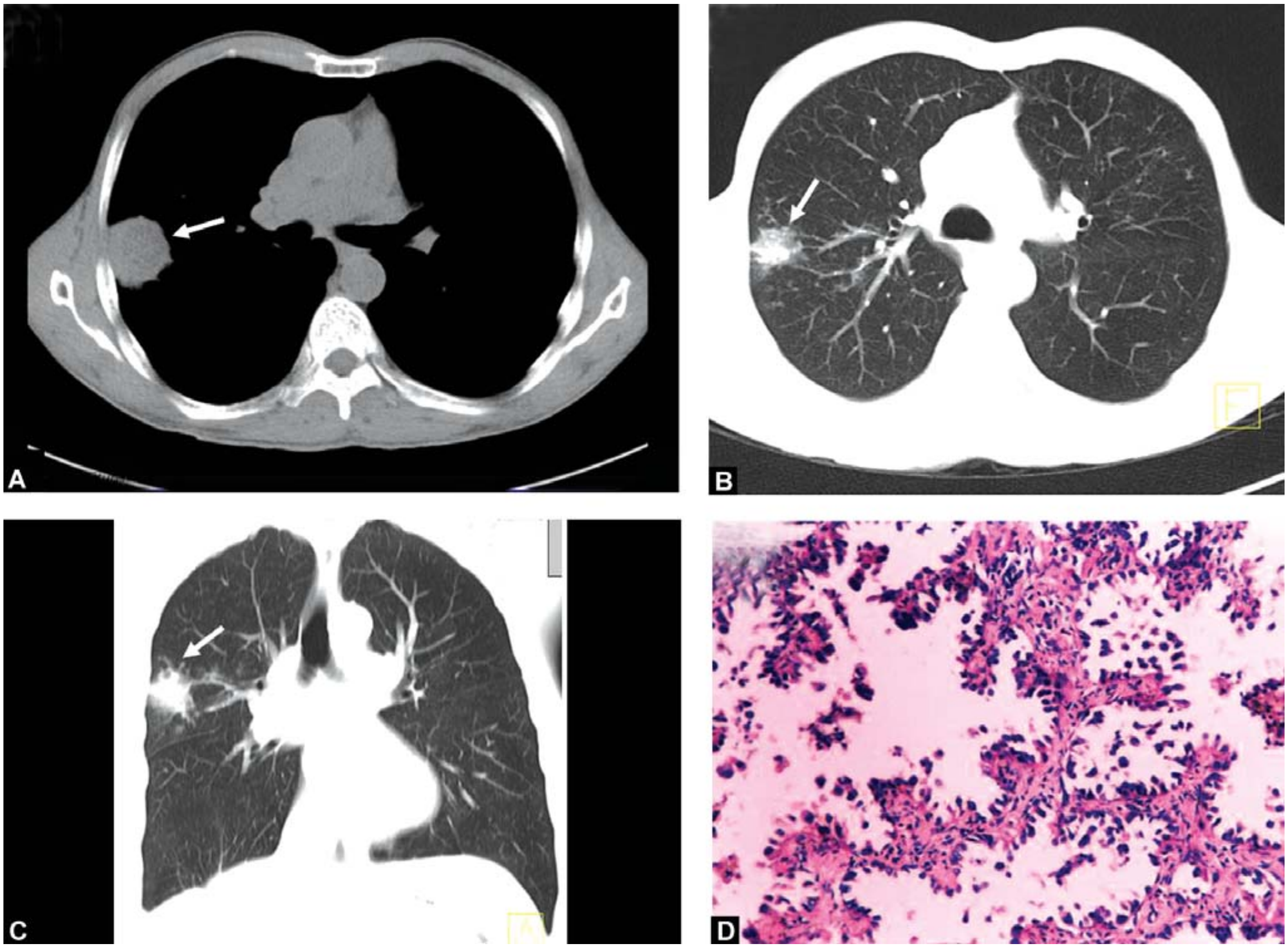
Fat: For practical purposes, presence of fat within an SPN with smooth or rounded margins is suggestive of a pulmonary hamartoma; nearly 60% of hamartomas contain fat. Exceptionally rarely, metastases from renal cell carcinoma or liposarcoma presenting as an SPN may show fat.[1,3,5,7]

Ground-glass attenuation: The use of MDCT has facilitated the detection of ''subsolid'' nodules that contain a component of ground-glass attenuation. These may be pure ground-glass SPNs, as well as partly solid lesions consisting of mixed solid and ground-glass lesions, which have been found to have a higher potential for being malignant. Atypical adenomatous hyperplasia, bronchioloalveolar carcinoma and invasive adenocarcinoma can present as subsolid nodules.[1,3,5,7]

The *halo sign* (Figs 120A.5A to D) has been described in invasive *Aspergillus* infection and bronchioloalveolar carcinoma and refers to a poorly defined rim of ground-glass attenuation around the SPN and the halo may represent hemorrhage, tumor infiltration or perinodular inflammation. The *reverse halo sign* (a focal round area of ground-glass attenuation surrounded by a ring of consolidation) has been described in cryptogenic organizing pneumonia and paracoccidioidomycosis.[5]

Calcification: The presence and pattern of calcification within the lesion offers important clues to the etiology of the SPN. Though the chest radiograph is useful in identifying calcification within the SPN, the diagnostic yield is low (sensitivity 50%; specificity 87%).[1,3,5,7] Nearly one-third of the SPNs that do not manifest calcification within the lesion on the chest radiograph, may show calcification on the chest CT.[3] Therefore, non-contrast chest CT (1–3 mm collimation) is considered to be the best technique to identify calcification within an SPN.[3,5] Certain patterns of calcification within the SPN, such as central, laminated, diffuse (Fig. 120A.6), and calcification within a smooth or lobulated nodule are suggestive of a benign lesion, such as a granuloma; popcorn calcification is suggestive of a hamartoma. Rarely, presence of eccentric calcification may be indicative of a calcified granuloma engulfed by a malignancy and amorphous calcification can be present due to dystrophic malignant calcification.

When calcification is not evident in the lesion, CT densitometry can be helpful. With the advent of the modern MDCT, a reference CT phantom is no longer being used and the average attenuation of an SPN can be measured directly. Attenuation values of 200 Hounsfield Units (HU) or greater within a smoothly



Figs 120A.5A to D: Non-contrast enhanced CT of the chest (mediastinal window) showing a peripherally located solitary pulmonary nodule (A). CT of the chest (lung window) (B) and coronal reconstruction (C) of the same patient showing ground-glass attenuation surrounding the nodule suggestive of *halo sign.* Photomicrograph of the excised lesion (D) suggestive of bronchioloalveolar cell carcinoma (Hematoxylin and eosin; X 200). (*Courtesy:* Dr KV Sreedhar Babu, Department of Pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati)

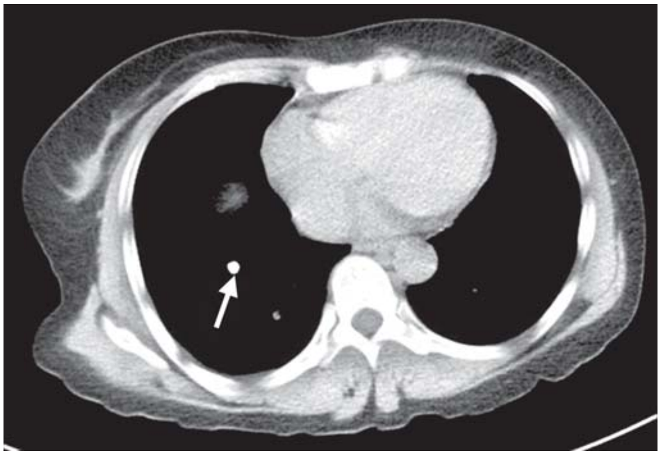


Fig. 120A.6: Non-contrast enhanced CT of the chest (mediastinal window) showing a calcified nodule (arrow)

marginated nodule is considered to be the evidence of microscopic calcification and suggests a benign etiology.[3]

Cavitation: Cavitation can be observed in benign (e.g. abscess, tuberculosis) or malignant (e.g. squamous cell carcinoma) SPNs.[1,3,5,7] However, estimating the cavity wall thickness can be helpful; wall thickness of 5 mm or less suggests a benign lesion, whereas, wall thickness of 15 mm or more is suggestive of a malignant lesion.[1,27]

Other internal characteristics: Detection of cystic or ''bubbly'' lucencies within an SPN (Fig. 120A.7) is highly suggestive of a malignant etiology (e.g. lung cancer, especially adenocarcinomas with bronchioloalveolar cell features). Evidence of air bronchogram within an SPN is suggestive of a malignant etiology (especially bronchioloalveolar carcinoma, rarely pulmonary lymphoma);

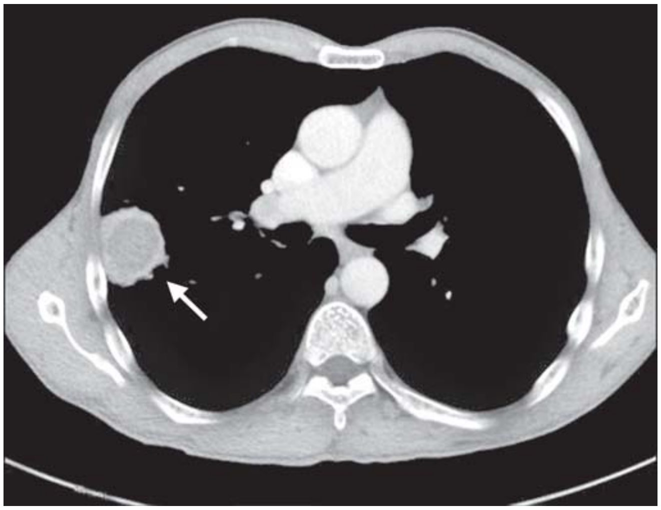


Fig. 120A.7: Contrast enhanced CT of the chest (mediastinal window) showing cystic lucency within the SPN (arrow)

sometimes, benign lesions, such as sarcoidosis and round pneumonia[28,29] may manifest air bronchogram. Presence of subsolid SPNs, in which the nodule has a component of ground-glass attenuation is suggestive of malignancy, especially bronchioloalveolar carcinoma.[1,30]

Contrast enhancement: Contrast enhancement, also called "wash-in" (an increase in the attenuation of a lesion greater than 15 HU after intravenous contrast), of an SPN can help in providing a clue to its etiological origins. The SPNs that enhance less than 15 HU are almost certainly benign (sensitivity 98%, specificity 58%, accuracy 77%).[31] Malignant lesions, by virtue of increased vascularity tend to enhance avidly with the administration of intravenous contrast; typically, malignant SPNs enhance more than 20 (HU).[1,3,31,32] However, benign lesions like active granuloma, hamartoma, arteriovenous malformation, and organizing pneumonia can also manifest in the form of contrast enhancement.[33] Recently "wash-out" or decrease in attenuation over the 15 minutes following contrast injection has also been found to be useful.[5]

Growth: Since, an SPN is assumed to be a sphere and the volume of a sphere is given by the mathematical expression $4\pi r^3/3$ (where r = radius of the sphere) or $\pi d r^3/6$ (where d = diameter), an increase in nodule diameter by 26% corresponds approximately to one doubling in tumor volume. The doubling time can be calculated by using the below mentioned formula:

$dt = (t \times \log 2) / \{3 \times [\log (d2/d1)]\}$,

where

dt = doubling time (days)

t = time in days between the chest radiographs

d2 = diameter of the nodule at the time of the current CT/chest radiograph

d1 = diameter of the nodule at the time of the previous CT/chest radiograph

It has been estimated that the doubling time for majority of malignant nodules is between 20 and 300 days.[34-36] If the SPN has been stable for at least 2 years, it is likely to be benign and usually does not require further evaluation.[1,3,5,7,8, 34-36]

Magnetic Resonance Imaging

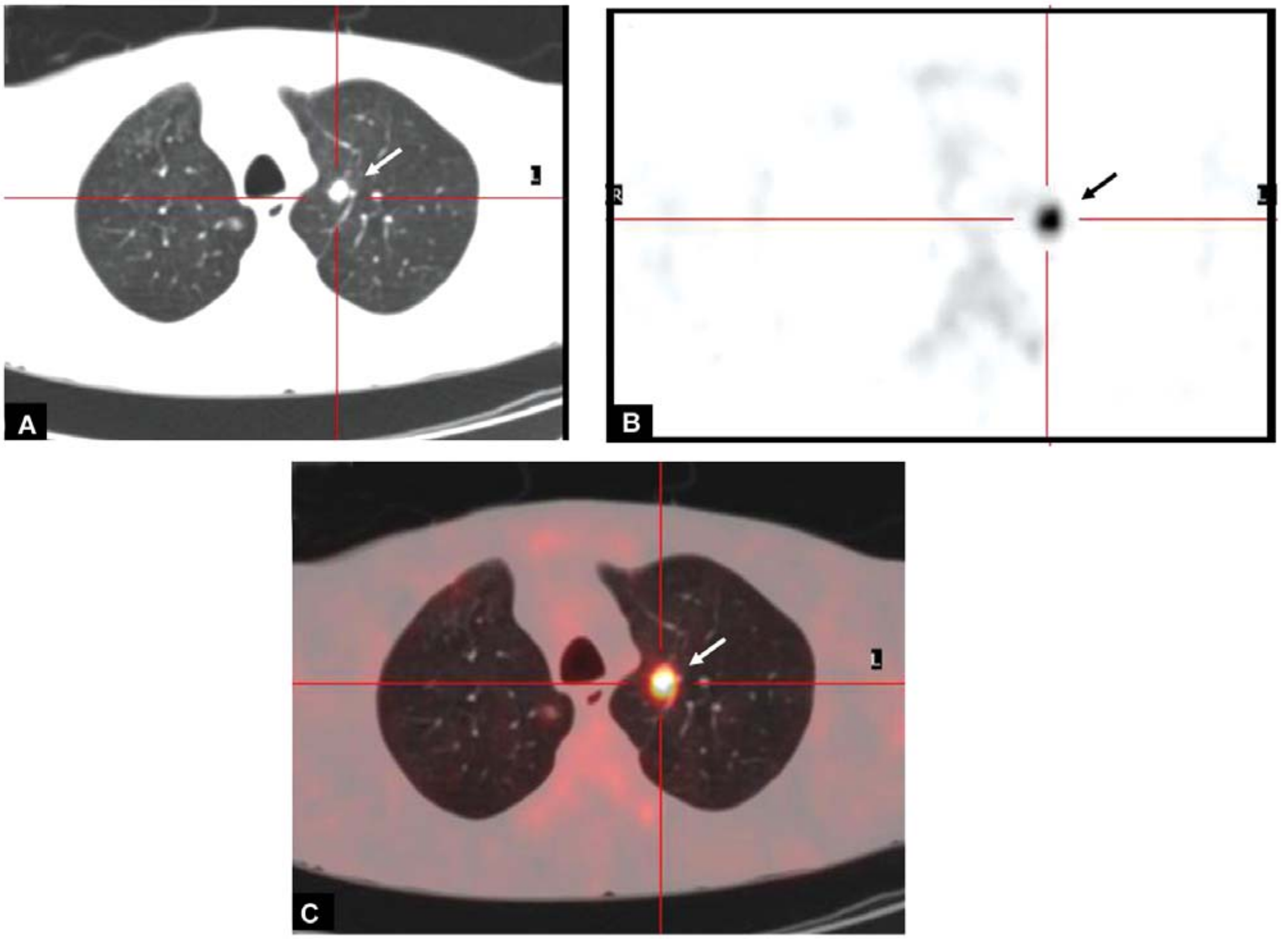
Magnetic Resonance Imaging (MRI), in spite of having the advantage of avoiding ionizing radiation, has been less frequently utilized than MDCT in the evaluation of lung nodules because of its limited spatial resolution, effect of respiratory and cardiac motion on sequences with low temporal resolution. However, Half-Fourier Acquisition Single-Shot Turbo Spin-Echo (HASTE) imaging has emerged as the sequence of choice for MRI of the lungs. This technique facilitates identification of malignant tissues that manifest high signal intensity (due to high T2 relaxivity) against a back-drop of surrounding air-filled, low-signal, lung parenchyma; vessels are identified as flow voids without any apparent signal. For SPNs 5–10 mm in size, HASTE sequence has been found to have a sensitivity of close to 95%.[37, 38]

The different Turbo Spin-Echo (TSE) and 3D gradient-echo [volume interpolated breath-hold (VIBE)] MRI sequences of the lung for detecting pulmonary metastases,[39] the enhancement characteristics of nodules on MRI, such as maximal enhancement ratio and slope of contrast uptake are also being explored as potential imaging modalities for SPNs. These issues merit further study.

Nuclear Medicine Imaging

Positron Emission Tomography CT (PET-CT) (Figs 120A.8A to C) using the radiopharmaceutical 18F labeled 2-deoxy-D-glucose (FDG) has been used to characterize an SPN as malignant or benign.[1,3,5] The FDG standardized uptake value (SUVmax) estimation is used as a semiquantitative method of evaluation of SPNs. In malignant SPNs, metabolism of glucose is typically increased and an SUVmax cut-off of 2.5 has been used to differentiate benign from malignant SPNs.[40]

For SPNs greater than 10 mm in size, FDG-PET has a sensitivity and specificity of 97% and 78% respectively for characterizing it as malignant.[41] However, malignant causes of an SPN, such as a well-differentiated adenocarcinoma of the lung (especially with a bronchiolo-



Figs 120A.8A to C: CT of the chest (lung window) (A), F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) (B) showing an SPN (arrow). PET-CT image of the same patient showing increased uptake in the nodule (arrow)
[*Courtesy:* Dr TC Kalawat, Department of Nuclear Medicine, Sri Venkateswara Institute of Medical Sciences, Tirupati]

alveolar cell carcinoma) and a peripheral carcinoid tumor can produce a false-negative PET-CT result. The PET-CT has a low sensitivity for lesions less than 1 cm in diameter and the use of this technique in this setting is limited; however, if PET-CT results are positive, it would almost certainly prompt biopsy or resection. Common causes resulting in a false-positive PET result include active granulomatous inflammation, focal areas of organizing or resolving pneumonia, and rarely hamartomas.

Computer-aided Diagnosis (CAD)

The CAD techniques have been developed as a method of assisting interpretation by the means of computerized image analysis. The CAD, acting as a second interpreter, facilitates the assessment of nodule size, volume, attenuation, and enhancement characteristics by performing the global analysis of high-resolution MDCT data of the entire nodule. Some reports suggest that CAD may be useful in identifying clinically significant nodules that have been missed by the radiologists.[42-44] Further refinements in CAD, such as the integration of multifunctional CAD platforms into Picture Archiving and Communication Systems (PACS) that provide easy accessibility during reader interpretation may facilitate more widespread use of these techniques.[2] The salient imaging features that facilitate categorization of an SPN as benign is shown in Table 120A.4.

Tissue Sampling Techniques

In spite of the widespread use of various imaging techniques, characterization of some SPNs as benign or

TABLE 120A.4: Radiologic features suggestive of benign and malignant solitary pulmonary nodules

Radiologic feature	*Benign*	*Malignant*
Size of the lesion	Smaller the size of lesion, lesser is the risk of malignancy	Larger the size of lesion, greater is the risk of malignancy
Border	Smooth	Irregular or spiculated (*corona radiata*)
Density	Dense, solid	Nonsolid, ground-glass
Calcification	Concentric, central, popcorn-like, or homogeneous patterns common	Usually noncalcified or eccentric calcification
Satellite lesions	Common in granulomatous lesions	Rare
Wall thickness in a cavity	<5 mm	>15 mm
Doubling time	<1 month; >1 year	1 month to 1 year

malignant is not possible and will warrant tissue sampling and histopathological or cytopathological diagnosis. Various methods, such as image-guided transthoracic Fine Needle Aspiration Cytology (FNAC), needle biopsy, bronchoscopic biopsy with or without electromagnetic navigation systems, Video-Assisted Thoracoscopic Surgery (VATS), or open thoracotomy have been employed for procuring the tissue.[1,3,5,7-9]

Image-guided procedures: Image-guided transthoracic needle FNAC biopsy is frequently used for confirming the etiological diagnosis in patients with SPN in whom the pretest probability of a malignant lesion is high. The test is performed under CT-guidance or ultrasonography guidance (peripherally located or pleural-based lesions). This technique is highly accurate in ascertaining the etiological diagnosis in malignant SPNs (sensitivity >90% for lesions >5 mm in size). Contraindications for transthoracic FNAC and biopsy are an uncooperative patient, presence of a bleeding diathesis, severe bullous emphysema and prior pneumonectomy. Important complications of transthoracic needle biopsy include pneumothorax (seen in 20% of patients) and bleeding, which is usually minor and self-limiting.[1,3,5,7-9]

Video-assisted thoracoscopic surgery: The VATS technique facilitates the procurement of tissue frozen section examination to assist in the decision about whether to proceed with a full lobectomy, especially from peripherally located SPNs and some centrally located SPNs in the lower lobe. Presently VATS offers a lower morbidity and a shorter hospital stay compared with conventional thoracotomy.[1,9,45]

Fiberoptic bronchoscopy: The sensitivity of fiberoptic bronchoscopy (FOB) for detecting a malignant SPN ranges from 10% for SPNs that are less than 1.5 cm diameter) to 40 to 60% for SPNs that are 2–3 cm in diameter. Other factors that influence diagnostic yield of FOB include, its proximity to the bronchial tree and the prevalence of cancer in the given area.[9,46,47]

MANAGEMENT

The management depends on several factors, including the degree of surgical risk, the presence or absence of comorbid conditions, the patient's preferences, and the radiological and surgical capability and expertise available at the center where the patient is being evaluated. The eventual goal is to ascertain the etiological diagnosis so that appropriate therapy can be instituted.

There are no consensus guidelines for the evaluation and management of an incidentally detected SPN. Evidence-based recommendations for the follow-up and management of SPNs incidentally detected based on the American College of Chest Physicians guidelines[7] and the Fleischner Society Guidelines[8] are shown in Figures 120A.9 and 120A.10. A separate algorithm is provided for the evaluation and management of SPNs smaller than 8 mm (Fig. 120A.10) because of the less likelihood of malignancy in lesions that are smaller than 8 mm. These algorithms reflect the current evidence-based guidelines that are available and are likely to evolve as more information becomes available.

Initially, SPNs greater than 8 mm in size should be evaluated on past chest radiographs or CT (if available) to assess the stability of size. If the SPN has been stable for more than two years, such a patient may be may be followed-up without intervention unless morphological features are suggestive of malignancy. For SPNs 8 mm or larger (Fig. 120A.9), patients are categorized based on of low, intermediate and high pretest probability of

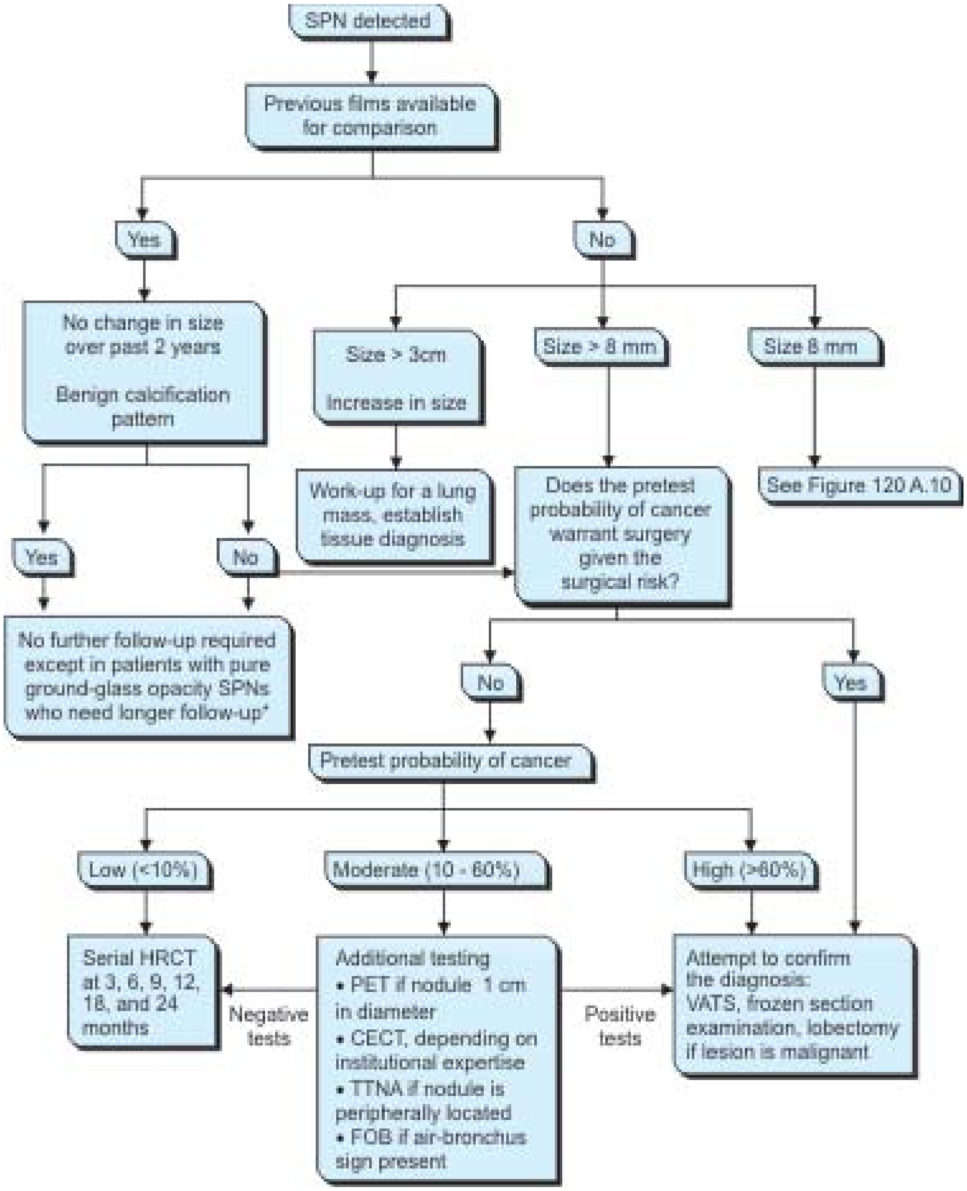

SPN detected
Previous films available for comparison
Yes
No
No change in size over past 2 years
Benign calcification pattern
Size > 3cm
Increase in size
Size > 8 mm
Size 8 mm
Work-up for a lung mass, establish tissue diagnosis
Does the pretest probability of cancer warrant surgery given the surgical risk?
See Figure 120 A.10
Yes
No
No further follow-up required except in patients with pure ground-glass opacity SPNs who need longer follow-up*
No
Yes
Pretest probability of cancer
Low (<10%)
Moderate (10 - 60%)
High (>60%)
Serial HRCT at 3, 6, 9, 12, 18, and 24 months
Negative tests
Additional testing
• PET if nodule 1 cm in diameter
• CECT, depending on institutional expertise
• TTNA if nodule is peripherally located
• FOB if air-bronchus sign present
Positive tests
Attempt to confirm the diagnosis: VATS, frozen section examination, lobectomy if lesion is malignant

Fig. 120A.9: Diagnostic work-up of a patient presenting with an SPN ≥ 8 mm

* see text for details

SPN: solitary pulmonary nodule; PET: positron-emission tomography; TTNA: transthoracic needle aspiration; CECT: contrast-enhanced computed tomography; FOB: fiberoptic bronchoscopy; VATS: video-assisted thoracoscopic surgery.

Based on references 7-9

cancer. As surgical excision is the definitive treatment for lung cancer, the guidelines,[7,8] recommend a more limited evaluation of patients who are not fit to undergo surgical excision. However, biopsy may still be considered to ascertain the etiological diagnosis in these patients so as to provide appropriate therapy. The evaluation of patients who are fit to undergo lung resection is guided by their pretest probability of a malignant SPN (Fig. 120A.9). The algorithm for lesions smaller than 8 mm (Fig. 120A.10) categorizes the patients into separate treatment groups based on the presence or absence of risk factors for lung cancer. Patients with a low risk for malignancy require less frequent CT follow-up.

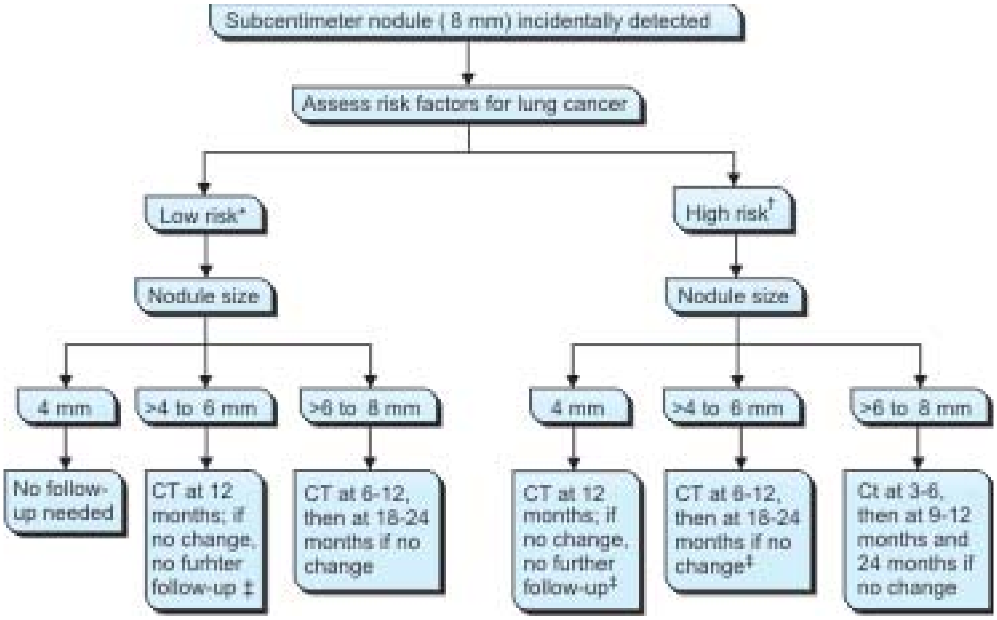

Subcentimeter nodule (8 mm) incidentally detected
Assess risk factors for lung cancer
Low risk*
High risk†
Nodule size
Nodule size
4 mm
>4 to 6 mm
>6 to 8 mm
4 mm
>4 to 6 mm
>6 to 8 mm
No follow-up needed
CT at 12 months; if no change, no furhter follow-up ‡
CT at 6-12, then at 18-24 months if no change
CT at 12 months; if no change, no further follow-up‡
CT at 6-12, then at 18-24 months if no change‡
Ct at 3-6, then at 9-12 months and 24 months if no change

Fig. 120A.10: Diagnostic work-up of a patient presenting with an incidentally detected SPN <8 mm
* low risk= minimal or absent history of smoking and of other known risk factors
† high risk= history of smoking or of other known risk factors
‡ non-solid (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma
SPN = solitary pulmonary nodule
Based on references 7-9

CONCLUSION

The goal of evaluating a patient presenting with an SPN is to correctly differentiate malignant SPNs from benign lesions so that appropriate therapy is instituted. The approach to a patient with an SPN is based on the pretest probability of cancer, determined according to the size of the nodule, the presence or absence of risk factors for lung cancer, such as history of tobacco smoking, the patient's age and imaging features of the SPN. When the pretest probability of cancer is low, the nodule should be monitored with serial high-resolution CT. When the probability of cancer is high, diagnostic work-up should be directed to establish the histopathological or cytopathological tissue diagnosis.

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120B

Hematopoietic and Lymphoid Neoplasm of Lungs

Pankaj Malhotra

INTRODUCTION

Lungs can be involved in several lymphohematopoietic neoplasms, either primarily or secondarily.[1-4] In primary lung involvement, the diagnosis is usually not suspected and it is the cytology or biopsy of the resected tissue that gives first clue to the diagnosis. Lung involvement in secondary neoplasms is not uncommon; however, again the proof comes by Broncheoalveolar Lavage (BAL) fluid analysis/histopathology of the mass because the differential diagnosis includes infections that are far more common than the lung involvement by neoplasms. After the diagnosis, the work-up of these patients is fairly standardized. The prognosis depends upon several factors such as the age of the patient, duration of symptoms, performance status of patient, comorbidities and staging of the disease.

The lungs can suffer not because of lymphoma per se but also due to side effects of the systemic chemotherapy or radiotherapy to treat lymphomas.[5-7] Lastly, it is important to know about the lung functions at baseline before instituting chemotherapy or radiotherapy because some anti-neoplastic drugs require modification in presence of lung dysfunction.

LYMPHOMAS

Lymphomas are diverse groups of neoplastic disorders primarily known to have their origin from the lymphnodes.[8] They are generally classified as Hodgkin's Lymphoma (HL) and non-Hodgkin's Lymphoma (NHL) based on the histopathology and immunohistochemistry of the involved tissue or mass. NHL constitutes approximately 80 to 85% of all lymphomas. The treatment and prognosis is different in both lymphomas and hence it is important to differentiate the two entities. Most lymphomas origin from the lymph nodes (nodal lymphomas), but they can arise from lymphatic tissue present in organs other than lymph nodes, labeled as extranodal. Primary involvement of the lungs (trachea, bronchus, lung parenchyma) is rare accounting for less than 1% of all extranodal lymphomas.[2-3] However, involvement of the mediastinal group of lymph nodes is quiet common.

Lymphomas are usually systemic diseases and definition of primary and secondary involvement of body site is sometimes arbitrary in nature. When lymphomas present for the first time in the tracheobronchial tree or lung parenchyma and these sites have major disease load, they are called primary lymphomas of the lungs.[1-4] When the bulk of the disease lies in other organs along with lymphomatous involvement of the lungs, this is classified as secondary lung involvement.[9,10] The secondary involvement of the lungs can occur either through circulation or spread from neighboring sites (Fig. 120B.1). Even though the definition is somewhat arbitrary, it is important to classify the involvement because it has therapeutic and prognostic implications (vide infra).

For purpose of simplification both lymphomas are discussed separately, but for a few general considerations. The diagnostic work-up for both HL and NHL is similar as discussed below:

General Considerations

Lymphomas usually have their origin from the lymph nodes or lymphoid follicles present in the organ.[8] The

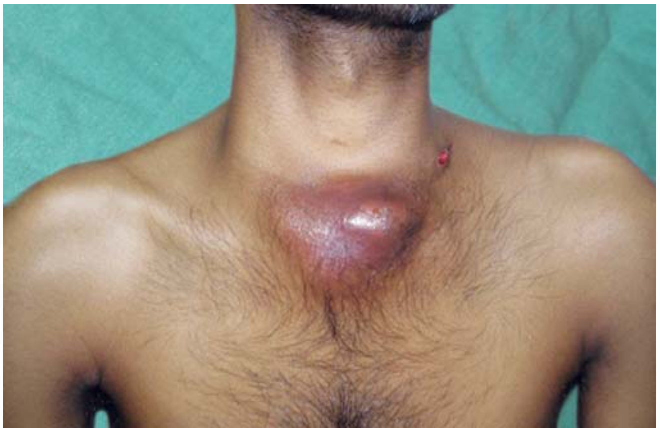

Fig. 120B.1: Hodgkin's lymphoma presenting as chest wall mass in a 22-year-old gentleman

duration of symptoms can vary from weeks, months and sometimes years depending upon the aggressiveness of the disease. Younger age is generally associated with more aggressive disease while both low-grade and high-grade presentations of lymphomas are common as age advances.[8] The systemic symptoms such as fever, weight loss and night sweats, if present classify the patient into category B while their absence is denoted as A. Similarly, the extranodal site involvement by lymphoma is categorized and written as E. Involvement of spleen is considered as nodal and depicted as S. Tumor mass of size more than 10 cm is labeled as X. Thus, a patient with primary NHL of the lung with size of 14 cm without systemic symptoms would be labeled as Primary NHL Lung, stage 1EX A.

Any mass of more than 10 cm generally requires local radiotherapy after the completion of chemotherapy. The diagnosis of lymphoma requires a proper categorization of lymphoma into the most recent WHO classification of hematopoietic and lymphoid neoplasms.[11] WHO classification of lymphomas is based on the morphology of lymphoma (B, T and NK cell lineage), immunophenotyping, chromosomal and molecular characteristics (Table 120B.1).

Once the diagnosis of lymphoma is made, proper staging is required. Staging of both HL and NHL is done by Ann Arbor (Table 120B.2). Detailed investigations are required for proper work-up of patient with lymphoma (Table 120B.3). The staging helps in prognostication as well as making therapeutic decisions whether only chemotherapy, only radiotherapy or both chemotherapy and radiotherapy, is required. Rarely, the surgery may be curative in localized lymphoma of the lung parenchyma when complete resection of the lesion is possible.

Prognosis of NHL is defined by International Prognostic Index (IPI).[12] This is based on age, stage of the disease, LDH, performance status of the patient and extranodal site involvement (Table 120B.4). The higher the stage, the bad is the prognosis. There is a similar prognostic score for HL also based on hemoglobin, WBC count, age, stage, serum albumin and lymphocytopenia. While on treatment, nonresponsiveness to 1–2 cycles of chemotherapy is probably the most important adverse feature. The response criteria to systemic chemotherapy are now fairly standardized (Table 120B.5).[13]

Overview of Primary Lung Involvement by Lymphomas

Introduction

Involvement of tracheobronchial tree and lung parenchyma by lymphomas without involvement of adjacent lymph nodes or other structures is quiet rare. The diagnosis requires demonstration of clonal lymphoid proliferation in the lung parenchyma, trachea or bronchi without detectable involvement of extrapulmonary sites at diagnosis and during the subsequent three months.[1-4]

Epidemiology

Due to rarity of these cases, epidemiology of primary NHL and HL is difficult to comment, however, they account for less than 1% of all extranodal lymphomas. From the isolated case report and series, it appears that most cases are reported in the middle age and older age group.[14-20] In some series, female population predominate. Systemic symptoms (B symptoms) are more common at presentation. There are no known risk factors for the development of these lymphomas except for the low-grade primary NHL of lung (MALT lymphomas, discussed below).

Presentation

Patients can usually present with persistent cough, hemoptysis, dyspnea, wheezing, chest pain, or discomfort or stridor. Patient may have fever, weight loss and night sweats (B symptoms). Chest skiagram is usually the first investigation that is required in these patients. This may show the presence of nodule, mass, atelectasis, cavitation or other shadow.[21-24] The differential diagnosis consists of infectious diseases (tuberculosis, histoplasmosis) or noninfectious diseases (Sarcoidosis, Wegener's granulomatosis).[25-27] Sometimes, both lymphoma and infectious process may coexist in the lung and hence a biopsy is a must in these cases.

TABLE 120B.1: WHO classification of lymphomas

Precursor B-cell neoplasm

Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)

Mature (peripheral) B-cell neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic lymphoma/leukemia, unclassifiable
- Lymphoplasmacytic lymphoma
- Heavy chain diseases
- Plasma cell neoplasms
- Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- Follicular lymphoma
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- T-cell/histiocytic-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV 8-assocaited multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin's lymphoma

T-cell and NK-cell neoplasms

Precursor T-cell neoplasm

Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)

Mature (peripheral) T/NK-cell neoplasms

- T-cell prolymphocytic leukemia
- T-cell granular lymphocytic leukemia
- Chronic lymphoproliferative disorders of NK cells
- Aggressive NK-cell leukemia
- EBV-positive T-cell lymphoproliferative disorders of childhood
- Adult T-cell lymphoma/leukemia
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis like T-cell lymphoma
- Mycosis fungoides
- Sèzary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Primary cutaneous gamma-delta T-cell lymphomas
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma (ALCL), ALK positive
- Anaplastic large cell lymphoma (ALCL), ALK negative

Immunodeficiency-associated lymphoproliferative disorders

- Lymphoproliferative diseases associated with primary immune disorders
- Lymphomas associated with HIV infection
- Post-transplant lymphoproliferative disorders
- Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

Histiocytic and dendritic cell neoplasms

- Histiocytic sarcoma
- Tumors derived from Langerhans cells
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Other rare dendritic cell tumors
- Disseminated juvenile xanthogranuloma

Hodgkin's lymphoma

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin Lymphoma
  Nodular sclerosis classical Hodgkin's lymphoma
  Mixed cellularity classical Hodgkin's lymphoma
  Lymphocyte-rich classical Hodgkin's lymphoma
  Lymphocyte-depleted classical Hodgkin's lymphoma

TABLE 120B.2: Ann Arbor staging of lymphomas

Stage I: Involvement of a single lymph node or of a single extranodal organ or site (IE)

Stage II: Involvement of two or more lymph node regions on the same side of the diaphragm, or localized involvement of an extranodal site or organ (II E) and one or more lymph node regions on the same side of the diaphragm

Stage III: Involvement of lymph node regions on both sides of the diaphragm, which may be accompanied by localized involvement of an extranodal organ or site (III E) or spleen (III S) or both (III SE)

Stage IV: Diffuse or disseminated involvement of one or more distant extranodal organs with or without associated lymph node involvement

1. Fever >38°C, night sweats and weight loss >10% of body weight in the last six months of diagnosis are defined as systemic symptoms (presence of any one systemic symptom is defined as B symptoms whereas absence of all three symptoms is defined as A in the staging system)
2. Spleen involvement is considered as nodal

TABLE 120B.3: Work-up of a lymphoma patient

1. Lymph node biopsy (excisional or core) with immunohistochemistry
2. CECT neck/chest/abdomen including pelvis
3. Complete blood counts, ESR and bone marrow examination (aspiration and trephine biopsy)
4. Biochemical (Urea, creatinine, uric acid, calcium, phosphorus, bilirubin, SGOT, SGPT, alkaline phosphatase, blood sugar)
5. EKG, echocardiography or MUGA scan
6. Urine examination
7. Serum LDH, Serum β2 microglobulin
8. HbsAg, Anti HCV, HIV
9. PET CT scan

Work-up in resource constraints settings
Chest X-ray and ultrasound abdomen instead of CT or PET CT scan

TABLE 120B.4: International prognostic Index for on-Hodgkin's lymphoma

One point is assigned for each of the following risk factors:

- Age greater than 60 years
- Ann Arbor Stage III or IV disease
- Serum lactate dehydrogenase more than normal
- ECOG performance status of 2 or more than 2
- Involvement of more than one extranodal site

Risk group	*Number of factors*
• Low	0, 1
• Low intermediate	2
• High intermediate	3
• High	4, 5

Adapted from NEJM 1993; 329:987-994.

TABLE 120B.5: Response definitions in NHL

Response	*Definition*	*Nodal masses*	*Spleen, liver*	*Bone marrow*
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology
PR	Regression of measurable disease and no new sites	>/= 50% decrease in SPD of up to six largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	>/= 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by >/= 50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, >/=50% increase in SPD of more than one node, or >/=50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement lesions

Abbreviations: CR, complete remission; FDG, [18F] fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.
Adapted from: Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25:579-86.

Diagnosis

Sputum examination for malignant cytology sometimes can give a clue to the diagnosis. The usual investigations that are carried out are bronchoscopy and transbronchial lung biopsy, or open lung biopsy. An adequate tissue specimen is the first and foremost requirement.[28-31] Morphology along with immunochemical stains and rarely molecular analysis from the tissue specimen will clinch the diagnosis. If adequate tissue specimen is not possible, sometimes cytology with immunocytochemistry can suggest and confirm the diagnosis.

Treatment and Outcome

Patients who present with obstructive endobronchial lesions require rigid bronchoscopy and stenting.[32,33] Sometimes laser therapy with Neodymium: Yttrium-Aluminum Garnet Laser (Nd:YAG) or Photodynamic Laser Therapy (PDT) has been used in these life-threatening obstructive lesions. In earlier case reports and case series, surgery alone or surgery followed by radiotherapy was used with good results.[34] Lately, chemotherapy is used more frequently in primary lymphomas of the lungs because of the adverse long-term side effects of radiotherapy given to lung parenchyma. The principle of treatment varies according to the histology as well as to the burden/staging of the lymphoma.[35]

Secondary Lung Involvement in Hodgkin's Lymphoma

The mediastinal lymph nodes are involved in almost two third patients with HL,[21] while the lung parenchymal involvement occurs in 10% of patients, which is usually the extension from the involved lymphnodes.[22] The most common histological type of HL is the nodular sclerosis variety. If the mediastinal lymphadenopathy is more than one-third the size of the internal thoracic diameter, it is defined as bulky disease and these patients are candidates for mediastinal radiation after the chemotherapy. In order of decreasing frequency, the nodes involved are in the anterior mediastinum, paratracheal, hilar, subcarinal, peridiaphragmatic, paraesophageal and internal mammary nodes.[22] The extension into the lung parenchyma occurs in the form of interstitial linear infiltrates or small nodules. If this extension is in direct continuity of the involved lymph nodes, a separate procedure to document lung involvement by HL may not be necessary.[24] In many cases, these lesions may occur because of an infectious process and hence if possible, fine needle aspiration, bronchial lavage or rarely an open biopsy may be required for documentation.

HL is considered as one of the curable malignancy depending upon the stage of the disease.[8] Hence, it is very important to know the stage of the disease before administration of chemotherapy. HL is also very sensitive to radiation therapy. The treatment of HL has evolved from only radiotherapy to chemotherapy alone or combination of both chemotherapy and radiotherapy. As a general rule, in the stage I and II disease, 2–4 cycles of chemotherapy (ABVD) followed by radiotherapy are generally used. Stage III and IV HL is usually treated by chemotherapy alone. However, at any stage if the bulky disease is present at baseline (defined as tumor size more than 10 cm), radiotherapy is always combined with chemotherapy.

HL with secondary lung involvement is treated initially with chemotherapy to reduce the size of tumor since radiation injures the lung parenchyma. Bleomycin included in the treatment protocol (ABVD) is also toxic to lung and thus these patients should be monitored closely with pulmonary function tests. In females, who receive mediastinal radiation to treat their HL, the future development of breast carcinoma is also high, thus these patients require monitoring by regular mammography, generally starting at least five years prior to the recommended age of screening in general patients.[8]

Primary Lung Involvement in Non-Hodgkin's Lymphoma

The involvement of lymph nodes in NHL is generally noncontiguous (as opposed to contiguous spread in HL).[8] The involvement of the lungs can occur in up to 40% patients of NHL. NHL's are usually graded into low-grade and high-grade types. The most common variety of low-grade lymphoma is mucosa associated lymphoid tissue (MALT) while diffuse large B-cell and lymphoblastic lymphoma are the common high-grade lymphomas involving the lungs. The treatment and prognosis is different for low-grade and high-grade NHL, hence they are separately discussed below.

MALT Lymphoma

The most common type of primary pulmonary lymphoma is related to bronchus-associated lymphoid tissue clonal proliferation and is grouped under the category of mucosa associated lymphoid tissue lymphoma.[36-38] These are low-grade B-lineage NHL with primary origin in the lymphoid tissue present in the bronchus or lung parenchyma and is due to the prolonged antigenic stimulation of any cause. This is akin to gastrointestinal MALT lymphomas which occur mostly due to persistent antigenic stimulation

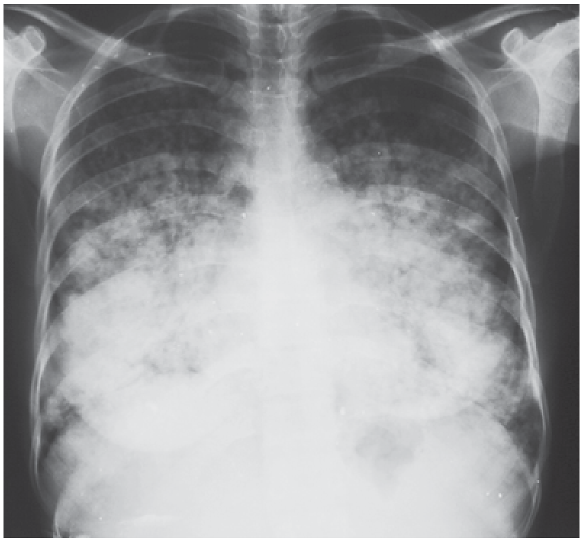

Fig. 120B.2: Mucosa associated lymphoid tissue lymphoma presentation in a 40-year old lady

caused by *Helicobacter pylori* infection. However, in the lung parenchyma, no single organism has been identified and at present cause of MALT lymphoma of the lung is attributed either due to the recurrent infections or due to autoimmune/rheumatological disorders of the body.[39-42] Patients may be asymptomatic and lesions are detected on routine chest skiagram or they may have nonspecific chest symptoms that may occur due to other causes (Fig. 120B.2).[42] Due to rarity of these lymphomas, it is mostly on histology and immunohistochemistry on resected tissue that the diagnosis is made. In approximately 25% of patients, MALT lymphoma can present simultaneously at other sites such as the orbit, the salivary glands and the bone marrow. The differential diagnosis consists of other lung conditions in which lymphocyte proliferation occurs such as follicular hyperplasia, lymphocytic interstitial pneumonia (usually bilateral) or hypersensitivity pneumonitis. Sometimes, the molecular techniques are required to accurately make the diagnosis of MALT lymphoma. These lymphomas when present for a very long period of time, can transform into a high-grade variety with systemic symptoms.

Low-grade lymphomas are considered incurable and hence treatment is instituted only when the disease is symptomatic or progressive. Mostly, these lymphomas get treated either with single agent chemotherapy like chlorambucil, cyclophosphamide, deaminase inhibitors, monoclonal CD20 positive antibody or combination of these.[8] The final treatment decision is taken based on the stage of the disease, age and performance status of the patient. Rarely, surgery alone or combined with radiotherapy is considered in these cases. The responses are excellent, but the disease tends to come back after some time.[41]

Secondary Involvement of Lungs by High-grade NHL

High-grade NHL generally presents with large mediastinal masses. The most common types are Precursor T-cell lymphoblastic lymphoma/leukemia and primary mediastinal large B-cell lymphoma.

Primary Mediastinal Large Cell Lymphoma

Primary mediastinal large B-cell lymphoma is a specific entity in WHO classification of lymphoma.[11] They arise from thymus and constitute 2–3% of all NHL. They have slight female preponderance and usually present in younger age groups.[43-45] Most presenting symptoms occur because of a rapidly enlarging mediastinal mass compressing various mediastinal structures. The rapidly enlarging mass can infiltrate into the adjacent lung parenchyma, chest wall, pleura and pericardium. Thus, the presenting symptoms can be cough, hoarseness of voice, chest pain and dyspnea. Systemic B symptoms are present in one fifth of patients. The work-up of these patients is the same as for other high-grade NHL. Mediastinal lymph node core biopsy either ultrasound guided, endoscopic guided or by thoracoscopy is required to accurately classify this condition. The treatment is similar to that for other diffuse large B-cell lymphoma (RCHOP) though many physicians treat with third generation chemotherapy regimens.[43] Most patients do require radiotherapy; postchemotherapy as the mediastinal mass is usually more than 10 cm at presentation. If the treatment is initiated early, the response rates are similar to those seen with diffuse large B-cell lymphoma at other sites (60 to 70% depending upon the IPI).

Precursor T-cell Leukemia/Lymphoma

In the WHO classification of lymphohematopoietic disorders, the distinction between high grade lymphoma and leukemia has not been made because the treatment of both conditions is similar.[11] T-cell lymphoma/leukemia usually presents with large mediastinal mass in young males and generally carries poor prognosis. The presenting symptoms occur because of rapidly enlarging mediastinal mass compressing on the adjacent structures. In most cases, the disease is associated with HTLV-1 infection. The treatment is done with intensive chemotherapy, and in many cases allogeneic stem cell transplantation may be required afterwards.

LYMPHOMATOID GRANULOMATOSIS (LYG)

This is another condition which can be confused with various malignant as well nonmalignant disorders of the lung.[8] The cause of this condition is unknown but it is mostly present in patients with immunological abnormalities. The disease is characterized by lung nodules or masses mostly in the lower lobes or periphery of the lung fields.[1] In a substantial number of patients, central nervous system abnormalities in the form of seizures or focal deficit and dermatological involvement in the form of erythematous skin rashes, skin nodules or ulcers can occur. The disorder has been described as akin to post-transplant lymphoproliferative disorder. The disease usually presents in the middle to elderly age population and the usual symptoms are cough, hemoptysis and dyspnea.

The diagnosis is always made from surgical biopsy of the resected nodule or mass. Wegener's granulomatosis and T-cell lymphoma constitute the close differential diagnoses. Similar to WG, there is a granuloma formation but the cells are atypical, immature and most B-cell show infectivity with Epstein-Barr Virus (EBV). Similar to T-cell lymphoma, the granulomas are surrounded by abundant reactive T-cells, but there is absence of cytopenias and paraproteinemias, usually seen in T-cell lymphomas. LYG histologically is further graded into three types depending upon the number of cells infected with EBV. The aggressiveness of the disease increases as the histological grade increases from one to three. The treatment thus also varies depending upon the histological grade. Histological grade one and sometimes two can be observed without any treatment whereas grade three LYG always require treatment, usually akin to that for patients with diffuse large B-cell lymphoma.[8]

SECONDARY INVOLVEMENT OF LUNG BY OTHER SYSTEMIC HEMATOPOIETIC AND LYMPHOID DISORDERS[46-48]

Most malignant hematopoietic and lymphoid disorders are systemic in nature and the lungs are secondarily involved. This section will cover those disorders which have not been covered above.

Castleman Disease[46]

Castleman disease (angiofollicular lymph node hyperplasia) was first described in 1954 as a benign localized mass of lymph nodes in the mediastinum. Later on, additional types of this condition were recognized. The disease can be unicentric or multicentric, divided histologically into hyaline-vascular variant and plasma cell variant.

Unicentric CD present like a single mass lesion that can present in the mediastinum, pleura, chest wall and rarely in the lungs. Mostly young adults and middle-aged individuals are affected. The disease is mostly asymptomatic unless it presses on some of the important nerves or vessels. Resection of the mass is curable in these patients. No treatment is required If the disease is asymptomatic. Prevalence of unicentric plasma cell variant is rare than the multicentric plasma cell variant. Multicentric plasma cell variant usually presents in the middle age to elderly age group. The disease has become more common in the presence of HIV infection. The lesions can occur in the mediastinum, lungs and various extrathoracic and retroperitoneal regions. Systemic symptoms such as fever, weight loss and fatigue are usually present in most of the patients. In many instances, the disease has been linked to the presence of human herpes virus 8 infections that can be demonstrated in the resected tissue specimen. Patients with multicentric Castleman disease require treatment in the form of systemic chemotherapy. If it is associated with HIV infection, antiretroviral therapy should be instituted as soon as possible though sometimes the flare up of the disease is known. Unicentric Castleman disease is generally curable with the surgical resection.

Plasma Cell Dyscrasias[47, 48]

Plasma cell dyscrasias comprise a variety of disorders such as monoclonal gammopathy of unknown significance, multiple myeloma, Waldenström's macroglobulinemia and primary amyloidosis. All these disorders are characterized by neoplastic proliferation of immunoglobulin producing plasma cells. Lungs are secondarily involved in the disease process. The manifestations in the lungs occur in the form of parenchymal nodules or interstitial infiltrates. The diagnosis is made from other systemic features demonstrating the clonal proliferation of plasma cells in the form of monoclonal band in the serum or urine. Lung biopsy is often required to rule out involvement by an infectious disease. The treatment is directed towards the systemic disease. Major lung involvement is associated with poor prognosis.

Post-transplant Lymphoproliferative Disorders (PTLDs)

Lymphoproliferative disorders developing after organ transplantation is considered as a distinct entity with a prevalence rate of up to 20% in different series.[11] Their spectrum ranges from benign polyclonal lymphoproliferation to malignant lymphomas. Most disorders occur during the first year after transplantation.[49] Epstein -Barr virus infection acquired post-transplant is one of the important risk factor besides the degree of immunosuppression. There is some variation in the prevalence of PTLDs following different organ transplantation. The risk is probably greater among post lung and heart transplantation because the degree of immunosuppression is higher.

Intrathoracic presentation of PTLD occurs in up to 29% patients.[50] The presentation is mostly in the form of lung nodules; patch airspace disease and mediastinal lymphadenopathy. The differential diagnosis revolves around infectious diseases that can occur in patients on immunosuppression; hence a surgical biopsy of the lesion or image guided biopsy from the intrathoracic lymph node is mandatory. More than 90% of the lesions show positivity with EBV infection. Initial treatment consists of reduction in immunosuppression that probably works only in early lesions. In advanced lesions combination chemotherapy is the treatment of choice.[51] The prognosis depends upon multiple factors such as the stage and the grade of the lesion, transplanted organ function and performance status of the patient. The mortality is usually high reaching up to 50% in some of the series.

Chemotherapeutic Drugs Lung Toxicity

Use of antineoplastic drugs can result in lung toxicity which is very difficult to distinguish from infectious diseases that occur in patients with hematological malignancies.[52] However, lung toxicity of anti-cancer drugs is a known complication.[7] Lung involvement can present with nonspecific interstitial pneumonitis, organizing pneumonia, desquamative interstitial pneumonia, eosinophilic pneumonia, granulomatous pneumonitis, diffuse alveolar hemorrhage, retinoic acid syndrome, noncardiogenic pulmonary edema and acute respiratory distress syndrome.[52-58] The classes of drugs involved in causation of these symptoms are anthracyclines, purine analogs, anti-angiogenesis drugs, monoclonal antibodies, proteosome inhibitor, alkylating agents, antibiotics, arsenic trioxide and all transretinoic acid, to name a few. The respiratory symptoms appear usually 2–14 days after the start of the offending drug. Most patients are initially treated for infectious complications which are far more common than the drug toxicity. However, the index of suspicion should be kept high in patients where no infectious agents are identified and temporal correlation of symptoms is related to the administration of the drugs.[7] The distinction between the two entities would lead to administration of corticosteroids in drug induced toxicity with gratifying results.

PYOTHORAX ASSOCIATED LYMPHOMAS

As the name suggests, lymphoma that develop in chronic pyothorax cavity are labeled as pyothorax associated lymphoma. This entity was first described in Japan in 1987 when the authors noted development of lymphoma among patients who were treated with artificial pneumothorax as a treatment of their pulmonary tuberculosis some 30–67 years back.[59,60] The postulation put forward by authors was that chronic long-standing inflammation in the pleura was responsible for the development of this lymphoma. The hypothesis is similar to what has been given for the development of MALT lymphoma developing at other sites. Further research into this type of lymphoma suggested association of Epstein-Barr virus infection. Hence, almost all pyothorax associated lymphomas are associated with B-lineage mostly due to diffuse large B-cell type of lymphoma.[61,62]

The median age of patients at the time of presentation is above 70 years and generally patients have other comorbidities. The presenting symptoms are pain in the chest or the back along with systemic symptoms such as the fever and the weight loss. Chest skiagram is usually the first investigation followed by either CT or MRI scans. The differential diagnosis includes other chest tumors such as the mesothelioma, and the lung carcinoma. The diagnosis is achieved by performing a core biopsy of the mass and with immunohistochemistry.[63] Further, staging of lymphoma is done as mentioned earlier. Bone marrow involvement by lymphoma is rare. The treatment is given with chemotherapy as used for other large B-cell lymphoma. Sometimes, radiation is required if the tumor does not resolve completely after the chemotherapy. The prognosis is dismal in most cases because of the presence of comorbidities.[64]

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Mediastinal Disorders

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INTRODUCTION

Mediastinum is thoracic cavity which lies between the lungs. It is bound laterally by the parietal pleurae, anteriorly by the sternum, posteriorly by the vertebral column and paravertebral gutters, superiorly by the thoracic inlet and inferiorly by the diaphragm. Interest in mediastinum stems from myriad of vital structures it encloses (Table 121.1) and their associated diseases with classical clinical, as well as radiological presentations. The lack of distinct anatomical planes between compartments, similar clinical manifestations due to spectrum of diseases, and relative inaccessibility of the structures make evaluation of mediastinal disorders a daunting task.

After a brief overview of anatomy and relevant radiological investigations, specific disorders will be discussed with emphasis on clinical manifestations and disease management.

The Mediastinal Anatomy and Compartments

Subdivision of mediastinum has been attempted by clinicians, radiologists and surgeons resulting in numerous classifications and resultant confusion. Classification proposed by Shields in 1972 divides mediastinum into three compartments; anterior, middle (visceral) and posterior (paravertebral sulcus). This is simple and useful classification, as further subdivisions in the absence of distinct anatomical planes are redundant because neither disease nor air can be contained within the compartments. The only resistance to spread of either is the mediastinal pleural reflections laterally; superior communication with neck and inferiorly with retroperitoneum ensures free dissemination. The boundaries of anterior compartment are the sternum, the first rib and an imaginary curved line following the anterior heart border and brachiocephalic vessels from the diaphragm to the thoracic inlet. The middle (visceral) compartment extends from the posterior limit of the

TABLE 121.1: Contents of mediastinal compartments

Anterior	*Middle*	*Posterior*
Pericardial fat	Heart and Pericardium	Azygous and hemizygous veins
Thymus gland	Trachea, main bronchus and Hila	Esophagus
Substernal extensions of thyroid and parathyroid glands	Innominate veins and superior vena cava Aortic arch and great vessels Phrenic and vagus nerves	Azygous and hemizygous veins Descending aorta Sympathetic trunk
Lymph nodes	Lymph nodes	Intercostal nerves Thoracic duct
Connective tissue	Connective tissue	Connective tissue

anterior compartment to the anterior surface of the vertebral columns and then to the thoracic inlet. The posterior compartment (paravertebral sulcus) extends from the anterior surface of the vertebral column to the anterior surface of the paravertebral ribs.

Lymphatics

As with the compartments of mediastinum, the lymphatics are interconnected and involvement of adjacent stations is extremely common in disease. Separation to distinct stations forms the cornerstone in the management of bronchogenic carcinoma. Naruke's division into 14 stations is widely used for this purpose.

IMAGING OF MEDIASTINUM

Conventional Chest Radiograph

Conventional chest radiograph is the first step in the evaluation of any chest symptom and mediastinal disease is no different. In fact, as many as 40% of mediastinal masses may be detected during routine chest radiograph.[1] Radiographs with posteroanterior (PA) and laterolateral (LL) views represent the basic imaging modality in the study of the chest and mediastinum. Chest radiography allows localization of the pathological process; orthogonal projections can demonstrate site, size and density and the presence of calcifications, thereby narrowing the range of differential diagnoses. Additional views (oblique or lordotic) may be useful for distinguishing true images from composition images. Moreover, fluoroscopic examination and opacification of the esophagus will provide valuable complementary information.

Radiologically, a line is formed when certain conditions are met. There is a difference in density between two adjacent tissues; the two tissues are separated by a curved surface; the beam hits this surface tangentially. These conditions occur often in chest radiography where the reflections of the lungs (ventilated and therefore radiolucent) on the mediastinum (radiopaque) form several "lines", known as mediastinal lines. If the line has a double interface (air-mediastinum-air), it may be called a "stripe".[2] In the anterior mediastinum, PA view reveals the anterior junction line and lateral view, the retrosternal line.[3] Normal morphology of these lines is a reliable indication of normality of the single mediastinal compartments; the presence of space-occupying lesions will cause their displacement, distortion or cancellation. Mass may on the other hand be plainly visible protruding from either side of mediastinum. Chest radiography is almost always able to indicate the presence and site of mediastinal disease, but apart from a few exceptions, it cannot define its nature, organ of origin or the presence of possible infiltrative features. Further investigations are therefore needed to characterize the disease.

Computerized Tomography (CT)

Axial imaging avoids the problem of overlapping tissues with similar density: Demonstration of mediastinal spaces with their lymph nodes, relation with surrounding structures and blood vessels represent the most important contributions of CT. Indications include characterization of lesions previously identified on standard X-ray and assessment of the mediastinum in patients with a clinical suspicion of disease but negative X-ray.[4,5] Improved resolution ensures better delineation of structures including point of origin, extension and relation to adjacent organs. This also helps in directing diagnostic procedures like fine needle aspiration or biopsy.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging is used less frequently compared with CT in the evaluation of mediastinal masses, mainly because of its limited availability and higher cost; however, MRI has a capacity for multiplanar imaging and the ability to image vessels, and it can provide better tissue characterization than CT. Additionally, MRI is excellent in the evaluation of regions of complex anatomy such as the thoracic inlet, the perihilar, paracardiac and peridiaphragmatic regions, and for the assessment of posterior mediastinal or paravertebral masses.[6]

Ultrasonography

Traditional ultrasonography (US) has role in evaluation of anterior mediastinal masses in children, especially thymic masses. Esophageal ultrasonography (EUS) and endobronchial ultrasonography (eBUS) are increasingly being used to detect mediastinal involvement in bronchogenic and esophageal carcinoma and guiding diagnostic aspiration of lymph nodes that would otherwise not be possible by conventional methods.

Radionuclide Imaging

Positron emission tomography (PET) with or without CT has almost become a prerequisite in the preoperative evaluation of bronchogenic carcinoma for assessing respectability. Radioactive iodine scans are useful in detecting mediastinal extension of suspected thyroid neoplasms. Technetium-99m (Tc-99m) sestamibi can be used to detect parathyroid tissue.

Pneumomediastinum

Free air in the mediastinum detected on a chest X-ray or chest computed tomography test is pneumomediastinum.[7] It is spontaneous when occurring without surgical or medical procedures, chest trauma or mechanical ventilation and in the absence of underlying lung disease. Secondary pneumomediastinum, though a rare entity, is far more common especially in recent times with mechanical ventilation patients. Both the entities vary distinctly in the pathophysiology, clinical presentations and are discussed separately. The key to understand the distribution of extraalveolar air lies in the recognition of the common facial planes that unite these areas. Anatomical continuity may lead to extensive subcutaneous emphysema over the head and neck area, interstitial emphysema, pneumoperitoneum or air may dissect the pleural layers/pericardium leading to associated pneumothorax/pneumopericardium. The source of air includes alveolar in spontaneous and pneumomediastinum associated with mechanical ventilation. Other areas of origin include head and neck where it could be secondary to infection by gas producing organisms or dental procedures requiring use of compressed gas at high pressures. Upper respiratory tract, tracheobronchial tree and extrathoracic gas are the source in trauma patients; uncommon sources include pneumoperitoneum and pneumoretroperitoneum in postsurgical patients.

Spontaneous Pneumomediastinum (SPM)

This entity was first recognized in 1939 by Hamman with the demonstration of crepitations synchronous with heart which is classically described as "Hamman's crunch". Idiopathic SPM is rare with a reported incidence of 0.001 to 0.01% among all adult inpatients.[7] Most cases are young males; the age is distributed roughly from 18–25 years old and males account for 73.1%.[8] No relation is reported with either smoking or other environmental factors. Pressure differences across the alveolar membrane resulting from rapid increments of airway pressure cause terminal alveolar rupture. Most commonly, this results from straining against a closed glottis, as during vomiting, coughing or exercising. Other factors such as direct toxic effects of heat induced by inhalation of illegal drugs and the thinner alveolar wall due to malnutrition may result in the rupture.[9] This rupture occurs without pleural dissection, which causes air to enter the lung interstitium and then migrate towards the mediastinum, occasionally the pericardium and the retropharyngeal and the retroperitoneal space, along the bronchovascular bundle by the pressure gradient between the peripheral and the hilum of the lung, the so-called Macklin effect.[10]

Most common presenting symptoms are chest pain and dyspnea. The pain typically radiates to the neck or back and is aggravated by bending forward, swallowing or deep inspiration. Other symptoms include cough and dysphonia. Differential diagnosis in any young person presenting with acute chest symptoms should include SPM. Severity of symptoms is usually moderate and patients tend to present within 24 hours of onset of symptoms. History regarding trigger events may help in clinching the diagnosis but no trigger is identified in up to 40 % of cases. Subcutaneous emphysema detected in up to 62% of the reported cases is the most common physical finding and is usually restricted to the head and neck region. Hamman's crunch is reported in 30% of cases, careful auscultation with placement in left lateral position improves the chances.[11]

Radiological Findings

Common findings in chest radiograph PA view are air streaks in the superior mediastinum (sometimes they reach to the neck), the prominent silhouette of the heart (especially on the left) and subcutaneous emphysema of the shoulder and neck. All the findings may not be identified in a given patient. The double bronchial wall sign (bronchial wall sandwiched between inner and outer air) and the continuous diaphragm sign (the diaphragm of both sides appearing connected by leaked air between the inferior surface of heart and diaphragm) are uncommon but characteristic signs when present.[8] Lateral views are more sensitive in detecting air and must be used when the clinical suspicion is high and frontal radiographs are unrevealing. One must resort to computerized tomography when strong clinical suspicion is present with normal chest radiograph. CT is also informative regarding additional lung disease and in complicated pneumomediastium like Boerhaave syndrome.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes pneumothorax, pulmonary thromboembolism, pericarditis and acute coronary syndrome. Since all differentials are more common in emergency setting, the risk of them being missed while a patient is being evaluated for SPM is slim. Whilst SPM is detected, one should be careful to rule out Boerhaave syndrome as it carries high mortality unlike SPM.

Treatment and Clinical Course

Symptoms tend to subside in 24–48 hours with complete radiological resolution. Symptomatic therapy with analgesics is all that is required in most of the cases. Antibiotics may be considered in the presence of signs of inflammation like fever after ruling out other differentials. Subcutaneous emphysema is drained using tunneled intravenous catheter if extensive and an associated pneumothorax is managed by chest tube drainage. Recovery is total with recurrence uncommon (1.2%) unlike in spontaneous pneumothorax.[8]

Pneumomediastinum in Mechanically Ventilated Patients

Mechanically ventilated patients who are subjected to high tidal volumes, high peak inspiratory pressures, high positive end expiratory pressures (PEEP) and are fighting the ventilator are at high risk for developing pneumomediastinum.[12] Air trapping (auto PEEP) due to high frequency or underlying obstructive lung disease may also lead to increase in peak inspiratory pressures. Unlike SPM, pneumomediastinum in mechanically ventilated patients can be life threatening due to continuous positive pressure increasing the likelihood of associated tension pneumothorax. This may be detected incidentally on chest radiograph; but once detected, serial screening with chest radiograph is required to detect pneumothorax. If a pneumothorax occurs; chest tube drainage is indicated regardless of the size, if the patient continues to require positive pressure ventilation. In the presence of only pneumomediastinum, a step to curb increase in peak inspiratory pressures is taken, if the patient cannot be immediately weaned off the ventilator. Patient-triggered, pressure limited ventilation (e.g. inspiratory pressure support) or low-rate intermittent mandatory ventilation would probably be preferable to mandatory volume-limited ventilation if clinically feasible.[13] Prophylactic bilateral chest tube insertion is not recommended in the absence of sudden deterioration.

MEDIASTINITIS

Inflammation of the mediastinal structures is defined as mediastinitis. Based on the duration and severity of symptoms it may be broadly classified to acute and chronic. Clinical presentation is dramatic and is often life threatening in acute mediastinitis whereas chronic inflammation tends to present as mediastinal mass.

Acute Mediastinitis

Infection is the most common cause of acute mediastinitis but predominant inflammation could also occur with secondary infection as in esophageal rupture. Based on etiology, specific compartments may be more commonly involved but with time inflammation spreads to all. With the advent of invasive endoscopic therapeutic procedures esophageal perforation is the most common cause of acute mediastinitis. Other common causes include infection following sternotomy, descending necrotizing mediastinitis following neck infections, infection from tracheobronchial tree and rarely direct involvement as in anthrax mediastinitis.

Patients are usually gravely ill, high index of suspicion is the key especially in post procedure patients as in esophageal manipulation or cardiac surgery as they tend to deteriorate rapidly developing multiorgan dysfunction within few hours. Computerized tomography of the chest with contrast enhancement is the investigation of choice in these patients. Treatment of these patients require appropriate antibiotics and surgical debridement (Table 121.2).

Chronic Mediastinitis

The active end of the spectrum encompasses granulomatous mediastinitis and at the other end mediastinal fibrosis represents the sequelae. The former tends to be asymptomatic whereas the latter presents as mass with symptomatic profile depending on the part of mediastinum which is involved. Histoplasmosis and tuberculosis are fine examples which demonstrate the etiology of chronic mediastinitis. Both being as infection in the lungs with mediastinal adenitis secondary to regional drainage. There can be associated perinodal inflammation in a subset of individuals with a residual breakdown of conglomerate of lymph nodes akin to matting seen in the periphery. This mass gets covered by a fibrous capsule and tends to calcify as it is usually seen in chest radiograph as a sequelae. In some individuals, the fibrous capsule tends to increase in thickness with compression and invasion of adjacent organs. The reason for its occurrence in certain individuals and not in others is unclear. Goodwin and associates postulated that prolonged gradual seepage of some soluble antigen or other substance from the involved lymph nodes, at least in patients with histoplasmosis, causes fibrosis.[14] In some

TABLE 121.2: Management of acute mediastinitis

Etiology	*Investigation*	*Antibiotics*	*Surgical procedure*
Descending necrotizing mediastinitis	Contrast enhanced CT of neck and chest	Anaerobic and gram negative organisms	Surgical drainage
Esophageal manipulation	Contrast esophagogram, contrast enhanced CT of chest	Gram-negative organisms, methicillin resistant *Staph.* aureus (MRSA)	Debridement and closure of perforation
Boerhaave syndrome	Contrast esophagogram, contrast enhanced CT of chest	Gram-negative organisms	Debridement and closure of perforation
Post sternotomy	Contrast enhanced CT of chest	Pseudomonas and MRSA	Extensive sternal and mediastinal debridement
Tracheobronchial perforation	contrast enhanced CT of chest	Gram-negative organisms, MRSA	Stenting/open surgical repair
Anthrax mediastinitis	Chest radiograph, contrast enhanced CT	Ciprofloxacin or doxicycline + clindamycin	

patients with concomitant retroperitoneal fibrosis, autoimmune phenomena might be responsible.

Clinical Manifestations

Predominant symptoms are manifestations of mass effect on the adjacent organs. Cardinal symptoms include cough, chest pain, hemoptysis and dyspnea. Trachea or any of the major bronchi can be involved but compression or erosion of the right middle lobe is most common and may present as right middle lobe syndrome. Right paratracheal region involvement may lead to compression of superior vena cava, leading to superior vena cava (SVC) syndrome. Though malignancy accounts for up to 95% of SVC syndromes encountered in clinical practice, fibrosing mediastinitis is the most common nonmalignant cause. Extrinsic esophageal compression presents as dysphagea and perforation as hematemesis or tracheoesophageal fistula. Recurrent laryngeal nerve compression leads to hoarseness of voice. Pulmonary vascular involvement can lead to pulmonary hypertension and cor pulmonale.

Management

Chest radiology reveals mediastinal enlargement, definite diagnosis requires mediastinal sampling by exploratory laparotomy to exclude malignancy. During the same, debulking of the mediastinum should be attempted while being careful to avoid injury to surrounding structures. Antitubercular or antifungal can be given if specific infections are identified. Anti-inflammatory agents like steroids have been used with equivocal results but may be considered in an individual patient. Mechanical compression can be relieved by endovascular, esophageal or endobronchial stenting where appropriate.

TUMORS AND CYSTS OF MEDIASTINUM

Mediastinal mass may be congenital or acquired in origin, the contents of the mediastinal compartments serve as points of origin. Hence localization of the mass in mediastinum gives a clue towards etiology but can be confirmed only by tissue sampling. The contents of the respective compartments have been summarized in Table 121.1. Anterior mediastinal mass most commonly arises from thymus, lymph nodes, thyroid or primitive germ cells. The middle compartment which mostly comprises of tracheobronchial tree, heart and esophagus is the site for duplication cysts. Posterior mediastinum abuts the vertebral body, enclosing the sympathetic trunk and vagal nerve; mass arising from this region is likely to be of neural origin. Location of the mass, age of presentation and presence of symptoms are the three major determinants of whether the mass is benign or malignant in etiology. Although majority of mediastinal masses are benign (2/3rd), anterior mediastinal (59%) and symptomatic lesions (85%) are more likely to be malignant.[1] Symptoms are broadly classified into local and systemic. The local symptoms are secondary to the mass effect and compromise of surrounding structures. Common symptoms include cough (60%); chest pain (30%); and dyspnea (16%). Systemic manifestations are due to the release of excess hormones, antibodies or cytokines and are typically seen in malignant neoplasm as a part of paraneoplastic syndrome. These include cachexia, anorexia, fever, neurologic and endocrine manifestations.

Mediastinal imaging has been discussed in detail at the beginning of the chapter. Recapitulating the salient points, the initial workup of a suspected mediastinal mass involves obtaining PA and lateral chest radiographs. This can provide information pertaining to the size, anatomic location, density, and composition of the mass. CT scanning is used to further characterize mediastinal masses and their relationship to surrounding structures as well as to identify cystic, vascular, and soft-tissue structures.[15]

The role of MRI is primarily in ruling out or evaluating a neurogenic tumor. Magnetic resonance imaging is also valuable to evaluate the extent of vascular invasion or cardiac involvement.[16]

Mediastinal Sampling

Tissue diagnosis of mediastinal lesions can be performed using surgical techniques such as thoracoscopy, cervical mediastinoscopy, extended cervical mediastinoscopy and anterior mediastinostomy and needle biopsy techniques, such as image-guided percutaneous needle biopsy, transbronchial needle biopsy including endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-FNA) and transesophageal endoscopic ultrasound guided fine-needle aspiration biopsy (EUS-FNA).[17] Minimally invasive transcutaneous or transpulmonary image guided fine-needle aspiration or biopsy is preferred over open surgical techniques as the diagnostic yield is comparable with a dramatic reduction in complication rates. Choice of the procedure is also dictated by its local availability, institutional and physician preference, patient's condition and location as well as size of the lesion.

Transbronchial needle aspiration (TBNA) through a flexible bronchoscope is the time tested method for sampling enlarged subcarinal and hilar lymph nodes. This is limited by the absence of real time imaging and hence can be used only in the presence of lymph nodes of at least 1.5–2 cm in diameter. The reported sensitivity when used to stage non small cell carcinoma is 25–81%.[18] Endobronchial ultrasound-guided transbronchial needle aspiration, has been documented to have high diagnostic value, with sensitivity of more than 90% in the staging of non-small cell lung cancer.[19] Transesophageal endoscopic ultrasound (EUS) guided needle biopsy allows access to the lower paratracheal, subcarinal, aortopulmonary and paraesophageal regions. The reported sensitivity of EUS-guided biopsy in the mediastinum is 82 to 96%.[18] However, anterior lymph nodes, including those in the pretracheal and high right paratracheal regions, are not accessible because of the interposition of the air-filled trachea.

Before the advent of minimally invasive techniques, all patients of bronchogenic carcinoma planned for resection were subjected to cervical mediastinoscopy. Even now this is the procedure of choice when multiple lymph node stations need to be sampled for accurate staging. It allows direct visualization and sampling of pretracheal, paratracheal and anterior subcarinal lymph nodes and is reported to yield a diagnosis in 83 to 89% of patients with lung cancer.[20,21] It is done under general anesthesia with 1 to 3% risk of major complications and aortopulmonary, retrotracheal, posterior subcarinal and inferior mediastinal lymph nodes are inaccessible. Extended cervical mediastinoscopy, anterior mediastinotomy and thoracoscopy are alternative surgical techniques, which can be used to assess mediastinal regions not accessible by standard mediastinoscopy.

Percutaneous transthoracic needle biopsy using image guidance under local anesthesia and conscious sedation allows access to virtually all mediastinal regions including those that are inaccessible by mediastinoscopy, transbronchial biopsy and EUS-guided biopsy. The accuracy of transthoracic biopsy for the diagnosis of mediastinal lesions ranges from 75 to 90%.[20,21] A major limitation of this technique is the risk of pneumothorax, reported to occur in anywhere from 10–60% of cases. If encountered, it can be managed by percutaneous single time aspiration or by chest tube drainage.

ANTERIOR MEDIASTINAL MASS

Thymic tumors and cysts constitute most of anterior mediastinal masses (Table 121.3).

Thymoma

Thymomas account for 20% of anterior mediastinal neoplasms in adults.[22] Systemic manifestations such as myasthenia gravis (30–50%), hypogammaglobulinemia (10%) and pure red cell aplasia (PRCA) may be the primary presentation and the mediastinal mass may be detected incidentally during evaluation. Thymomas have a wide spectrum of histologic diversity and are classified based on cell type predominance as lymphocytic, epithelial or spindle cell variants. There is a strong association between histologic subtype and invasiveness as well as

TABLE 121.3: Tumors and cysts of thymus

Tumor	*Incidence*	*Association*	*Poor prognostic markers*	*Treatment*
Thymoma	20% of anterior mediastinal mass	Myasthenia gravis, hypo-gammaglobulinemia, PRCA	Metastasis,size >10 cm, tracheal/vascular compression, age >30 years,epithelial or mixed histology, PRCA	Surgical resection, palliative chemotherapy and radiation
Thymic carcinoma	Rare	—	Tumor margin infiltration, absence of a lobular growth pattern,high-grade atypia and necrosis, >10 mitoses per high power field	Surgical resection, palliative chemotherapy and radiation
Thymic Carcinoid	8% of MEN 1 syndrome	Cushing's and multiple endocrine neoplasia (MEN) syndrome	Regional and distant metastasis	Surgical resection, chemo-therapy and radiation not effective
Thymolipoma	Rare	-	Benign	Surgical resection
Thymic cysts	Rare	Inflammation, Hodgkin's disease or other congenital abnormality	Acquired or congenital, benign	Surgical resection

prognosis. Thymomas are usually solid tumors but may have cystic areas due to degeneration, necrosis or hemorrhage. Thirty-four percent of thymomas invade through their own capsules, extending into surrounding structures.[23,24] There can be transdiaphragmatic or pleural extension but distal lymphatic or hematogenous spread is rare. As classification system proposed by the World Health Organization is based on cytologic differences, which may be helpful in determining treatment regimens and predicting survival.[25]

The Masaoka clinical staging system is based on the degree of invasion of the tumor through the capsule into the surrounding structures, which has important implications for prognosis.[26] In the study by Okumura et al.[27], the Masaoka staging system was shown to be useful as an independent predictor of survival in patients with thymoma. Diagnosis is easily established by percutaneous image guided fine needle aspiration, but capsular invasion can only be made out on histopathologic examination of excision biopsy. Surgical excision is the standard of care for both invasive and non-invasive thymomas as it is the only potentially curative option. Adjunctive chemotherapy and radiation is used for locally invasive or metastatic disease, or inoperable tumors.

Mediastinal Germ Cell Tumors (GCTs)

Speculations regarding etiology have ranged from the opinion that these tumors are really of gonadal origin and represent spread from an occult or "burned out" primary tumor to the view that these tumors are of true extragonadal origin with separate clinical and biological behaviors. Primitive germ cells that fail to migrate completely during early embryonic development is the currently accepted theory regarding the origin of GCTs. They constitute about 15% of anterior mediastinal masses. GCTs are classified into the following three groups based on cell type: Benign teratomas; seminomas; and embryonal tumors/malignant teratomas/ nonseminomatous GCTs.

Teratomas

Teratomas are derived from at least two of the three primitive germs layers. They are subclassified into mature and immature (malignant) teratomas, based on the cell of origin. Mature teratomas are more common and are histologically well defined. Ectodermal tissues, which usually predominate, include skin, hair, sweat glands and tooth-like structures. Mesodermal tissues, such as fat, cartilage, bone and smooth muscle are less common, as are endodermal structures like respiratory and intestinal epithelium.[28] Malignant teratomas contain fetal or neuroendocrine tissue, have a favorable prognosis in children but can recur or metastasize.

Mature teratomas tend to be silent or may present with the cardinal mediastinal symptoms. Occasionally, the presentation may be dramatic with the expectoration of hair or sebum due endobronchial rupture of teratoma or rarely malignant transformation. Typical radiological picture is well-defined round or lobulated mass with up to 26% showing calcification due to presence of bone or teeth elements. Computed tomography or MRI may reveal sebaceous elements or fat, which may further support the diagnosis and help in assessing resectability. Complete surgical resection is the treatment of choice and adjuvant chemotherapy is indicated if resection is incomplete.

Medistinal Seminoma

Approximately 40% of mediastinal GCTs are seminoma, occurring most commonly in males between second and the fourth decade. Apart from the usual presenting features of mediastinal mass, gynecomastia and weight loss may occur as paraneoplastic manifestations. Beta human chorionic gonadotropin (β-HCG) is elevated in up to 10% of patients but an elevated alpha fetoprotein (AFP) suggests an alternate diagnosis. Radiographically, seminomas are bulky, lobulated, homogenous masses. Local invasion is rare, but metastasis to lymph nodes and bone does occur.[29] Computed tomography and gallium scanning is used to evaluate the extent of disease. Unlike other mediastinal tumors discussed till now, seminomas are highly radiosensitive. Management may involve only radiotherapy or chemotherapy and radiotherapy or a neoadjuvant chemotherapy followed by surgery. Five-year survival ranges between 54% with radiotherapy alone[30] to more than 90% with chemotherapy with or without radiation[31] among various studies.

Nonseminomatous GCTs

The nonseminomatous malignant germ cell tumors include embryonal cell carcinoma, endodermal sinus tumor, choriocarcinoma or mixed germ cell tumors composed of multiple histologic features. These are malignant and typically cause symptoms in young adult men. Unlike seminomas, lactate dehydrogenase and serologic markers such as AFP and β-HCG are frequently positive. Another unique association is with hematologic malignancies with up to 20% of the patients having Klinefelter's syndrome.[29] Radiologically, these are large, irregular, anterior mediastinal masses, often with extensive, central, irregular and heterogeneous areas of low attenuation due to necrosis, hemorrhage and/or cyst formation. Invasion of adjacent structures with associated pleural and pericardial effusions are common. Tumor may protrude through the chest wall and distal metastasis is not uncommon. Chemotherapy with bleomycin, etoposide and cisplatin is the current standard of care for patients with nonseminomatous malignant GCTs. Complete response is rare, with most patients requiring resection of residual tumor. As compared to seminomas, nonseminomatous GCTs have a poor long-term survival with only 46% alive at five years in contrast to 86%.[32]

Mediastinal Goiter

Clinically mediastinal extension of goiter is detected by inability to identify the lower border of thyroid during examination. Incidence is in the range of 1 to 15% among patients undergoing thyroidectomy. Most patients are euthyroid; Goiter appears as lobulated, encapsulated and heterogenous tumors with classic cervicomediastinal continuity seen on CT. There will be avid uptake of radioiodine if there is functional thyroid tissue. Due to retrosternal position, diagnostic sampling is difficult and exploratory laparotomy with complete surgical excision is recommended as malignancy develops in a significant number.

Mediastinal Lymphomas

Mediastinal involvement as a part of systemic disease is a common manifestation of lymphomas and figures among the top differentials while evaluating mediastinal lymphadenopathy. Primary mediastinal lymphoma is relatively rare entity accounting for only around 10% of all mediastinal lymphomas. Nodular sclerosing type of Hodgkin's lymphoma, large B-cell lymphoma and lymphoblastic lymphoma are the three most common lymphomas with mediastinal involvement.[29] Presentations are similar to other mediastinal masses with constitutional symptoms (B symptoms) predominating at times especially in Hodgkin's lymphoma. They can present as mediastinal emergencies with superior vena cava syndrome or pericardial tamponade leaving little time for establishing diagnosis. Diagnosis is achieved by sampling peripheral or mediastinal lymph nodes whichever is less invasive. Ann Arbor staging system is based on the number of lymph node regions and or other organ systems involved by the disease process. The treatment of mediastinal lymphomas is no different from lymphomas elsewhere and it involves primarily appropriate chemotherapy. Adjuvant radiotherapy may be justified in stage I or II a disease or in the presence of superior vena cava syndrome. Relapsed disease is usually treated with high dose chemotherapy followed by bone marrow transplantation.

TUMORS OF THE MIDDLE MEDIASTINUM

Mediastinal Cysts

These are congenital anomalies resulting from defects during embryonic development. They occur most commonly in the middle mediastinum but neural derived cysts are found in the posterior mediastinum. Their presentation can be insidious due to compression of adjacent structures or acute due to infection or rupture. They comprise 12 to 20% of mediastinal masses and the most common type of mediastinal cyst are foregut cysts, with enterogenous cysts (50 to 70%) and bronchogenic cysts (7 to 15%) being the major subtypes.[29]

Bronchogenic Cyst

Approximately 40% of the bronchogenic cysts are symptomatic with cough, dyspnea or chest pain whereas the rest are detected during routine chest radiographs.[33] The lung bud develops caudally from the laryngotracheal tube, beginning in the fourth week of gestation. By the fifth week, the single bud has divided into right and left main bronchi, which grow into the surrounding splanchnic mesenchyme and are destined to become bronchial cartilage and smooth muscle as well as visceral pleura. Dichotomous branching of the primitive bronchi continues until about the 24th week, when the terminal bronchioles begin to give rise to primitive alveoli. Throughout this period of embryogenesis, abnormal bronchi and bronchioles may form larger saccular structures, which are clinically recognized as bronchogenic cysts and are lined with ciliated, pseudostratified, columnar epithelium and contain bronchial glands and cartilaginous plates. Anomalies that occur early are contained within the mediastinum and are mostly commonly seen abutting the trachea, carina or hila. Less frequently, errors occurring late in embryogenesis may result in intraparenchymal bronchogenic cysts. They are seen as well-defined rounded masses on chest radiographs and on CT have similar Hounsfield unit as water. Air fluid level signifies either bronchial communication or secondary infection. Diagnosis is confirmed by imaged guided or endobronchial needle aspiration. Symptomatic cysts are managed by either surgical resection or therapeutic aspiration with or without instillation of sclerosing agent (ethanol or bleomycin) but controversy exist regarding the management of asymptomatic cysts. Subjecting such patients to a major surgery must be weighed against potential long-term complications including malignancy.

Enterogenous Cyst

Enterogenous cysts arise from the dorsal foregut and are lined by squamous or enteric (alimentary) epithelium and may contain gastric or pancreatic tissue. It is also known as esophageal duplication cyst and represents the failure of esophagus to separate from the respiratory tract, a process which normally occurs around the fifth week during embryogenesis. Communication to the alimentary tract is rare and is usually spherical with cystic consistency. Twelve percent may have associated other malformations of the gastrointestinal tract. Majority of the patients present in early childhood and due to presence of gastric or pancreatic tissue, there is a potential for hemorrhage or rupture. There is predilection for the right side and symptomatic dyspnea is rare. In asymptomatic patients, the most common clue leading to this diagnosis is the coexistence of other gastrointestinal duplications. Radiological manifestations are similar to bronchogenic cysts but these have slightly thicker wall and are nearer to esophagus. Barium meal may show indentation along the posterior wall and a technetium pertechnetate nuclear scan may suggest the presence of ectopic gastric mucosa within the chest. The potential for rupture mandates surgical resection of all enterogenous cysts after confirming diagnosis. The presence of gastric lining mucosa also predisposes these patients for the development of adenocarcinoma and hence the need for long-term follow-up post surgery.

Pericardial Cysts

Unlike other cystic lesions of the middle mediastinum, pericardial cysts are often detected in the fourth to fifth decade. Therefore the case for at least some of them being acquired is strong but majority of them seem to be form from the persistence of parietal recess during embryogenesis. Most are asymptomatic but can present with hemodynamic compromise secondary to cardiac compression or arrhythmia. Their estimated incidence is 1 in 1,00,000.[33] The most common presenting site is the cardiophrenic angle on the right side and can be mistaken for foramen of morgagni hernia or thickened pericardial fat. They are also called “spring water cysts” because of their characteristic radiologic picture showing low density clear serous fluid content. Pericardial cysts have no malignant potential and can therefore be followed up once diagnosis is established. Symptomatic cysts are resected by either an open or endoscopic approach.

Lymphangiomas

Lymphangiomas classically present as cervical swelling and are identified clinically by the presence of fluctuation and transluminescence due to presence of clear fluid. In up to 10% of patients there can be a mediastinal extension with associated chylothorax and hemangioma. These are congenital malformation of the lymphatics leading to saccular dilatation and cyst formation. Cervical lymphangiomas typically present in early childhood but isolated mediastinal lesions may present during adult life with symptoms of mediastinal compression. Radiographically, these lesions appear cystic and can be confused with pericardial cysts, although lymphangiomas are more likely to have a loculated appearance.[34] The use of lymphangiographic contrast media combined with CT scanning can also differentiate these lesions. Complete surgical resection is the treatment of choice, however in cases complicated by adjuvant radiotherapy may be used.[35] Lymphangiomatosis (LAM), a type of cystic interstitial lung disease, seen almost exclusively in women may be an advanced form of lymphangioma of chest.

TUMORS OF THE POSTERIOR MEDIASTINUM

Neuroenteric Cysts

Enterogenous cysts that are in continuation or adjacent to vertebral anomalies are called neuroenteric cysts. Neurenteric cysts are very rare congenital anomalies. Result due to failure or incomplete separation of the notochord from the primitive foregut. Associated vertebral anomalies include butterfly vertebrae, hemivertebrae and anterior spina bifida. These cysts may present early in life often before the first year of life with triad of respiratory symptoms, mediastinal mass and vertebral anomaly. Evaluation should include imaging of the chest with CT and a complete spinal imaging using MRI spine. Treatment usually requires cooperation between neurosurgeon and cardiothoracic surgeon for spinal decompression, vertebral reconstruction and mediastinal resection. Given the complexity of the procedures, usually a staged approach is preferred and residual neurologic deficit may be present.

Neurogenic Tumors

Neurogenic tumors arise from various neural elements like peripheral nerve roots (neurofibroma, schwannoma, neurogenic sarcoma), from the sympathetic ganglia (ganglioneuroma, ganglioneuroblastoma and neuroblastoma), from aorticosympathetic paraganglia (paravertebral paraganglioma), or rarely from the intrathoracic spinal canal (e.g. meningocele or meningomyelocele).[36] They constitute about 20% of all mediastinal masses and roughly 95% of them lie in the posterior mediastinum. Nearly three fourth of them are benign and half are asymptomatic; however, they can occasionally cause compressive or neurologic symptoms.[37]

Nerve Sheath Tumors

They constitute about half to two-third of the neural tumors of the posterior mediastinum. These are benign and extremely slow growing tumors consisting of neurilemmoma or schwannomas and neurofibromas. The former are encapsulated, firm masses consisting of Schwann cells whereas the latter are soft, friable, nonencapsulated and associated with neurobifromatosis. They appear as sharply marginated spherical masses on radiographs with often signs of erosion of adjacent spine. The classic dumbbell appearance due to growth of tumor through the interevertebral foramina is seen in only 10% of the tumors. Complete surgical resection is the standard of care and adjuvant chemotherapy or radiotherapy may be considered if resection is incomplete. Paraparesis and Horner's syndrome are potential complications of surgery.

Malignant nerve sheath tumors are the spindle sarcomas of posterior mediastinum, and include malignant neurofibromas, malignant schwannomas and neurogenic fibrosarcomas. They are generally symptomatic, with pain and nerve deficits being the predominant symptoms. Complete surgical resection with or without adjuvant chemotherapy or radiotherapy is the treatment of choice.

TUMORS OF AUTONOMIC NERVOUS SYSTEM

These tumors arise from neuronal cells rather than from the nerve sheath. They are either benign or encapsulated like the ganglioneuroma or can be fast growing, malignant and nonencapsulated like the neuroblastoma. They arise either from the adrenals or from the sympathetic ganglia of the posterior mediastinum. Surgery is the treatment of choice for benign tumors and localized malignant tumors can be excised completely. If the resection is incomplete, treatment regimen includes postoperative chemotherapy and radiotherapy.

SUPERIOR VENA CAVA SYNDROME (SVCS)

No review of mediastinum would be complete without an overview of this dramatic syndrome which, once seen in clinical practice remains etched in the memory of any clinician. SVCS is a common complication of lung cancer and non-Hodgkin's lymphoma (NHL). Two to four percent of lung cancer and NHL develop SVCS and together, they constitute about 90% of the cases of SVCS seen in modern practice.[38] Benign causes constitute around 5–10% of the cases and are usually due smoldering infections secondary to tuberculosis or fungus, thrombosis due to iatrogenic procedures like central venous or Swan-Ganz catheter or pacemaker leads.

Severity of the presenting complaints depends on the site of occlusion (site distal to azygos vein is more symptomatic than proximal) and the rate of onset of occlusion. If the occlusion is insidious onset then the collaterals effectively decompress the system and hence the symptoms are minimal. Collaterals include azygos, intercostal, mediastinal, paravertebral, hemiazygos, thoracoepigastric, internal mammary, thoracoacromioclavicular and anterior chest wall veins. Collaterals often take several weeks to dilate and accommodate the diverted blood from SVC. Clinically, the site of obstruction is at the level of SVC is identified by the above downward direction of flow in the collaterals both above and below the umbilicus. Patients present with symptoms of dyspnea, orthopnea, chest pain, hemoptysis, swelling of neck, upper limbs and face, dilated veins in the upper chest wall, headaches, confusion and rarely seizures due raised intra cranial tension. Radiologic examination with a contrast enhanced CT will identify the mass lesion and the presence of collaterals on CT is highly sensitive and specific for presence of SVCS.[39] If suspected, CT angiography can detect the site and extent of the thrombus.

Evaluation of these patients should be quick as they can deteriorate rapidly. Careful general examination should be carried out to look for peripheral lymphadenopathy as the access to such tissue is easier. Patients often have pleural effusions but these are often secondary to venous hypertension and are unlikely to yield the diagnosis but should be examined nonetheless. Patient's orthpnea may preclude image guided sampling of the mediastinal mass as these procedures require the patient to lie supine. Under such circumstances, endoscopic stenting of the SVC is the treatment of choice in relieving the symptoms when diagnosis is not established. Stenting provides near total relief of symptoms within 24–72 hours and subsequently the patient is able to undergo mediastinal sampling.[40] Once diagnosis is established, patients may undergo chemotherapy in cases of lung cancer and lymphoma or radiotherapy in cases small cell carcinoma of lung.

All patients should receive supportive care with oxygen supplementation, head end elevation, restriction of fluids and diuretics. Use of steroids before tissue diagnosis is established should be discouraged as it may lead to architectural distortion making subsequent biopsies difficult to interpret. Median life expectancy in patients with SVCS is approximately six months with a range of 1.5–9.5 months; however, estimates vary widely and are dependent on the underlying malignant condition.

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122

Diseases of Thoracic Cage

Balamugesh T

INTRODUCTION

The chest wall comprises of the rib cage, rib cage muscles and the diaphragm. Disorders involving the chest wall may ultimately affect ventilation and eventually lead to respiratory failure. The important nonmuscular conditions of the chest wall are briefly discussed.

KYPHOSCOLIOSIS

Kyphoscoliosis is a group of conditions in which the patients have scoliosis (lateral curvature of the spine) and kyphosis (backward curvature of spine) (Fig. 122.1). Based on the etiology, the curvature abnormalities can be considered in three groups:

1. *Congenital:* Neurofibromatosis, Friedreich's ataxia, muscular dystrophy, Ehlers-Danlos syndrome, Marfan's syndrome, etc.
2. Paralytic: Poliomyelitis, muscular dystrophy, cerebral palsy, Friedreich's ataxia
3. Idiopathic

Kyphoscoliosis is idiopathic in approximately 80% cases, with a female predominance (4:1).

The severity of kyphoscoliosis is determined radiologically using the Cobb angle. Two lines are drawn parallel to the upper border of the highest and the lower border of the lowest vertebral body of the curvature as seen on an anteroposterior radiograph of the spine respectively. The angle made by two lines drawn perpendicular to these lines at the intersection point is measured (Fig. 122.2). An angle of more than 10 degrees defines scoliosis, and of more than 100 degrees is indicative of severe scoliosis with a higher risk of progression to respiratory failure.

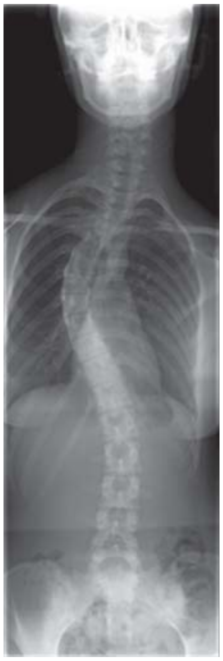

Fig. 122.1: X-ray spine showing scoliosis (Image courtesy: Dr Frank Gaillard, www.radiopedia.org, used with permission)

Pulmonary Function Tests

Predicted values for lung function in patients with kyphoscoliosis should be calculated on the basis of arm span measurements because of reduction in height due to spinal deformity.[1] Restrictive ventilatory pattern is seen in patients with severe kyphoscoliosis with

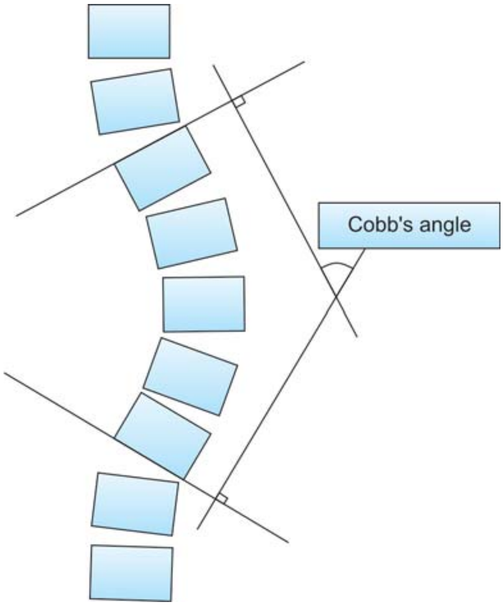

Fig. 122.2: Cobb's angle

reduction in vital capacity (VC) and total lung capacity (TLC).[2,3]This is due to reduction in chest wall compliance. In order to reduce the work of breathing, the patients adopt a pattern of rapid shallow breathing. This in turn leads to reduction in lung compliance due to micro-atelectasis and increases the dead space ventilation. Those with paralytic kyphoscoliosis have a pronounced reduction in inspiratory muscle strength and a greater reduction in VC. Even in those with Cobb's angle greater than 50°, there is significant reduction in inspiratory and expiratory muscle strength attributed to altered chest wall geometry and resultant mechanical disadvantage of the respiratory muscles.

Some patients have airway obstruction in addition to lung restriction; this is due to the presence of bronchial torsion and compression of the central airways.[4] The increase in oxygen cost of breathing may place these patients at a high risk of respiratory muscle fatigue. The residual volume (RV) is normal with an increase in RV/TLC ratio. Diffusing capacity for carbon monoxide (DLCO) is reduced in proportion to the reduction in lung volumes, giving normal values for transfer factor (KCO).[5] In some patients, DLCO is disproportionately reduced and is attributed to failure of alveolar development and pulmonary hypertension.[6] The maximum oxygen consumption during exercise is reduced. The neural drive for breathing as measured by mouth occlusion pressure at 100ms (P 0.1) is normal or increased. But the ventilatory response to carbon-dioxide (CO_2) is decreased due to the reduced mobility of the stiffened chest wall.[5]

Sleep Disordered Breathing

The most common abnormality in patients with kyphoscoliosis during sleep is hypoventilation. In awake state, the intercostal and accessory muscles are recruited to assist the diaphragm in displacing the stiff chest wall. When sleeping, these patients may hypoventilate due to hypotonia of the intercostal and accessory muscles and decreased neural drive to diaphragm.[7] Since the chest wall movement is compromised, any degree of diaphragmatic dysfunction can aggravate hypoventilation during sleep. Untreated nocturnal desaturation can further worsen the respiratory muscle function leading to respiratory failure and cor pulmonale. The prevalence of obstructive sleep apnea is the same as in the general population, but if present, can further worsen the nocturnal hypoventilation.[8]

Prognosis

Prognosis is worse in those with a greater Cobb's angle and curvature at a higher level in the spine. In congenital and paralytic kyphoscoliosis, there can be progressive worsening skeletal deformity leading to respiratory failure. Individuals with idiopathic kyphoscoliosis have a more benign course. Once cor pulmonale develops, there is a rapid downhill course unless the treatment is started. Death usually occurs as a result of respiratory failure or cardiac diseases and the risks are high in juvenile and post polio scoliosis patients.[9] Pregnancy is poorly tolerated if the VC is less than 1 liter.

Medical Management

General measures include immunization against pneumococcal and influenza infections, prompt treatment of respiratory infections, smoking cessation, avoidance of sedatives, maintenance of ideal body weight and prevention of physical deconditioning by exercise. Supplemental oxygen may be required during activity or exercise.

Specific treatment of nocturnal hypoventilation whenever indicated, is provided by non-invasive positive pressure ventilation using a nasal or full-face mask (Table 122.1). Volume-preset and pressure-preset ventilators have equivalent physiological benefits.

The benefits of noninvasive nocturnal ventilation in patients with kyphoscoliosis include the improvements in quality of life, gas exchange, sleep architecture; and a reduction in pulmonary artery pressure.[11,12,13] Long-term noninvasive ventilation also reduces the number of hospitalizations due to respiratory failure. There are no remarkable changes in VC and respiratory muscle strength. The improvement in respiratory failure is due

TABLE 122.1: Indication for NIV[10]

Symptoms (e.g. fatigue, morning headaches, dyspnea)
OR
Signs of cor pulmonale
AND one of the following:

1. Daytime arterial $PCO_2 \geq 45$ mm Hg
2. Nocturnal oxygen saturation ≤ 88% for five consecutive minutes
3. Progressive neuromuscular disease with maximal inspiratory pressure (Pimax) <60 cm H_2O or FVC <50% of predicted

to increased ventilatory response to CO_2, prevention of respiratory muscle fatigue and reversal of microatelectasis. Negative pressure ventilation by cuirass, body wrap ventilators, or tank ventilators can aggravate upper airway obstruction during sleep and is usually not recommended.

Surgery for Kyphoscoliosis

Surgery plays an important role in those with kyphoscoliosis secondary to neurological disorders among children and adolescents.[14] Operative treatment traditionally consists of spinal fusion and/or insertion of Harrington rods, which may result in short term improvement of lung function. However, surgery can sometimes result in chronic back pain or further spinal deformities. Initial results of further refinements in surgical techniques are promising.[15]

Thoracoplasty

Thoracoplasty is a surgical technique that was used to collapse the lungs affected by tuberculosis, prior to the advent of antitubercular drugs (Fig. 122.3). It consists of various combinations of rib removal, artificial pneumothorax, phrenic nerve resection and compression of lung by insertion of foreign material. The patients who undergo thoracoplasty subsequently develop restrictive lung disease and chronic respiratory failure, as their age advances.

The severity of dysfunction is related to the number of ribs removed, presence of fibrothorax, degree of fibrosis of the underlying lung, phrenic nerve damage and the degree of scoliosis. There are significant associations between the development of cardiorespiratory or respiratory failure and factors such as the preoperative contralateral artificial pneumothorax, older age at operation, the presence of cavities before operation, and male sex.[16] Currently, thoracoplasty is used in rare situations such as post pneumonectomy complications, persistent tubercular bronchopleural fistula and sputum positive drug resistant tuberculosis.[17]

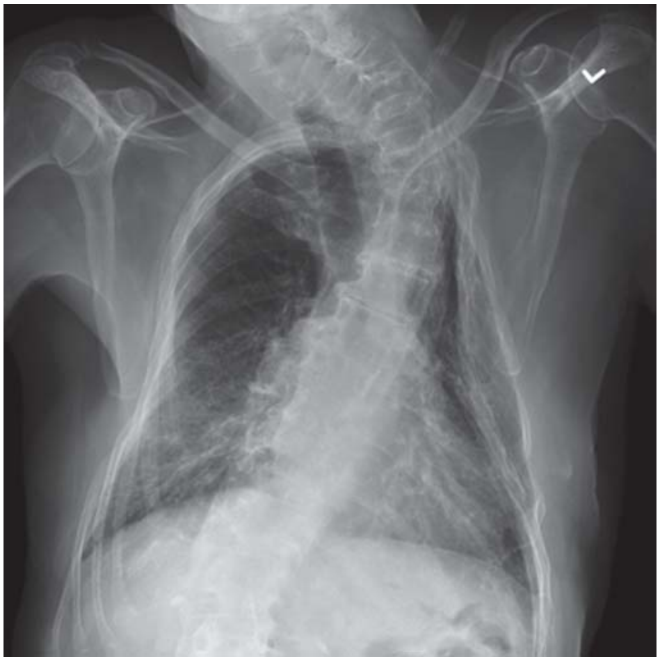

Fig. 122.3: Thoracoplasy (*Courtesy:* Dr. Frank Gaillard, www.radiopedia.org, used with permission)

In a series of 139 patients who underwent thoracoplasty in India, the indications for surgery were: Tubercular empyema (84 patients), pyogenic empyema (33 patients), postoperative empyema with bronchopleural fistula (8 patients), drug resistant pulmonary tuberculosis (2 patients) and recurrent hemoptysis (2 patients).[18] Successful outcome, i.e. the control of sepsis, closure of bronchopleural fistula, sputum conversion and control of hemoptysis, was achieved in the majority of patients. There were four deaths in the entire series. Thoracoplasty is therefore, still relevant in the developing countries where pulmonary tuberculosis continues to pose a challenging and persisting problem. In a recent series of 37 patients who underwent thoracoplasty and intrathoracic muscle transposition, the commonest indication was post pneumonectomy/lobectomy empyema.[19] Treatment of respiratory failure in post-thoracoplasty patients is the same as for those with kyphoscoliosis.[19]

PECTUS EXCAVATUM

Pectus excavatum, also known as "funnel chest", is characterized by excessive depression of sternum. It is the most common chest deformity seen by pediatricians. It is present in 0.4% of school children, more common among boys than girls.[20] The etiology is not clear, but a defect in the connective tissue surrounding the sternum and imbalance of forces counteracting the inward pull

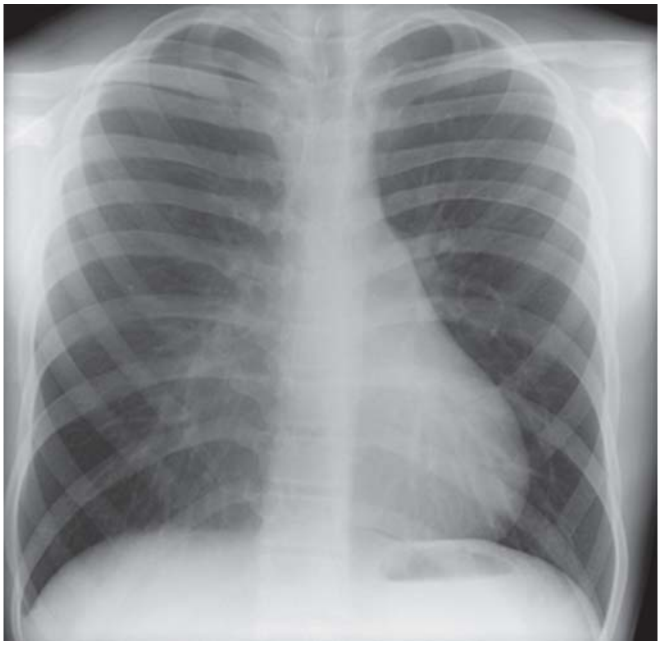

Fig. 122.4: Pectus excavatum: Chest radiograph PA view – Right paracardiac opacity due to parasternal soft tissue, could be mistaken for middle lobe infiltrate. (Image courtesy: Dr. Frank Gaillard, www.radiopedia.org, used with permission)

of diaphragm on xiphisternum during development has been implicated.[21] Upper airway obstruction due to enlarged tonsils and adenoids predisposes to pectus excavatum.[22] Marfan's syndrome is associated with a high incidence of pectus excavatum. Incidence of congenital heart disease is also higher among those with pectus excavatum.

Most individuals with pectus excavatum remain asymptomatic, but for their cosmetic appearances. Dyspnea, out of proportion to the mild restrictive ventilatory defect may be seen. Majority of them have cardiac murmurs mimicking pulmonary stenosis caused by cardiac displacement. Chest radiographs frequently show a right paracardiac opacity due to parasternal soft tissues and should not be mistaken for middle lobe infiltration (Fig. 122.4).[20] Similarly, electrocardiogram may show abnormalities such as T-wave inversion in right chest leads, right axis deviation, P wave inversion in V1 and a QR pattern.[23]

More than 3 cm distance between anterior chest wall and the sternal depression and less than 10 cm distance between the posterior border of the sternum and the anterior border of the thoracic vertebra as seen on the lateral chest radiographs suggest severe deformity (Fig. 122.5). The degree of the deformity is measured by the computerized tomography scan as the ratio of transverse to anteroposterior diameter at the level of deepest sternal depression (Fig. 122.6). A ratio of more that 3.25 is considered to be severe excavatum.

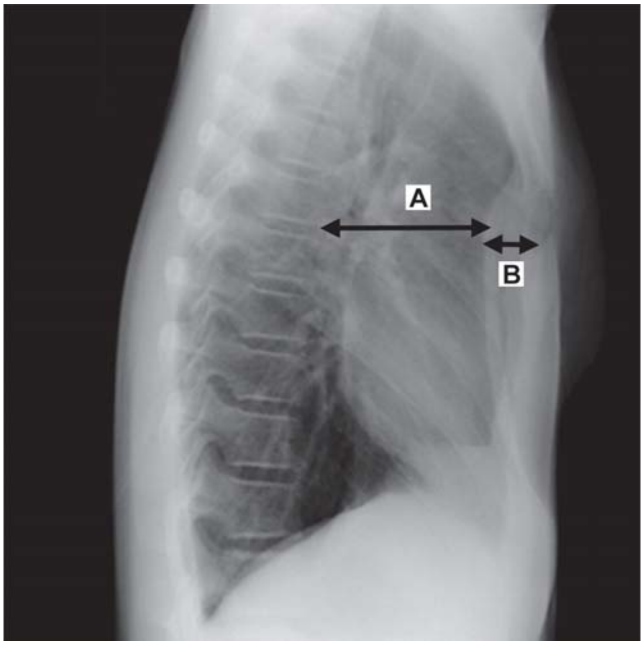

Fig. 122.5: Pectus excavatum: Chest radiograph—lateral view, < 10 cm distance between the posterior border of the sternum and the anterior border of the thoracic vertebra (A) and > 3 cm distance between anterior chest wall and the sternal depression. (B) suggests severe deformity (*Courtesy:* Dr Frank Gaillard, www.radiopedia.org, used with permission)

Pulmonary function tests are usually normal or mildly reduced in those with severe excavatum.[24,25] The reduced exercise tolerance out of proportion to lung function, can be attributed to reduced venous return secondary to right ventricular compression by the depressed sternum.

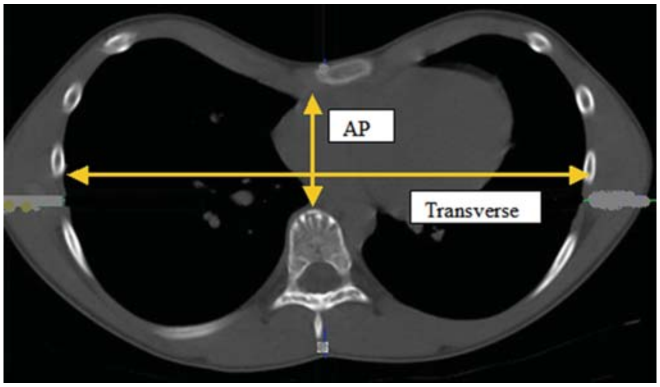

Fig. 122.6: Pectum excavatum: Ratio of transverse to anteroposterior diameter at the level of deepest sternal depression more than 3.25 suggests severe deformity

Patients with minimal deformity can benefit from a program of physical therapy to improve posture and the appearance of the chest. Surgery is necessary only in severe situations or for cosmetic purposes. The earlier surgeries like the Ravitch repair are associated with many complications.[26] Less invasive procedures like the Nuss procedure and sternochondroplasty, which were developed in the last decade, are relatively safer.[27,28] In the Nuss procedure, a curved bar is inserted behind the sternum to displace the sternum ventrally. These procedures are not always associated with improvement in pulmonary function or exercise capacity.

PECTUS CARINATUM

In this condition (also called "pigeon breast"), the sternum excessively protrudes anteriorly. It may be associated with other congenital anomalies especially cardiac lesions and coarctation of aorta.[29] Pectus carinatum may result from premature obliteration of the sternal sutures due to inadequate segmentation during fetal life or due to mal-attachment of diaphragm.[30] There is no functional defect with pectus carinatum and surgery is indicated only for cosmetic reasons.

ANKYLOSING SPONDYLOSIS

Ankylosing spondylosis (AS) belongs to a group of conditions having a strong association with HLA-B27 in which there is an inflammation of the axial skeleton. There is inflammation and bony ankylosis of vertebral structures, costovertebral and sternoclavicular joints, which leads to reduction in chest expansion. Chest expansion of less than 2.5 cm in a young adult at the level of fourth intercostal space along with back pain should raise the suspicion of AS. Exercise intolerance and dyspnea are uncommon, unless there is associated underlying lung fibrosis, diaphragmatic dysfunction or cardiac disease.

There is reduction in VC and TLC respectively to 70 and 80% of the predicted value. Since the rib cage is fixed during inspiration, the RV is increased leading to an increase in RV/TLC ratio.[31] Modest decrease in respiratory muscle strength is observed and it is attributed to the intercostal muscle atrophy, secondary to reduced rib cage mobility. About 1 to 4% of patients, especially men with chronic disease, develop fibrobullous upper lobe disease.[32] Apical fibrosis can be detected on high resolution computed tomography (CT) scan in about 90% patients.[33] The cause of apical fibrobullous changes is unknown. Various theories have been postulated which include diminished upper lobe ventilation due to chest wall rigidity, altered apical mechanical stress due to rigid thoracic spine, recurrent pulmonary infection due to impaired cough, and respiratory mechanics as a result of thoracic rigidity.[34] Aspergillomas may form in the cavities or bullae. Other rare complications include pleural effusion, pneumothorax, airway obstruction by cricoarytenoid joint ankylosis and amyloidosis of the lung.[35-37]

Treatment is focused on symptom relief and maintenance of posture and mobility. Physiotherapy to improve chest wall movements and breathing exercises are important. Use of tumor necrosis factor (TNF) antagonists have recently revolutionized the management of patients with AS.[38]

OBESITY

The prevalence of obesity is increasing worldwide. The body mass index (BMI) is positively associated with morbidity and mortality. An individual with a BMI between 18.5 and 24.9 kg/m^2 is normal; a BMI between 25 and 29.9 kg/m^2 is overweight, and a BMI greater than 30 kg/m^2 is obese. Those having a BMI of greater than 40 kg/m^2 (morbid obesity) are especially predisposed towards developing restrictive lung disease. Some investigators have concluded that Indians are more predisposed to develop obesity related complications due to their different body, genetic and metabolic composition.[39] According to the new guidelines released by the Union Health Ministry of India, a person having a BMI greater than 23 kg/m^2 would be considered overweight.[40]

The respiratory morbidity due to obesity can be considered under the following three categories:

1. Simple obesity (SO) with minimal effects on respiration,
2. Morbid obesity (MO) with eucapnic individuals having compromised pulmonary function, and
3. Obesity hypoventilation syndrome (OHS) with hypercapnia during the awake state. Obstructive sleep apnea can coexist with any of these conditions.

Pulmonary Function Tests

Forced vital capacity (FVC) and TLC are usually preserved in SO, but reduced in OHS. The fat in the chest wall and abdomen causes reduction in functional reserve capacity (FRC) with near normal RV (Fig. 122.7). This results in markedly reduced expiratory reserve volume

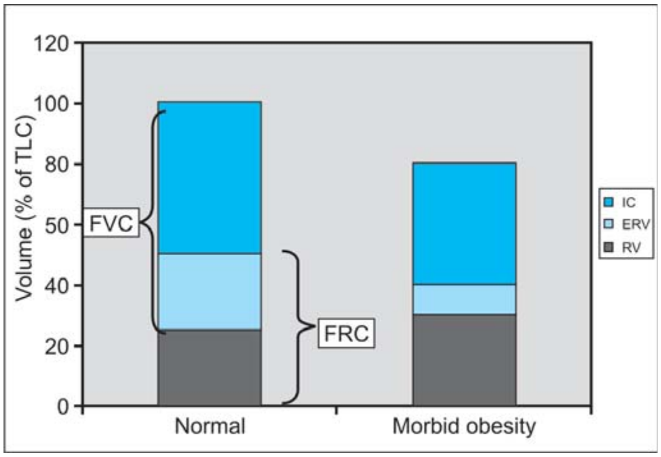

Fig. 122.7: Pulmonary function changes in obesity: Reduction in ERV with preservation of RV, Reduction in FVC

(ERV).[41] Similar degrees of obesity in SO and OHS can cause much more reduction in ERV in OHS due to difference in distribution of body fat. Even if FEV1/FVC ratio is normal, the specific conductance of airways is reduced to 50 to 70%, which is more evident in the supine position.[42] The cause of increased airway resistance in obesity appears to lie in the lung tissue and small airways rather than in the large airways. This leads to expiratory flow limitation and orthopnea.

Patients with OHS adapt to increased elastic and resistive loads by adopting rapid, shallow breathing pattern. The work of breathing and oxygen cost of breathing are markedly increased in OHS.[43] The increased oxygen consumption required for quiet breathing might place obese patients at risk of respiratory failure during conditions characterized by increased ventilatory demands, such as an intercurrent illness. Respiratory muscle strength is preserved in SO, but reduced in OHS due to deconditioning and fatty infiltration of muscles. This, along with disordered respiratory control and blunted respiratory drive, contribute to hypercapnia in OHS.

Severely obese patients tend to have a widened alveolar-arterial oxygen tension gradient and hypoxia. The mechanism responsible for hypoxemia is primarily a ventilation-perfusion mismatch that results from airway closure.[44] Hypoxia is also contributed by hypoventilation and venous admixture occurring in lung bases due to alveolar collapse.[45]

Treatment

Weight loss induced by either diet or surgery helps in improvement of ERV and hypoxia in patients with OHS. However, there is difficulty in losing weight and maintaining it in the majority of patients. In patients with OHS, noninvasive ventilation helps in improving gas exchange and daytime symptoms.

FLAIL CHEST

This is a condition in which fractures of ribs produce a segment of rib cage that moves paradoxically during respiration. Generally, double fractures of three or more contiguous ribs or a combination of sternal and rib fractures are required to produce a flail segment. The most common cause of flail chest is trauma due to fall or due to automobile accidents. Rarely, pathological fractures of ribs can cause a flail segment. During inspiration, the negative intrapleural pressure causes the flail segment to get displaced inward instead of expanding outward (Figs 122.8A and B). The most common site of flail segment is lateral chest wall, posteriorly. Respiratory failure caused by flail chest has a multifactorial etiology:

- Hypoventilation caused by paradoxical movement of flail segment and restricted chest wall movements due to pain. The VC and FRC may be reduced to 50% of the predicted value.
- Regional atelectasis caused by ineffective cough reflex and hypoventilation.
- Pulmonary contusion, hemothorax or pneumothorax, which is frequently associated with flail chest.
- Inspiratory muscle dysfunction due to muscle spasm and altered recruitment pattern causing increased work of breathing.

Treatment consists of adequate pain relief to prevent atelectasis and improve tidal volume. It can be achieved with medications, intercostal nerve blocks and epidural anesthesia. Stabilizing the flail segment by external strappings is not very successful. Positive pressure ventilation can provide effective stabilization by eliminating the negative intrapleural pressure. Earlier, mechanical ventilation was used for providing the ventilation. More recently, noninvasive continuous positive airway ventilation together with regional anesthesia has been found to reduce morbidity and avoid complications.[46] In case of severe injuries, a variety of surgical procedures have been described for fracture fixation and improvement of respiratory mechanics.

MISCELLANEOUS CONDITIONS

Cervical Ribs

Cervical ribs occur in about 0.5% of the population.[47] They arise from the seventh cervical vertebra and are

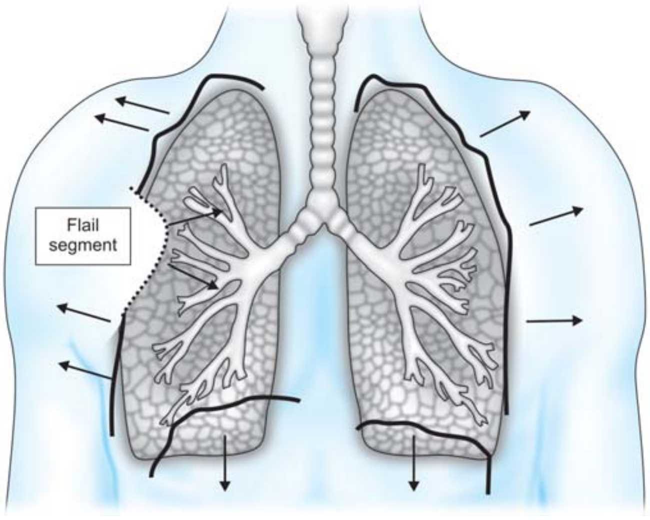

Fig. 122.8A: During inspiration the flail segment paradoxically moves inwards

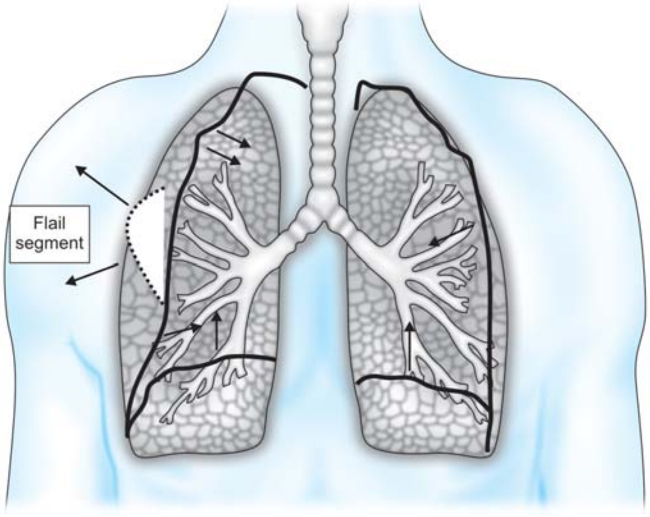

Fig. 122.8B: During expiration the flail segment moves outwards

bilateral in 80% cases (Fig. 122.9).[48,49] They are usually asymptomatic, but rarely can cause thoracic outlet syndrome due to compression of subclavian vessels or cervical nerve roots. The presence of symptoms is not dependent on the size of the rib, since the fibrous attachment itself may cause compression. While the neurological complications can be managed by shoulder muscle strengthening exercises, rib resection may be required to address the vascular complications.

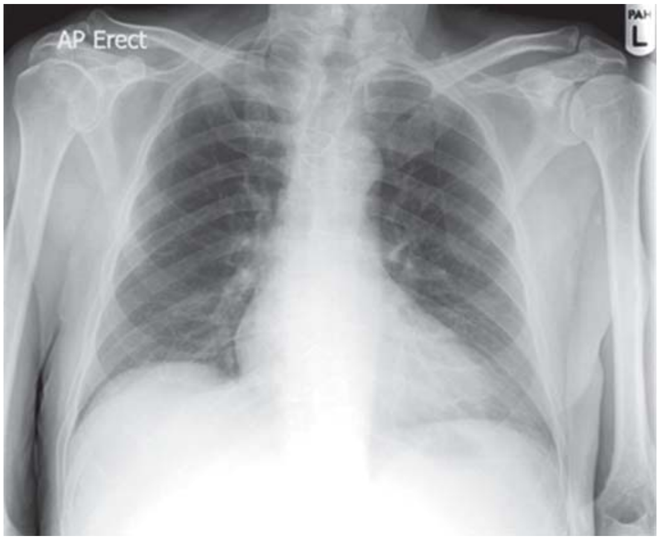

Fig. 122.9: Right cervical rib (Image courtesy: Dr Jeremy Jones, www.radiopedia.org, used with permission)

Tietze's Syndrome or Costochondritis

The etiology of this condition is unknown. It presents with pain and swelling of one or more of the upper six costal cartilages. It is more common in young adults with no sex predisposition and predominately affects the second costal cartilage. Coughing or deep breathing may exacerbate the pain. The condition may persist for weeks, months or years. Biopsy may show normal cartilage and there are no X-ray changes.[50] Ultrasonography shows thickened cartilage with inhomogeneously increased echogenicity, and hypoechoic halo, while CT scan may reveal thickened hypodense cartilage with blurred outline.[51,52] Recently, magnetic resonance imaging has been claimed to be the investigation of choice to reveal cartilage and bone abnormalities.[53] The main treatment consists of reassurance with or without administration of analgesics, to which the majority of patients respond. In those with severe pain, local steroid injection may be required.

Rib Notching

Erosion of the inferior border of ribs (inferior rib notching) is most commonly seen in patients with coarctation of aorta. It is due to the enlarged intercostal arteries, which through their pulsation cause erosion of ribs. The first two and the last three ribs are never involved.[54] Other causes of rib notching include subclavian artery obstruction, Takayasu's arteritis, pulmonary arteriovenous fistula and intercostal neuroma. Superior notching of third to sixth ribs is reported in patients with poliomyelitis and in those with connective tissue disorders.[55]

Tumors of the Chest Wall

Metastatic tumors of the chest wall are more common that the primary tumors. Lipoma and fibrosarcoma are the most common benign and malignant soft tissue tumors of the chest wall respectively. Osteochondroma and chondrosarcoma are the most common benign and malignant tumors of the bony thoracic skeleton respectively.

Tuberculosis of the Thoracic Cage

Costal cartilages, sternoclavicular and acromioclavicular joints can rarely be involved by tuberculosis. Multiple lesions of the costovertebral portions of the ribs may accompany tuberculosis of the spine with paravertebral abscess formation.

Cold abscess of the chest wall, which originates from tuberculosis of the intercostal lymph glands can be present at three sites:

1. Near the erector spinae muscles when pus tracks along the posterior primary division of the intercostal nerve;
2. Lateral chest wall, when pus tracks along the anterior division; and
3. Near costal cartilages.

Cold abscess commonly presents as a painless fluctuant swelling. Diagnosis is made by aspiration of the pus. Generally, it responds well to standard antitubercular chemotherapy.

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123

Diseases of Diaphragm

Balamugesh T

INTRODUCTION

The diaphragm is a musculotendinous sheet that separates the thoracic and abdominal contents into two compartments. It has three anatomic components:

1. Sternal portion: Arising from the xiphoid process of sternum
2. Costal portion: Arising from lower six ribs
3. Crural portion: Arising from external and internal arcuate ligaments and attaching to vertebrae.

The muscle fibers from all these three components insert into the boomerang-shaped central tendon.

Excursion of the diaphragm is estimated to account for 60 to 75% of vital capacity, the remaining being contributed by the intercostal and accessory muscles.[1] During quiet respiration, the mean right and left hemidiaphragmatic excursions are 53 ± 16 mm and 46 ± 12 mm, respectively.[2]

The diaphragm receives its nerve supply solely from the phrenic nerve, which originates predominantly from the fourth cervical ramus with contributions from the third and the fifth ramus. Any damage to the phrenic nerve along its long course through the neck and mediastinum can affect its function.

Causes of Diaphragmatic Disorders

The causes of diaphragmatic disorders can be classified based on anatomical and neurological causes.

1. *Anatomical*
    a. Congenital: Bochdalek hernia, Morgagni hernia, eventration of the diaphragm and diaphragmatic agenesis
    b. Acquired: Traumatic.
2. *Neurological*
    a. Central nervous system: Brain stem stroke
    b. Spinal cord: Syringomyelia, anterior horn cell diseases, poliomyelitis, Arnold-Chiari malformation, tetanus, Strychnine poisoning.
    c. Nerves: Guillain–Barré syndrome, neuropathy due to variety of causes, invasion of phrenic nerve by neoplasm (most common cause), damage to nerve by surgery or trauma, infectious neuritis (e.g. herpes zoster).
    d. Muscles: Myasthenia Gravis, myopathy (muscular dystrophy, Duchenne muscular dystrophy, metabolic myopathy, connective tissue disorders (e.g. polymyositis, “shrinking lung syndrome” in SLE), acid maltase deficiency, etc.

Signs and Symptoms

The onset of presentation depends greatly on the etiology causing diaphragmatic dysfunction. Unilateral diaphragmatic paralysis is generally asymptomatic. Exertional dyspnea is present, when there is concomitant pulmonary parenchymal or airway disease. Bilateral diaphragmatic paralysis presents with severe exertional dyspnea and orthopnea. Poor quality sleep and day-time fatigue are also frequent.

Physical examination may reveal rapid shallow breathing. There may be paradoxical abdominal wall retraction during inspiration. Percussion may suggest a raised diaphragm and reduced diaphragmatic excursion during inspiration. The intensity of breath sounds may be reduced on the affected side, upon auscultation. The compressed lung may give rise to crackles, just above the area of paralyzed diaphragm.

Diagnosis

Chest Radiography

Posteroanterior radiographs show the dome of right hemidiaphragm projecting into a plane ranging from the anterior end of the fifth rib to the sixth anterior interspace in about 95% of normal individuals.[3] In most people, the right hemidiaphragm projects half an interspace higher than the left, being at the same level as or lower than the left hemidiaphragm in only about 10% cases.[4] Diaphragmatic paralysis manifests in the form of an elevated hemidiaphragm. Linear atelectasis may be present at the lung bases. Chest X-ray may also reveal a thoracic mass lesion, which is responsible for phrenic nerve paralysis or a congenital diaphragmatic hernia.

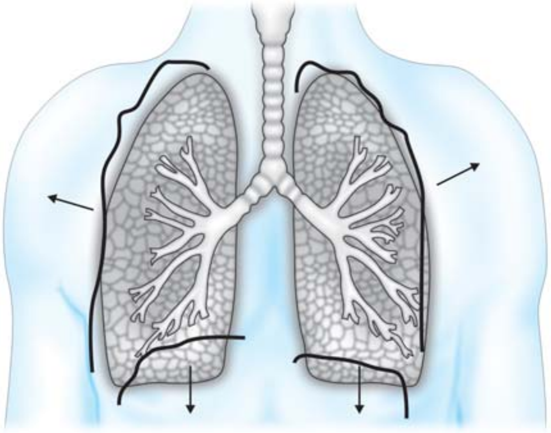

Fig. 123.1A: Normal inspiration. Chest wall moves outwards and diaphragm moves downwards

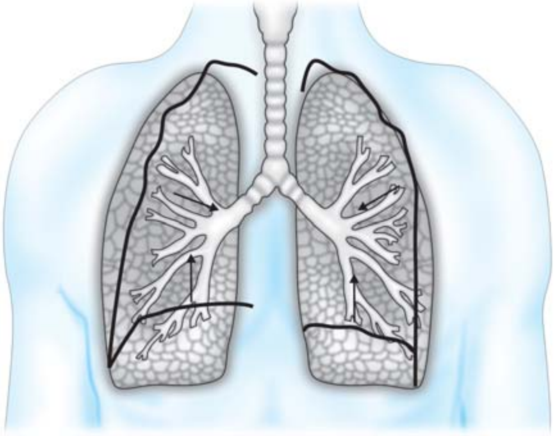

Fig. 123.1B: Normal expiration. Chest wall moves inwards and diaphragm moves upwards

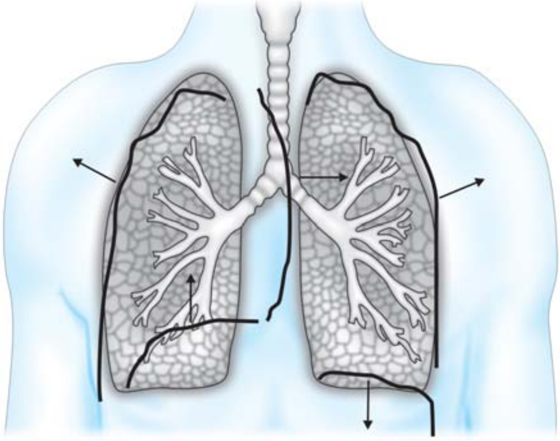

Fig. 123.1C: Right diaphragmatic palsy during inspiration: Paralyzed right diaphragm passively elevates in response to the more negative intrapleural pressure. The mediastinum shifts towards left

Fluoroscopy

Paradoxical upward movement of diaphragm by more than 2 cm on deep inspiratory effort against a closed airway ("sniff test") is suggestive of diaphragmatic paralysis.[5] However, in 6% of normal population, this can be found without any apparent reason. The cephalad movement of the paralyzed diaphragm during inspiration is accompanied by the outwards chest wall and the inwards abdominal wall motion, a phenomenon known as *thoracoabdominal paradox*.[6] Mediastinal swing found during respiration can be found in unilateral diaphragmatic palsy. In bilateral paralysis, sniff test may be misleading because of the cephalad movement of ribs, which may produce a false appearance of downward movement of diaphragm. Also, recruitment of abdominal expiratory muscles can cause a false-negative sniff test result. The movement of the diaphragm in normal, unilateral and bilateral diaphragmatic palsy can be schematically depicted (Figs 123.10 A to H).

Other Imaging Methods

Ultrasound scanning has been found to be more reliable than fluoroscopy in the evaluation of diaphragmatic movements. Ultrasound measurement of the thickness of the diaphragm can be used to determine if the diaphragm is paralyzed.[7] Computed tomography (CT) scan is helpful for identifying the presence of any mass lesion along the course of phrenic nerve causing the paralysis.

Pulmonary Function Tests

Restrictive ventilation defect is seen in patients with diaphragmatic paralysis. In unilateral paralysis, forced

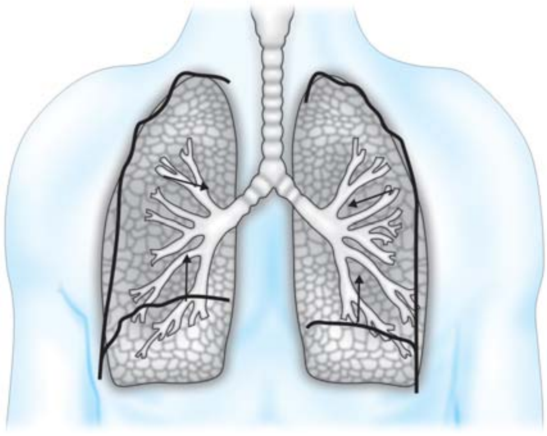

Fig. 123.1D: Right diaphragmatic palsy during expiration: On full expiration, a rise in intra-abdominal pressure evokes an even greater elevation

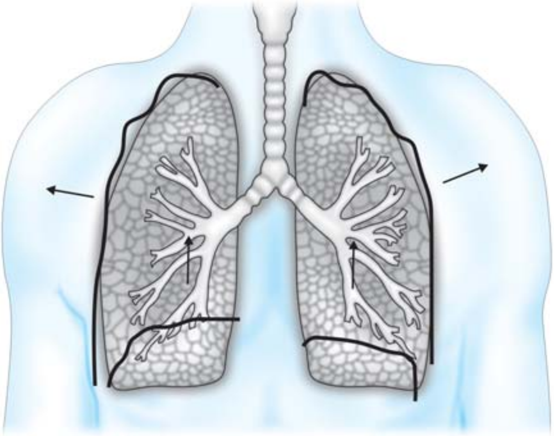

Fig. 123.1E: Bilateral diaphragmatic palsy on inspiration: On inspiration, the increased negative intrapleural pressure "sucks" both the diaphragms up and draws the abdominal wall in

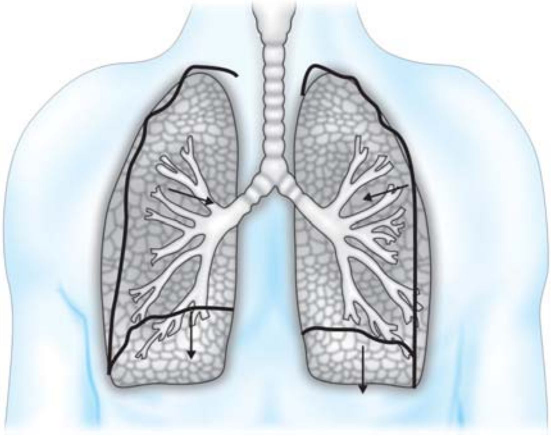

Fig. 123.1F: Bilateral diaphragmatic palsy on expiration to functional residual capacity (FRC): Diaphragm descends and the abdomen protrudes

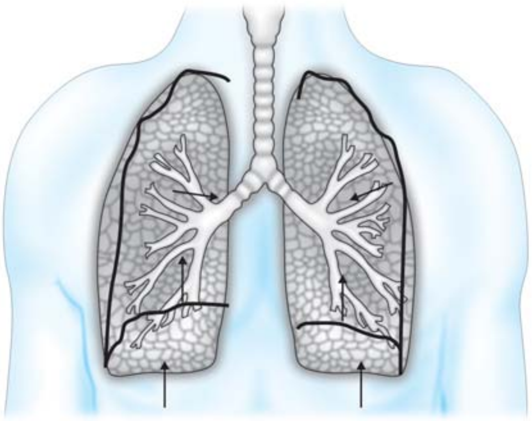

Fig. 123.1G: Bilateral diaphragmatic palsy on expiration to RV: On deeper expiration, there is active contraction of abdominal muscles and the diaphragm rises

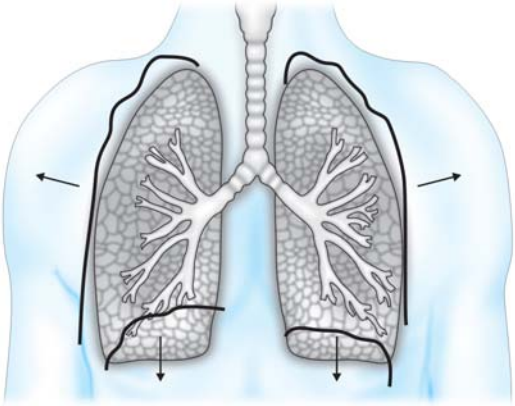

Fig. 123.1H: Bilateral diaphragmatic palsy early inspiration to FRC: Abdominal muscles relax associated with descent of the flaccid diaphragm, creating the false impression of active contraction

vital capacity (FVC) is reduced to about 75% of the predicted value, and the total lung capacity (TLC) is about 85% of predicted.[8] A 10% decrease in vital capacity (VC) in the supine position is typically present in normal individuals. In unilateral diaphragmatic weakness, the fall in VC is much more pronounced in supine position.[9] The maximal inspiratory pressure ($P_{I\text{-max}}$) decreases to a value of 60% predicted.[10] In patients with bilateral diaphragmatic paralysis, FVC is reduced by 50% and TLC by 55%.[11] The $P_{I\text{-max}}$ is less than 60 cm water.

Electrophysiological Studies

Phrenic nerve conduction studies are useful for detecting neurological causes of paralysis. Electromyograph of diaphragm and phrenic nerve stimulation studies help in the diagnosis of myopathic conditions involving the diaphragm.

Transdiaphragmatic pressure measurements can accurately quantify the degree of diaphragmatic weakness by measuring the difference between intragastric and intrapleural pressure. During normal inspiration, gastric pressure becomes more positive and esophageal pressure becomes more negative. In unilateral diaphragmatic paralysis, gastric pressure becomes more negative during inspiration, although to a lesser extent than the negative swing in esophageal pressure. In bilateral diaphragmatic paralysis, during tidal breathing, gastric pressure decreases to the same extent as esophageal pressure, resulting in no active transdiaphragmatic pressure generation.[12]

Management

Treatment of diaphragmatic dysfunction depends on the etiology. Surgery is indicated in the management of anatomic defects of the diaphragm. Most patients with bilateral diaphragmatic paralysis ultimately develop progressive ventilatory failure resulting from fatigue of the accessory muscles. These patients usually require non-invasive ventilation. Indications for non-invasive ventilation in neuromuscular disease are described in table 123.1.[13]

Phrenic nerve or diaphragmatic pacing are useful treatment modalities when the phrenic nerve is intact and the problem lies in the actual transmission of nerve impulse.[14]

Disorders of the Structure of Diaphragm

Eventration of Diaphragm

Eventration is a condition in which all or part of the diaphragm is largely composed of fibrous tissue with only a few interspersed muscle fibers. It is usually congenital. Complete eventration mostly occurs on the left side and is characterized by the elevation of left diaphragm. This hemidiaphragm may move paradoxically during "sniff test". The adult patients are usually asymptomatic, but occasionally they have dyspeptic symptoms. Dyspnea is common if eventration is associated with other lung diseases. In infants, eventration may occur on either side and can give rise to severe respiratory distress. Plication of the diaphragm is performed to keep the diaphragm in its normal position.[15]

TABLE 123.1: Indications for noninvasive ventilation in neuromuscular disease

Optimal non-ventilatory therapy of symptoms
and
Gas exchange abnormalities, which can be one of the following:

- Daytime hypercapnia ($pCO_2 > 45$)
- Nocturnal hypoventilation (O_2 sat < 88% for > 5 consecutive minutes)
- FVC < 50% predicted or maximal inspiratory procedure < 60% predicted

Other possible indications: Repeated hospitalizations for respiratory failure, and cor pulmonale.

Partial eventration occurs exclusively on the right side. It manifests as an anteromedial bulge of the diaphragm that moves downwards during inspiration with normal portions of the hemidiaphragm, but with some delay.[16] There is usually an accessory lobe of liver, which occupies the bulge.[17]

Diaphragmatic Hernias

It can present at various sites of the diaphragm (Fig. 123.2):

1. *Hiatus hernia:* Herniation through the esophageal hiatus is the most common type of diaphragmatic hernia. It may predispose to gastroesophageal reflux disease and can appear as a retrocardiac opacity with a fluid level on chest radiograph (Figs 123.3A and B).
2. *Bochdalek hernia:* The hernia is at the posterolateral part of the diaphragm and is the most common site for congenital diaphragmatic hernia.[18] The majority of patients present with respiratory distress immediately after birth. The mortality rate is 45 to 50%. It is more common on the left side and may be

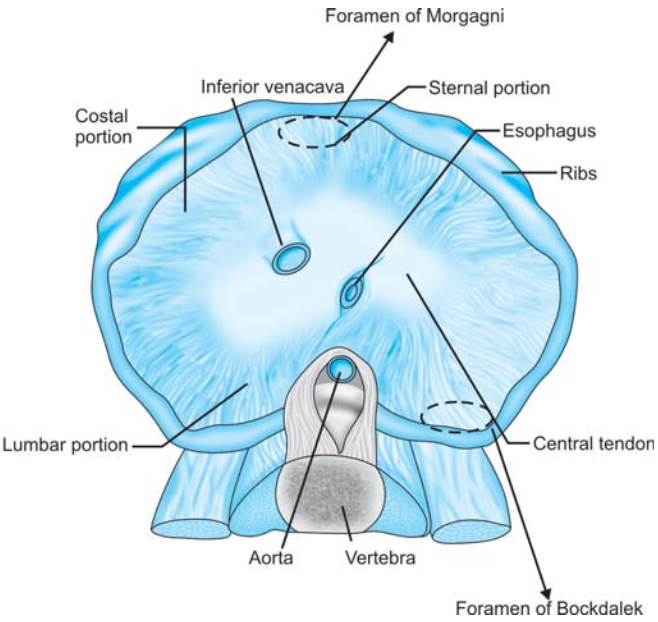

Fig. 123.2: Anatomy of diaphragm viewed from below

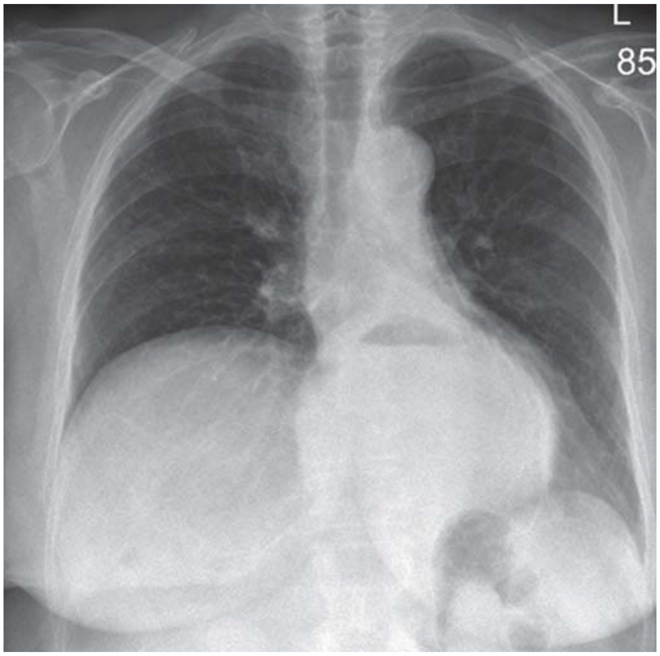

Fig. 123.3A: Hiatus hernia. Chest radiograph showing retrocardiac fluid level

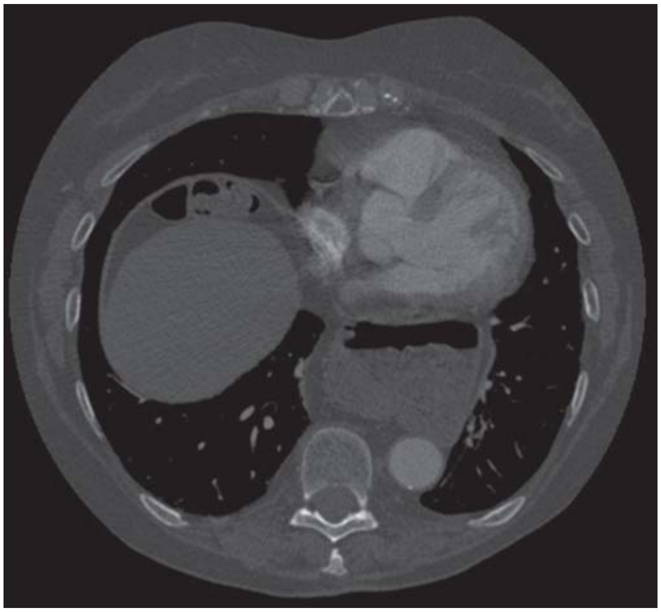

Fig. 123.3B: CT scan of the same patient showing stomach in the posterior mediastinum

associated with central nervous system anomalies and lung hypoplasia. X-ray examination reveals absence of diaphragm on the affected side and presence of abdominal contents in the thorax (Fig. 123.4). Presentation in adulthood is uncommon.[19]

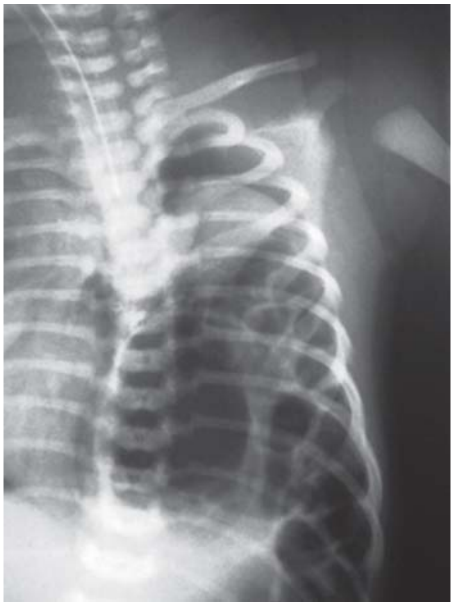

Fig. 123.4: Congenital diaphragmatic hernia. Absent diaphragm on the left side with presence of abdominal contents in the thorax. (Image courtesy: Dr Pradeep A Wijayagoonawardana, www.radiopedia.org, used with permission)

3. *Morgagni hernia:* Foramen of Morgagni is present anteromedially and is usually filled with loose connective tissue, but abdominal contents may herniate through the foramen, more commonly on the right (Fig. 123.2). Presentation in childhood is rare.[20] Chest X-ray shows as a rounded opacity in the cardiophrenic angle that may or may not contain gas.

Post-polio Syndrome (PPS)

Post-polio syndrome is a neurological disorder that produces a cluster of symptoms occurring in 22 to 64% of patients, 30–50 years after an attack of acute paralytic poliomyelitis.[21] The symptoms include the presence of progressive weakness, fatigue and less commonly muscle atrophy; breathing and swallowing difficulties; and sleep disorders. The criteria for diagnosis of PPS include documentation of paralytic polio, partial recovery of function followed by a period of stabilization, and progressive neurological deterioration.[22]

Respiratory insufficiency, which occurs in about 40%, is more common in those who had respiratory failure during the acute stage.[23] It usually results from respiratory muscle weakness with central hypoventilation and scoliosis.[24] Risk factors, which contribute to PPS, include severe initial episode, older age at initial episode, greater recovery from the first episode and over use of muscles.[25,26] Initially, respiratory failure manifests as nocturnal hypoventilation and then it progresses. Electromyography and muscle biopsy may show characteristic findings. The etiology is unknown, although premature exhaustion of the new sprouts that develop after acute poliomyelitis and of their motor neurons are important factors.[27] Other possible contributory factors include persistent poliovirus infection and an immune-mediated process. Treatment is primarily supportive and includes noninvasive ventilation, when required. Non-fatiguing strengthening exercises can improve strength and provide short-term benefit.

Syndromes of Inappropriate Respiratory Muscle Contraction

These disorders share some common features like inappropriate timing, asynchronous activity, or excessive contraction of respiratory muscles (Table 123.2).

1. *Hiccups:* Hiccups are produced by short, sharp contractions of the diaphragm and inspiratory intercostal muscles, coupled with transient closure to the glottis, which can occur upto 10 to 30 times per minute.[28]

Causes

a. Central nervous system: Multiple sclerosis, meningitis, encephalitis, cerebrovascular causes, brain tumor, post cranial surgery
b. Metabolic: Uremia, hyponatremia
c. Drugs: Alcohol intoxication, dexamethasone
d. Nerve irritation (vagus or phrenic nerve): Herpes zoster infection, inflammatory or neoplastic lesions of the mediastinum
e. Gastrointestinal: Esophageal irritation (neoplasm/ stent/ infection), stimulation of the diaphragm and/ or stomach by heat, cold, spasm, dilation, and distention.

TABLE 123.2: Syndromes of inappropriate respiratory muscle contraction

Syndrome	*Type of respiratory muscle involvement*
Hiccups	Spasmodic contraction of diaphragm and other inspiratory muscles
Respiratory myoclonus (tic, flutter of diaphragm)	Spasmodic contraction of diaphragm
Respiratory dyskinesia	Abnormal asynchronous pattern of breathing associated with neurocirculatory asthenia
Convulsive disorders	Status epilepticus, tetanus, strychnine poisoning

TABLE 123.3: Treatment of hiccups

General measures	*Drugs*
Stimulate the throat • Quickly swallow two heaped teaspoons of sugar, drink cold water or eat crushed ice, or rub with a clean cloth inside the top of the mouth. • Rapid pharyngeal stimulation with a nasogastric tube *Interrupt normal breathing* • Hold breath or breathe into paper bag • Pull knees to chest and lean forward (compress the chest)	The choice of drug should depend on the probable cause of hiccup. Metoclopramide Haloperidol Baclofen Chlorpromazine Anticonvulsants (Carbamazepine, Gabapentin) Calcium channel blocker

The pathogenesis of hiccups is unclear but seems to relate to supraspinal mechanism and reflex arcs. Numerous treatments for hiccups are described (Table 123.3)[29,30] Pharmacological therapy should be tried for those with persistent hiccup.

2. *Myoclonus:* Respiratory myoclonus (Leeuwenhoek's disease) is a rhythmic repetitive contraction of respiratory muscles, at a frequency of 30-300/min.[31] The pathogenesis is not clear, though some nervous system dysfunction at the level of the brain, spinal cord or phrenic nerve has been postulated. It is associated with palatal myoclonus.

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Section

15

PULMONARY CIRCULATORY DISORDERS

Ritesh Agarwal

124

Diffuse Alveolar Hemorrhage Syndromes, Wegener's Granulomatosis and Other Pulmonary Vasculitis

Eleni Stagaki, Vlasis Polychronopoulos

DIFFUSE ALVEOLAR HEMORRHAGE SYNDROMES

Diffuse Alveolar Hemorrhage (DAH) is a potentially life-threatening clinicopathological syndrome characterized by intralveolar bleeding, caused by the disruption of the pulmonary capillary lining due to a variety of conditions.[1,2] Hemoptysis, diffuse alveolar infiltrates and a drop in hematocrit consist the characteristic triad of DAH manifestations. Hemoptysis may be absent in upto one-third of the patients with Alveolar Hemorrhage (AH) and the severity of symptoms and signs—dyspnea, hypoxemia and cough associated with fever—depend on the extent of underlying disease. Therefore, DAH may be subclinically suspected when chest radiograph demonstrates new unexplained bilateral alveolar infiltrates in the face of falling hemoglobin and a hemorrhagic sequential Bronchoalveolar Lavage (BAL), in which sequential aliquots appear bloodier. The percentage of siderophages among the total alveolar macrophages recovered by BAL reported to indicate AH is atleast 25% in active DAH, even if the macroscopic appearance is not hemorrhagic.[3,4,5]

A number of distinct disorders can cause DAH. The identification of the underlying cause and prompt implementation of appropriate therapy is crucial for a patient presenting with DAH. The differential diagnosis of DAH includes diseases associated with the pathological finding of capillaritis (a cellular infiltrate of neutrophils in the capillaries and venules; and those associated with normal vessels, or bland hemorrhage (Table 124.1).

Diagnosis and Evaluation

The priority for DAH diagnosis is to first exclude other conditions that can be similar from the clinical and radiological point of view. Smoking-related micro-hemorrhage, congestive heart failure, pleural biopsy, vasculitis due to infection in immunocompromised host and hemosiderosis. Pulmonary alveolar hemorrhage may also be associated with thrombocytopenia (<50,000 cells/μL), other abnormal coagulation syndromes and renal failure.

Clinical Evaluation

The medical history should include all the pre-existing conditions that can cause AH (coagulopathy; mitral stenosis; recent bone marrow transplantation; pre-existing autoimmune disorders; drugs like penicillamine, propylthiouracil, cytotoxic drugs, amiodarone mito-mycin; all-trans retinoic acid; smoking history; and exposure to inhalation toxins, such as trimellitic anhydride or drug abuse, including crack cocaine abuse).

Clinical evaluation should include search for abnormalities suggesting systemic involvement. These include sinusitis, dermatological leukocytoclastic vasculitis, iridocyclitis, synovitis and glomerulonephritis.

Chest Radiography

The Chest Radiograph (CXR) or High-Resolution Computed Tomography (HRCT) are nonspecific and indicate air space disease that can be either patchy or diffuse in appearance. The presence of Kerley B lines on the chest radiograph suggests either another cause of diffuse alveolar hemorrhage (such as pulmonary veno-occlusive disease, mitral stenosis, or possibly pulmonary edema due to myocarditis, which can potentially complicate a systemic vasculitis or collagen vascular disease).

TABLE 124.1: Causes of Diffuse Alveolar Hemorrhage

Histological Findings of Capillaritis

- Primary idiopathic small vessel vasculitis
- Wegener's granulomatosis
- Churg-Strauss syndrome
- Microscopic polyangiitis
- Isolated pauci-immune pulmonary capillaritis
- Primary immune complex–mediated vasculitis
- Goodpasture's syndrome
- Henoch-Schönlein purpura
- Secondary vasculitis
- Classic autoimmune disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Antiphospholipid antibody syndrome
- Mixed connective tissue disease
- Polymyositis/dermatomyositis
- Essential cryoglobulinemia
- Behçet's disease
- Lung transplantation
- Bone-marrow transplantation
- Drug-induced (e.g. chemotherapeutic agents, propylthiouracil).

Absence of Capillaritis (Bland Hemorrhage)

- Idiopathic pulmonary hemosiderosis
- Coagulopathy
- Mitral stenosis
- Inhalation injury
- Goodpasture's syndrome
- Systemic lupus erythematosus
- Bone marrow transplantation (associated with diffuse alveolar damage)
- Drug-associated disease (e.g. chemotherapeutic agents).

Hematological Investigations

Initial blood testing should include complete blood count (CBC), chemistry group, coagulation status and baseline markers of inflammation [ESR (erythrocyte sedimentation rate and C-reactive protein)]. A urinalysis should always be ordered, because renal involvement is very often associated with pulmonary capillary disease. The typical finding consists of glomerular erythrocytes (usually in abundance) associated with proteinuria. The underlying pathology may be either a segmental necrotizing glomerulonephritis rapidly progressing to renal failure [Wegener's granulomatosis (WG), microscopic polyangiitis (MPA)] or other systemic vasculitides or even may be pauci-immune idiopathic glomerulonephritis (Goodpasture's syndrome). In addition to serology testing, including Anti-Neutrophilic Cytoplasmic Antibodies (ANCA), anti-GBM antibodies, antinuclear antibodies (ANA), anti-dsDNA antibodies, antiphospholipid antibodies, rheumatoid factor (RF), creatinine kinase and complement levels should be ordered to find out the underlying disorder.

Diffusion Capacity

Most patients with DAH are too ill to undergo pulmonary function testing. However, measurements of the carbon monoxide transfer coefficient corrected for lung volume (KCO) may show sequential increases over time because of the heightened availability of intra-alveolar hemoglobin for combination with carbon monoxide.

Histopathological Diagnosis

Although diagnostic biopsy remains the gold standard, there are some cases where a confident diagnosis can be made without tissue biopsy. So, the decision to obtain biopsy specimen (renal, lung, other site-skin, upper airway, etc.) should be made taking into consideration the risk of the procedure and the likelihood of biopsy findings to alter the therapeutic approach. When the lung is clinically involved, surgical lung biopsy almost always provides definitive pathological evidence. It should be kept in mind that DAH recurrence may lead to interstitial fibrotic lesions; pathology may also reveal areas of organizing pneumonia and this does not exclude DAH diagnosis.

Renal biopsy is preferred as more convenient. In typical cases with multiple organ involvement, biopsy site could be skin, nose, etc. for WG, or even be avoided if serology is compatible (ANCA for MPA or WG, ANA for Systemic Lupus Erythematosus (SLE), anti-GBM for Goodpasture's syndrome). Video-Assisted Thoracoscopic Surgery (VATS) is preferred from open lung biopsy as it is associated with less morbidity and mortality. At the time of surgery, some tissue should be frozen (for immunofluorescence studies), fixed in formalin (for hematoxylin-eosin and special stains), and placed in a saline solution for culture. Because of the variety of testing performed on the samples, the processing should be closely coordinated among the physicians and surgeons involved, and the pathologist should be alerted that vasculitis is in the differential diagnosis.

Percutaneous renal biopsy is commonly performed during the evaluation of an acute glomerulonephritis. Although features specific for vasculitis (e.g. granulomatous inflammation or necrotic vessels) are rarely found, the finding of a focal, segmental necrotizing glomerulonephritis without immune deposits (pauci-immune) generally reflects a systemic vasculitis.[5] It is important that in addition to conventional histopathology, immunofluorescence (and electron microscopic when appropriate) studies to be performed. The presence of characteristic immunofluorescence patterns, such as IgA deposition in Henoch-Schönlein purpura, linear IgG deposition in Goodpasture's syndrome, and irregular immunoglobulin and complement deposition in SLE, help provide a specific diagnosis.

However, the clinician should not wait for the laboratory or biopsy results to begin treatment, with high doses of steroids and cytoxan, when vasculitis is highly suspected from clinical findings (dyspnea, pale face, highly desaturated patient), HRCT (alveolar filling disease, rapidly moving consolidations) and simple laboratory tests (drop of hematocrit and glomerular erythrocytes in urine).

WEGENER'S GRANULOMATOSIS AND OTHER PULMONARY VASCULITIDES

Pulmonary vasculitis comprises a heterogeneous group of disorders associated with prominent inflammation and/or necrosis of the vessels of different sizes. Vasculitis can be separated into primary and secondary vasculitis. The majority of primary vasculitides are idiopathic in origin. Their wide spectrum of frequently overlapping clinical manifestations is defined by the size and location of the affected vessels, as well as by the nature of inflammatory infiltrate. In secondary vasculitides, there is usually an underlying disorder such as collagen vascular diseases, immunological abnormalities, infection, drugs and neoplasm.

The nomenclature that most experts have adopted in classifying "primary pulmonary vasculitides" is that of Chapel Hill Consensus Conference in 1992.[6]

Most current classification schemes of vasculitides are based on clinicopathological features shown in Table 124.2.

TABLE 124.2: Classification of the vasculitides

Primary Idiopathic Vasculitis

Small Vessel

- Wegener's granulomatosis
- Churg-Strauss syndrome
- Microscopic polyangiitis
- Idiopathic pauci-immune rapidly progressive glomerulonephritis
- Isolated pauci-immune pulmonary capillaritis.

Medium Vessel

- Polyarteritis nodosa
- Kawasaki disease.

Large Vessel

- Giant cell arteritis
- Takayasu's arteritis
- Primary immune complex–mediated vasculitis
- Goodpasture's syndrome
- Henoch-Schönlein purpura
- Behçet disease
- IgA nephropathy.

Secondary Vasculitis

- Classic autoimmune disease
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Polymyositis/dermatomyositis
- Scleroderma
- Antiphospholipid antibody syndrome
- Essential cryoglobulinemia
- Inflammatory bowel disease
- Hypocomplementemic urticarial vasculitis
- Drug-induced (e.g. propylthiouracil, diphenylhydantoin)
- Paraneoplastic.

Lung involvement is most commonly seen with the primary, idiopathic, small-vessel, or antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides, as Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. However, primary idiopathic medium and large-vessel vasculitis, primary immune complex–mediated vasculitis, and secondary vasculitis may also involve the lung.

Epidemiology

Pulmonary vasculitis is an uncommon condition and even Wegener's granulomatosis, perhaps the best known pulmonary vasculitis is rarely encountered in clinical practice. The estimated incidence is 20 to 100 cases/million and a prevalence of 150 to 450/million.[7] They can occur in people of all age groups, although the granulomatous vasculitides show a predilection for patients in their fifth and sixth decades and anaphylactoid purpura is more common among young children. The multicenter study by the American College of Rheumatology (ACR) of 1,020 patients of North America in 1990 estimated the incidence of various vasculitides as follows. A total of 807 satisfied the criteria for the diagnosis of the following types of primary vasculitides: giant-cell (temporal) arteritis (GCA) 27%, polyarteritis nodosa (PAN) 15%, Wegener's granulomatosis (WG) 11%, Henoch-Schönlein purpura (HSP) 10.5%, Takayasu arteritis 8% and Churg-Strauss (CSS) 2.5%.The rest 213 patients had secondary vasculitis mainly due to collagen diseases.

Specific Disorders

ANCA - Associated Vasculitides

The three primary systemic small vessel vasculitides are Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg Strauss (CSS) syndrome, which is the rarest of the three. Most patients with active WG and MPA and 40 to 70% of patients with CSS are ANCA positive (either p- or c-, sometimes both). Respiratory manifestations of ANCA associated vasculitides are much more common compared to all other systemic vasculitides.

Wegener's granulomatosis (WG): The Chapel Hill Consensus nomenclature has defined WG as the "granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels (i.e. capillaries, venules, arterioles and arteries)." The incidence of the disease is estimated upto 8.5/million (range 5.2 to 12.9/million) with a male-to-female ratio of 1:1. The disease usually involves Caucasians (80–97%) with a mean age at the time of diagnosis of 40–55 years, although any age may be affected.[8]

The most common presenting symptoms are related to the **upper respiratory tract.** These include nasal obstruction, serosanguinous secretion, epistaxis and destruction of nasal cartilage leading to saddle-nose deformity, ulcerative stomatitis, gingivitis, external ear chondritis, otitis media and mastoiditis. *Staphylococcus* is frequently detected in the nose and sinuses and has been linked to relapses of the disease.[9] **Airway involvement** is found in 15 to 55% of patients. Subglottic stenosis is the most frequent airway manifestation in WG. It is more often in young women and can cause life-threatening compromise of the airway.[10] A high index of suspicion is important in detecting this lesion as it is not related with disease extent and activity may be the only manifestation for the first year. Twenty percent of WG limited to respiratory tract (without AH) is ANCA-negative. It has nonspecific presenting symptoms (dyspnea, cough, voice changes) and is often treated as asthma. Although subglottic disease is optimally diagnosed by otolaryngological visualization, an extrathoracic obstruction may be suggested by changes in the flow-volume loop (Fig. 124.1).

Similarly significant mucosal inflammation and ulceration or fibrotic scarring can occur at any level of the tracheobronchial tree. Usually the disease is not detected at this early stage where upper respiratory tract is involved and patients are treated as chronic sinusitis. Every patient with such symptoms has to be thoroughly checked with chest CXR and simple ENT exams for the severity of Wegener disease.

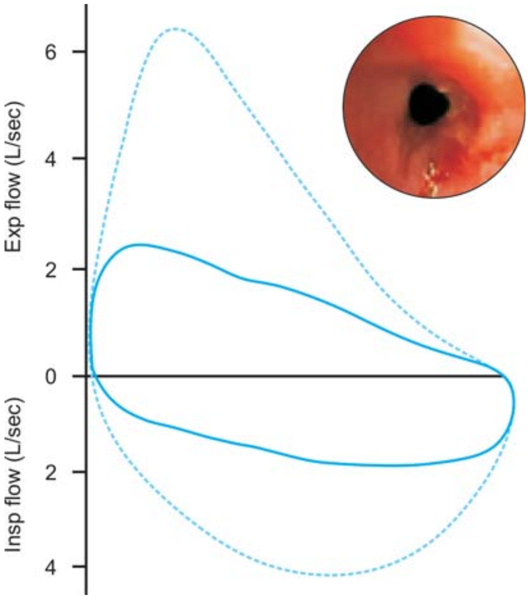
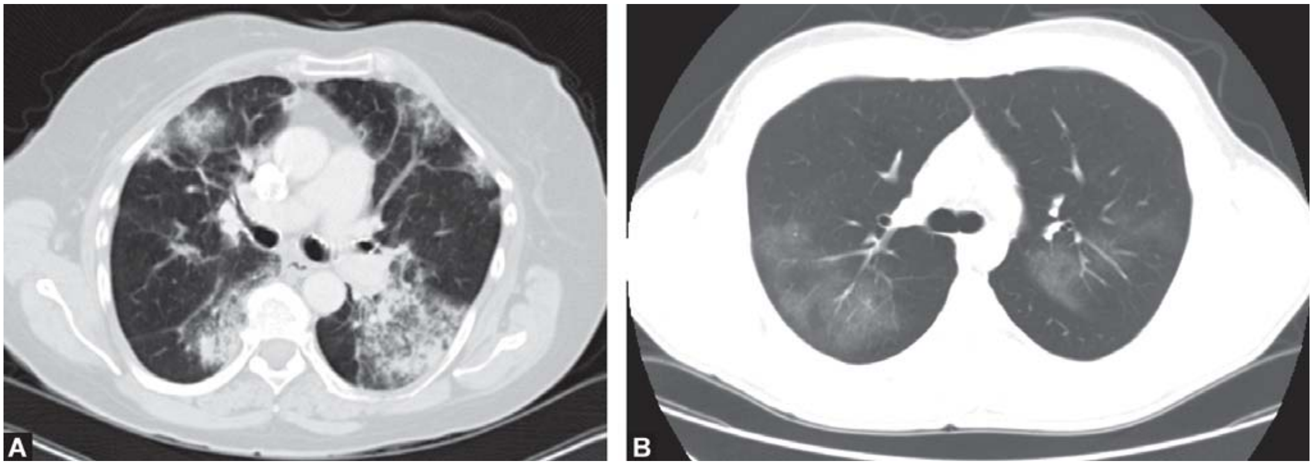


Fig. 124.1: Flow-volume tracings in a patient with significant midtracheal stenosis (inset) show typical features of a fixed major airway obstruction with flattening of both the inspiratory and expiratory flow-volume curves. Interrupted lines show predicted normal tracing[11]

Pulmonary involvement occurs at some stage of the disease in almost all patients, and chest radiographic abnormalities are presented in upto 85%.[11] Computed tomography is superior to chest radiography in assessing the presence and extent of pulmonary parenchymal abnormalities in patients with WG (Figs 124.2A and B). Solitary or multiple nodules or masses, that are cavitated in as many as 50% of patients, are the most common findings in the lungs. Airspace opacities are a second manifestation of Wegener's granulomatosis. Usually, these opacities with or without cavitating nodules involve a localized region and may present areas of consolidation with some hyperlucent regions, which mimic a lung abscess or lung cancer. These diffuse alveolar opacities most frequently are the result of pulmonary hemorrhage. Even at this stage the correct diagnosis may be missed and patients are treated as if they had pneumonia or lung cancer because of the presence of fever, cough, hemoptysis and endobronchial findings. Other less common pulmonary manifestations include atelectasis, reticular interstitial opacities, pleural abnormalities and mediastinal adenopathy.

Glomerulonephritis is one of the most serious disease manifestations of WG as it can progress rapidly



Figs 124.2A and B: Computed tomography appearance of alveolar hemorrhage . (A) and (B) Two representative images obtained from a patient with known Wegener's granulomatosis. Figure (A) shows how subtle the infiltrates can be

to complete renal failure in the absence of symptoms. Continued vigilance for glomerulonephritis is essential as it is present at diagnosis in only 20% of patients, but develops in 80% of patients at some point during the course of their disease. Renal disease manifests as crescent necrotizing glomerulonephritis characterized by urinary sediment with more than 5 RBCs per high-power field (HPF) or erythrocyte casts (early stage) and potentially a decline in renal function as evidenced by a rise in serum creatinine or a decrease in creatinine clearance (late stage).

Patients may report chronic, nonspecific constitutional complaints: fevers, night sweats, fatigue and weight loss. **The skin** is involved in 45% of patients with WG due to leukocytoclastic vasculitis and can lead to palpable purpura or skin ulcers. **The nervous system** is affected by vasculitis in 22% of patients. Clinical manifestations include mononeuritis multiplex and cranial nerve abnormalities. Large joint **arthritis**, polyarticular symmetric small and medium joint arthralgias, and myalgias may be found. **Ocular** findings include scleritis, keratitis, uveitis, episcleritis and conjunctivitis. **Cardiac** and **gastrointestinal** systems can rarely be involved in WG (Table 124.3).

Classification criteria have been developed by the American College of Rheumatology (ACR) for WG. **In the presence of vasculitis,** atleast two of the following criteria should be met for the purpose of classification of vasculitis as WG: (1) nasal or oral inflammation—defined as the development of painful or painless ulcers or purulent or bloody nasal discharge; (2) abnormal chest radiograph—the presence of cavitating or noncavitating nodules or fixed infiltrates; (3) an abnormal urinary sediment—microscopic hematuria with >5 red blood cells/high power field or red casts in the urine sediment; and (4) granulomatous inflammation—histological changes showing granulomatous inflammation within the wall of an artery or arteriole or in the perivascular or extravascular area on a biopsy specimen. The presence of any two or more criteria yields a sensitivity of 88.2% and a specificity of 92%.

ANCA

Three indirect immunofluorescent staining patterns, cytoplasmic ANCA(C-ANCA), perinuclear ANCA (P-ANCA), and atypical ANCA are described. ANCA that causes a cytoplasmic immunofluorescence pattern (C-ANCA) on ethanol-fixed neutrophils are caused by antibodies reacting with proteinase 3 (PR3-ANCA).[12] In contrast, a variety of antibodies can cause a perinuclear immunofluorescence pattern (P-ANCA) on ethanol-fixed neutrophils.

Only the PR3-ANCA with C-ANCA combination and the MPO-ANCA with P-ANCA combination are sensitive and specific for ANCA-associated vasculitides (AAV).[13] Positive and negative predictive values of ANCA testing for WG and MPA, are critically dependent on the pretest probability of the disease in the patient tested, as well as on the analytical accuracy of the test method. It is important to recognize that most patients with active severe disease are ANCA positive, but about 25% with limited WG have no detectable ANCA. C-ANCA is highly sensitive (90–95%) in active, systemic WG, with a specificity of approximately 90%. In the proper clinical setting (i.e. with a very high pretest

TABLE 124.3:Clinical Characteristics of the ANCA-Associated Vasculitides[42]

Variables	*WG*	*MPA*	*CSS*
Pulmonary	Very common, 70–95% of patients; symptoms may include cough, chest pain, dyspnea, or hemoptysis; Tracheobronchial and endobronchial disease also relatively frequent (10–50%)	Moderately common with 10–30% of patients experiencing involvement, most of which demonstrate alveolar hemorrhage	Asthma is essentially universal; patients may also have infiltrates/ eosinophilic pneumonia
Renal	RPGN occurs in 50-90% of patients	RPGN is essentially universal	RPGN occurs in 10–50% of patients
Upper Airway	Very common, 70–95% of patients; ulcerating and destructive lesions are suggestive	Variable	Sinusitis occurs in 20–70% of patients but often lacks the destructive nature seen in WG
Constitutional	Common; symptoms may include fatigue, malaise, fevers, and weight loss	Very common and often precedes RPGN	Common
Musculoskeletal	Arthralgias, arthritis and myalgias occur in approximately one half of patients	Arthralgias and myalgias in atleast one half of patients	Arthralgias and myalgias reported in up to one half of patients.
Ocular	Common, occurring in 25–50% of patients; sight-threatening disease including uveitis, ocular ulcers, alongwith a host of other complications may occur	Less common, 0–30% of patients	Uncommon
Cardiac	5–15%	10–20%	Common (30–50%) and a major cause of mortality in patients with CSS; may present with conduction delay, other ECG abnormality, systolic or diastolic dysfunction, or coronary artery involvement
Gastrointestinal	Uncommon	Common, 35–45%; complications usually resemble those of the other ANCA associated vasculitides (see CSS), although it is possible to see the visceral aneurysms most commonly associated with classic polyarteritis nodosa	Common (30–60%); another major cause of morbidity and mortality; may present with hemorrhage, abdominal pain, infarct, or perforated viscous.
Dermatological	Common; may include classic palpable purpura, but may also present with ulcers, nodules or vesicles	Common	Common
Neurological	May present with CNS disease or peripheral nervous system involvement	Mononeuritis multiplex occurs in 10–50%	Mononeuritis multiplex in > 50%
Chest Imaging	Abnormal chest imaging findings are very common (> 80%); may present with alveolar, interstitial or mixed infiltrates, or nodular or cavitary disease	Pulmonary infiltrates occur in 10–30%	Pulmonary infiltrates are common (40– 75%); may also see changes consistent with asthma (*e.g.* airway wall thickening and hyperinflation)
ANCA	ANCA-positive in >90% and c-ANCA/anti-PR3 ELISA positive in >85% with generalized active disease	ANCA-positive in 50–75% with most of these being p-ANCA/anti-MPO positive	ANCA positive in 45–70% with most of these being p-ANCA /anti-MPO positive

probability of disease), a positive C-ANCA/ anti-PR3 has sufficient PPV that biopsy may be deferred. False-positive ANCA test results have been reported. Particularly, subacute bacterial endocarditis has been reported with positive C-ANCA/PR3.[14] The clinical utility of the serial measurements of ANCA levels in follow-up is less well established. Although there is an association between ANCA titers and disease activity, if the only finding is the elevation of ANCA levels, this does not always predict disease relapse, but requires close follow-up of the patient with clinical and laboratory exams.[15]

Bronchoscopy

This study is helpful in the evaluation of alveolar hemorrhage, infection, airway disease, and endobronchial lesions. Transbronchial biopsy specimens are usually insufficient to diagnose vasculitis. Bronchoscopy may also be used as needed for palliative measures for narrowed airways (i.e. stents balloon dilatation).[10]

Diagnosis

Diagnosis needs tissue specimen for both WG and MPA. This can be achieved for WG disease by taking tissue from upper respiratory tract (URT), skin lesions or kidney, since transbronchial lung biopsy (TBLB) is of limited value. However, if the patient presents with the typical involvement of URT, renal and AH or pulmonary cavitating nodules and c-ANCA/PR3 positive, the diagnosis can be safely made.

Differential Diagnosis

Various forms of vasculitis (MPA, Goodpasture's syndrome, etc.) may lead to pulmonary hemorrhage or pulmonary-renal syndrome, similar to Wegener granulomatosis.

Pulmonary infarcts, septic pulmonary emboli, metastatic squamous cell carcinoma, fungal infection, rheumatoid nodules and lymphomatoid granulomatosis should be considered when the presentation includes multiple solid and cavitating nodules. In the presence of disease as consolidation with fever and hemoptysis differentiation should include infectious pneumonia, organizing pneumonia (OP) or eosinophilic pneumonia (EP) or drug toxicity. History, failure to respond to antibiotic treatment, transbronchial BAL and TBLB and more importantly the presence of significant drop of hematocrit and glomerular erythrocytes in the urine may provide the correct diagnosis.

The differential diagnosis of ENT manifestations includes sinus infection, cocaine abuse, sarcoidosis, primary NK/T-cell lymphoma/nasal type, etc., and tracheal stenosis differentiation includes postintubation stricture or trauma, relapsing polychondritis, sarcoidosis, inflammatory bowel disease, and amyloidosis.

Although the list of differential diagnoses and other problems is exceedingly broad and varied, the differential diagnosis can usually be limited by evaluating the radiographic findings in the context of the clinical history, simple laboratory exams (Hematocrit, hypoxemia, urinalysis) and the presence of PR3-ANCA**.**

Microscopic polyangiitis (MPA): MPA is a necrotizing systemic vasculitis with few or no immune deposits that affects small vessels (i.e. capillaries, venules or arterioles) and in contrast to WG there is no granulomatous formation. Since the discovery of ANCA, MPA has been differentiated from PAN. In addition to differences in the size of the vessels involved, lung involvement is rare in polyarteritis nodosa.

MPA more frequently affects men and the median age of onset is 50 years. Clinically, renal involvement, predominantly rapid progressive glomerulonephritis (RPGN), is a major feature of MPA, which is essentially universal. Most patients have systemic symptoms. Pulmonary involvement is seen in upto 30% of patients.[16] DAH with capillaritis pathology is the most common pulmonary manifestation.[17] Fleeting focal infiltrates to massive lung hemorrhage and hemoptysis can occur and is an important contributory factor to morbidity and mortality.[18] Ground-glass attenuation, consolidation, thickening of the bronchovascular bundles, nodular lung lesions, honeycombing, pulmonary interstitial fibrosis, obstructive lung disease, and pulmonary artery aneurysms have been observed in some patients with MP.[19-21]

Joint, skin, peripheral nervous system and gastro-intestinal (GI) involvement are also relatively common (Table 124.3). The vasculitis of MPA is indistinguishable from that of WG, and there may be a substantial clinical and ANCA overlap.

A positive P-ANCA is seen in 50 to 75% of patients, and anti-MPO is seen in 35 to 65% of patients, whereas a positive C-ANCA can be seen in 10 to 15% of patients. Histologically, a focal, segmental necrotizing vasculitis and a mixed inflammatory infiltrate without granulomata are seen.

Management of WG and MPA

The management of WG and MPA currently follows the same basic principles.

For treatment stratification, the disease activity is categorized as limited or severe. "Severe disease" is either life-threatening or threatening organs with irreversible loss of function and includes the following manifestations of the disease: Alveolar hemorrhage, glomerulonephritis, nervous system involvement including sensory-neural hearing loss and eye involvement (except mere episcleritis). Most of these manifestations are caused by capillaritis. All the other patients are thought to have limited disease and the symptoms in this case are the result of necrotizing granulomatous inflammation. Similarly, the European Vasculitis Study Group (EUVAS) recommends grading disease severity of the AAVs into the following five categories:[4]

- Localized: Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
- Early systemic: Any, without organ-threatening or life-threatening disease
- Generalized: Renal or other organ-threatening disease, serum creatinine level less than 5.6 mg/dL
- Severe: Renal or other vital-organ failure, serum creatinine level exceeding 5.6 mg/dL
- Refractory: Progressive disease unresponsive to glucocorticosteroids and cyclophosphamide.

Current standard therapy of ANCA- associated vasculitides (WG and MPA) is based on disease severity. The aim of the treatment is to control disease activity with minimal exposure to the toxicity of the drugs necessary to achieve this goal. The standard therapy for limited disease consists of the combination of oral glucocorticosteroids with methotrexate (MTX) 25 mg once a week, which is noninferior and has fewer side effects compared to cyclophosphamide (CYC).[22] In the largest reported group of patients with limited Wegener (WGET) >90% of patients achieved remission with this regimen and > 70% achieved sustained remission more than 6 months.[23]

The standard treatment for patients with severe WG or MPA is CYC at a dose of 2 mg/kg/day orally in combination with glucocorticosteroids. Glucocorticoids are usually given orally, but, if a rapid response is needed, such as in the case of RPGN and/or AH, intravenous pulse methylprednisolone (0.5-1 g/d for three consecutive days) can be used. Initial high-dose glucocorticoids (0.6-1 mg/kg/d) should be continued for atleast one month, tapered by 5 mg per week to 10 mg/day. Doses should not be reduced to less than 15 mg/d within the first three months. The dose should then be slowly tapered to a maintenance dose of 10 mg/d or less during remission. Consensus now is to limit the duration of CYC therapy to the first 3–6 months.[4] Once remission has been induced, CYC should be switched to either azathioprine (AZA) or MTX. AZA is preferred in patients with renal involvement and any degree of renal insufficiency. Mycophenolate mofetil (MMF) represents another alternative for AZA or MTX for remission maintenance. However, MMF is much more expensive and there are not many randomized trials comparing the effectiveness of the different remission maintenance agents.[24]

Whenever CYC is used for remission induction, consideration should be given to the patient's fertility. When a patient has persistent disease activity on maximal tolerated dose of CYC or has contradictions for the use of CYC then he is thought to have ***refractory disease***. The above mentioned treatment for severe disease is repeated when there is a severe flare.

Alternative newer therapies that could be used are:

Mycophenolate mofetil (MMF) is a derivative of the fungus *Penicillium stoloniferum* that, similar to azathioprine that limits purine synthesis. MMF may be considered in patients with MPO-ANCA-associated MPA and mild renal disease for remission induction in severe disease.

The addition of **plasma exchange therapy (PLEX)** to the standard cyclophosphamide - corticosteroid regimen has been shown beneficial to patients with rapidly progressive disease.[25]

B-cell depletion with **Rituximab (RTX),** a monoclonal anti-CD20 antibody that targets a subset of B-lymphocytes is currently used for patients with refractory disease. It may become a more widely used alternative to CYC, since it is considered a less toxic treatment, if the hypothesis of the RAVE trial is proven. In a recent series of 11 patients with active ANCA-associated remission was induced in all 11 patients, and ANCA titers became undetectable in eight patients.[26,27]

Anti-TNF therapy for AAV has been disappointing, and there is currently no role for these agents in AAV.[23] There are several reports on the use of other agents, such as antithymoglobulin, but toxicity limits their use.

Invasive bronchoscopy techniques or even surgery can be considered in the case of bronchial or subglottic stenosis, fibrotic changes deformities of the nose.

Follow-up

Patients with Wegener's granulomatosis (WG) should have regularly scheduled follow-up visits. Since recurrences occur frequently, patients should be monitored closely clinically, with radiological studies and laboratory examinations: CBC, serum creatinine levels, urinalysis, ESR, C-reactive protein, PR3-ANCA levels. All of the above exams, except ANCA, should be repeated in every two weeks.

Toxicity of the therapy should always be investigated. Infection due to treatment-related immunosuppression is a major contributor to morbidity and mortality in WG. Sometimes it is difficult to differentiate infection from disease flare. The physician should have a low threshold for treating suspicious symptoms with antibiotics. Prophylaxis against *Pneumocystis* pneumonia is essential while patients are receiving conventional therapy for WG (CYC-high doses of CS). TMP-SMX single-strength daily or double-strength formulation three times per week should be administered. Dapsone 100 mg daily can be used in sulfa-allergic patients.

All patients who require long-term glucocorticosteroid treatment are at risk for glucocorticosteroid-induced osteoporosis. Baseline bone mineral density should be evaluated. If the density is normal, patients should take daily calcium and vitamin D supplementation. If diminished at baseline or if long-term glucocorticosteroid use is anticipated, bisphosphonate therapy should be added.

Mesna should be administered to prevent hemorrhagic cystitis, which is a frequent complication of CYC and urine cytology should be performed in every six months as the potential long-term complication of CYC is the carcinoma of the bladder.

Churg-Strauss syndrome (CSS): According to the Chapel Hill Consensus Conference, a patient fulfills the definition for CSS if: asthma, peripheral eosinophilia, eosinophilic-rich granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to-medium-sized vessels are found. As mentioned previously, CSS is one of the three ANCA-associated vasculitides, where in more than half of the patients with active CSS, ANCA are detected. In 75% of these patients, the ANCA pattern is p/MPO positive, while 25% present with c-ANCA pattern.[28,29] CSS is the rarest of the three, with the incidence rates of definite CSS among asthma patients ranging from 0 to 67 per million person every year. Apart from the rarity of the syndrome, the fact that its various clinical manifestations rarely coincide makes CSS diagnosis a challenge for the clinician.

Disease usually develops in stages. The first (prodromal) stage is characterized by asthma, which is the disease predominant feature, with or without allergic rhinitis and nasal polyps. The second stage consists of peripheral blood eosinophilia (>10%) and eosinophilic tissue infiltration. The last phase is the most severe and consists of systemic vasculitis. Each of these stages can last for years and they do not always follow each other; any of them can be missed. However, asthma usually precedes vasculitis by a mean of seven years and usually is refractory to standard asthma treatment. The differential diagnosis is based on the predominant symptom, which can be different in each phase. If the symptoms are focused on respiratory system, other pulmonary eosinophilic syndromes, such as parasitic infections, drug reactions, acute and chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis and hypereosinophilic syndrome should be excluded, before CYC is induced in addition to steroids.

Respiratory tract involvement is common. The major pulmonary symptoms are related to asthma, which is present in all patients. In addition, radiographic imaging studies reveal transient peripheral alveolar-type infiltrates, present in >70% of the cases. Nodular lesions or eosinophilic pleural effusion can be seen occasionally. DAH is extremely rare, in contrast to WG and MPA. Peripheral nervous system involvement in the form of mononeuritis or polyneuritis multiplex, skin, heart, central nervous system and gastrointestinal system may also be involved. Renal involvement is less common than in WG and MPA and is usually mild. **(Table 124.3).** Laboratory findings include peripheral blood eosinophilia on complete blood count, elevation of serum IgE and markers of inflammation (C-reactive protein and erythrocyte sedimentation rate). As mentioned before in 40 to 70% of the patients, ANCA are detected, 75% of which are p-ANCA reacting with myeloperoxidase and 25% c-ANCA. The ANCA status appears to correlate with disease activity. Diagnosis needs histological specimen from peripheral nerve or lung and compatible clinical and serological findings.

There has been much discussion about possible pathogenic link between leukotriene receptor antagonist (montelukast, zafirlukast) and the onset of CSS. There is no evidence suggesting that these agents cause CSS, but that they allow dose reduction or discontinuation of oral corticosteroid in asthmatic patients, a fact that may lead to unmasking of CSS.

Patients with CSS respond very well to high dose systemic glucocorticosteroids. In patients with life-threatening manifestations of the disease, that is nervous system involvement, glomerulonephritis, heart involvement or DAH, cyclophosphamide should be added to glucocorticosteroids. Finally, other less toxic immunosuppressive drugs (methotrexate, azathioprine, etc.) could be used for remission maintenance. RTX has also been successfully used in CSS.[30]

Other Causes of Vasculitis Involving the Lungs

Systemic Lupus Erythematosus (SLE) and Other Collagen Vascular Disorders: DAH due to pulmonary capillaritis with prominent immune complex deposits in SLE is a rare, but life-threatening complication. Joint symptoms usually precede and patient is already diagnosed as having SLE; therefore diagnosing the cause of hemoptysis in such patient—provided that infectious pneumonia is excluded, is usually easy by finding high presence of siderophages in BAL and glomerular erythrocytes in urine.[31] Some anecdotal reports refer that hemoptysis may be presenting before any other involvement occurs and then the diagnosis may be delayed or missed. Almost always the onset is abrupt with pulmonary infiltrates, fever and hemoptysis. The latter may be absent in 50% making the differential diagnosis between infection and DAH difficult and diagnostic BAL is usually required. High mortality rates have been reported with AH in SLE.[32] Treatment consists of glucocorticosteroids and cyclophosphamide. PLEX has been suggested, but there is not enough data to prove its benefit yet.

A small vessel vasculitis (pulmonary capillaritis) has been reported in several patients with polymyositis, rheumatoid arthritis and mixed connective tissue disease.[33,34]

Giant Cell Arteritis: Giant cell arteritis (GCA) also called temporal arteritis, cranial arteritis and granulomatous arteritis is the most common primary vasculitis that affects large- and medium-sized vessels.[35] The incidence of GCA increases with age and is often associated with polymyalgia rheumatica. The most typical features of the disease include new-onset severe headache, a palpably tender or nodular temporal artery, visual symptoms, that is amaurosis fugax and visual loss. The gradual development of nonspecific systemic symptoms, such as low-grade fever, malaise and weight loss and an elevation of erythrocyte sedimentation rate (ESR) are common. Pulmonary complications, reported up to 25% of patients include cough, sore throat and hoarseness. Other abnormalities described in isolated cases include interstitial or nodular pulmonary lesions, pleural effusion, pulmonary infarction, lymphocytic alveolitis and aneurysms of the pulmonary artery. Therapy consists of corticosteroids, that usually lead to the resolution of pulmonary symptoms.

Takayasu's Arteritis: Takayasu's arteritis (TA) is chronic inflammatory vasculitis characterized by stenosis, occlusion and sometimes aneurysms of the large arteries, mainly the aorta and its main branches, including coronary and renal arteries.[36] TA is found predominantly in the Asia, Middle East and South Africa, although the disease has been described in Western population. The female/male ratio is 8.5:1 and the majority of patients are between 11 and 30 years of age. Early disease manifestations include constitutional symptoms, fever, weight loss and arthralgias. After weeks or months, vascular lesions appear and ischemic disease of the involved vessels develops. Variable pulses of the upper and lower extremities and intermittent claudication of the affected vascular territories are typical. Aortic insufficiency, renovascular hypertension and ischemia of the affected organs may be some complications of the progressive and relapsing disease.

Significant number of patients with TA have pulmonary artery involvement (approximately 50%). Pathology is similar to aorta and includes defects of the outer media of the arteries, ingrowth of granulation tissue-like capillaries, thickened fibrosed intima, transmular inflammation, lymphoplasmatic infiltrations with a variable amount of giant cells and subendothelial muscle proliferation. These morphological changes in pulmonary arterial wall, lead to pulmonary artery stenoses and occlusion and the development of pulmonary hypertension. Pulmonary symptoms include chest pain and hemoptysis, although they are not very often. Chest roentgenograms are not very helpful in detecting pulmonary involvement as they are usually normal. Conventional angiography, perfusion scan, computed tomography and magnetic resonance angiography usually provide valuable information.

Therapy of TA consists of glucocorticosteroids. Other immunosuppressive agent, such as methotrexate could be used for remission induction and as corticosteroid-sparing agents for remission maintenance. Unfortunately, relapses are often when the dose of corticosteroids is reduced to less than 10 mg/d. Surgery may be needed in patients with significant vascular disease.

Behçet Disease: Behçet disease (BD) is a chronic relapsing systemic inflammatory disorder characterized by aphthous oral ulcers along with two or more of the following: aphthous genital ulcers, uveitis, synovitis, cutaneous nodules or pustules, or meningoencephalitis. Most of the reported cases are from countries around the Mediterranean basin and Japan and the usual onset is in the third decade. Most studies have reported a predominance of men with disease over women. There is a strong association with the major histocompatibility complex antigen HLA-B5. Respiratory symptoms are not rare (about 10% of patients) and include hemoptysis, which can be massive, cough, chest pain and dyspnea. The vasculitis in BD may affect both arteries and veins, so that arterial aneurysms and major venous occlusion can occur accordingly. Aspirin and not anticoagulation has been advocated for thrombosis prevention. The most serious complications are pulmonary arteries aneurysms, erosion of the bronchial wall and arterial- bronchial wall fistulae that almost always are associated with hemoptysis, often fatal. Other manifestations of the diseases include lung infiltrates, recurrent pneumonias and bronchial occlusion. Fever, elevated ESR and anemia are common.[37]

Evaluation of thoracic involvement in BD, apart from chest radiographs, should include CT or MRI angiographs.

Immunosuppression with the combination of prednisone with another drug, such as colchicines, methotrexate, azathioprine or cyclosporine is recommended and may result in the resolution of pulmonary aneurysms. Anticoagulation should be avoided in case of arteritis. Prognosis is poor in patients with pulmonary involvement, since 30% die within 2 years due to fatal pulmonary hemorrhage.

Goodpasture's syndrome: Goodpasture's syndrome, also known as anti-basement membrane antibody disease (ABMA) is an extremely rare (one case per 1,000,000 population per year) autoimmune disorder, characterized by the presence of autoantibodies against the NC1-domain of the a3 chain of the glomerular basement membrane and, less commonly, the alveolar basement membranes.[38] This binding of antibodies, which is a cytotoxic (type II) reaction can be visualized as the linear deposition of immunoglobulin by direct immunofluorescent techniques and anti-GBM antibody can be found in the serum in >90% of the cases.

The disease predominantly affects Caucasians of any age, but mostly those in the second to third decades and the fifth to sixth decades of life, with a slight predominance in males. The cause of Goodpasture's syndrome is unknown, but influenza virus, hydrocarbon exposure or penicillamine and unknown genetic factors are known to stimulate anti-GBM antibody production.

Clinically the most common manifestations consist of DAH and RPGN with anti-GBM antibodies. These occur in 60 to 80% of patients with manifestations of pulmonary and renal disease, 20 to 40% with renal disease alone, and fewer than 10% have disease that is limited to the lungs.[39] DAH occurs in about half of the patients with ABMA and almost always precedes renal manifestations. An additional inhalation injury, particularly smoking, is required for the development of pulmonary manifestations of the disease. Active cigarette smoking increases the risk of DAH. In about 30% of the patients, p-ANCA-mpo positive are detected and AH is more likely to develop in those patients.

The most frequent histopathological feature of DAH is bland hemorrhage, without vasculitis, although some combined findings with vasculitis have been reported.

Immunosuppressive therapy in conjunction with PLEX is the treatment of choice in ABMA. The pulmonary outcome of ABMA is generally favorable, whereas chronic renal failure is common.[40]

Polyarteritis Nodosa: Polyarteritis nodosa (PAN) is characterized by necrotizing lesions affecting predominantly small- to-medium-sized muscular arteries.[41] PAN has been separated from microscopic polyangiitis and does not affect capillaries. Therefore, it does not cause alveolar hemorrhage or glomerulonephritis. Pulmonary involvement is very rare in patients with PAN. Anecdotal reports of cases of medium-sized bronchial and pulmonary arteries involvement in patients with PAN have been described. An association with hepatitis-B virus has been documented in a minority of patients diagnosed with PAN. Immunosuppression with antiviral agents is treatment of choice in such cases. Recurrences of the disease and ANCA are rare in PAN, in contrast to microscopic polyangiitis.

Infection

Among the primary vasculitides, those that affect the small vessels, Wegener's Granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis, are grouped together as the **ANCA-associated vasculitides.** The vasculitides associated with pathologic **granulomata** include Wegener's granulomatosis, Churg-Strauss syndrome, Takayasu's arteritis and giant cell arteritis.

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Pulmonary Hypertension: A Third World Prospective

Zeenat Safdar

INTRODUCTION

Pulmonary Hypertension (PH) is characterized by an increase in mean pulmonary artery pressure that may lead to right ventricular failure and premature death.[1] The pathophysiology of PH is complex and incompletely understood; however, the pathologic changes appear in part from an imbalance between mediators of vasodilatation (e.g. prostacyclin, Nitric Oxide [NO]) and vasoconstriction (e.g. Endothelin-1) in favor of the vasoconstrictive forces, and promotion of vascular smooth muscle cell proliferation in the small pulmonary arteries.

Pulmonary hypertension is defined hemodynamically by the presence of elevated mean Pulmonary Artery Pressure (PAP) of equal to or greater than 25 mm Hg.[2,3] The term primary pulmonary hypertension has been abandoned instead pulmonary hypertension is divided into five diagnostic groups as outlined in Table 125.1. The treatments discussed below are indicated for the Diagnostic Group I and their use in other diagnostic Groups is not recommended.

Pulmonary Arterial Hypertension [(PAH) Diagnostic Group I] is defined by a mean PAP $\geq$ 25 mm Hg with a Pulmonary Capillary Wedge (PCWP) or LVEDP of less than or equal to 15 mm Hg.[2,3] These criteria define PH associated with multiple other disease processes, including Chronic Obstructive Pulmonary Disease (COPD)[4] (Table 125.2). On the other hand, Pulmonary Venous Hypertension [(PVH) Diagnostic Group II] is defined by a mean PAP $\geq$ 25 mm Hg with a Pulmonary Capillary Wedge (PCWP) or LVEDP of more than or equal to 15 mm Hg (Table 125.2). These definition were used by the National Institute of Health Registry to define Primary Pulmonary Hypertension in the 1980's and recently revised at the 4th World Symposium on Pulmonary Hypertension.[5]

Prior to the availability of specific therapies, PAH (Diagnostic Group I) was considered a rapidly fatal illness with a median survival of 2.8 years.[2] Advances in the treatment have positively influenced prognosis and survival of these patients.[2,3] The revised PH classification proposed at the 3rd World Conference on Pulmonary Hypertension in Venice 2003 replaced the Evian classification of PH from 1998.[6] The major difference was the abandonment of the term primary pulmonary hypertension and classifying PAH as idiopathic, familial and associated with other conditions.[6] Recent revision of PH classification undertaken at the 4th World Symposium on Pulmonary Hypertension includes among other changes replacement of the term familial with heritable pulmonary arterial hypertension (Table 125.1).

Pulmonary hypertension and right ventricular enlargement occurring secondarily to chronic lung or chest wall disease, recognized as chronic cor pulmonale has been long considered as an independent disease, especially in the developing countries. The problem continues to pose a challenge in differential diagnosis and management of PH. Chronic cor pulmonale is a syndromic diagnosis, which occurs as a long-term complication of an underlying lung/chest wall or pulmonary vascular disease. It also encompasses the disorders of respiratory regulation and chronic central hypoventilation with hypoxemia and carbon dioxide retention. Pathophysiologically, the end result is the development of pulmonary hypertension that may lead to right ventricular failure.

TABLE 125.1: Updated Classification of Pulmonary Hypertension (Dana Point 2008)

Group I: Pulmonary Arterial Hypertension (PAH)

- Idiopathic PAH
- Heritable – BMPR2, Alk1, unknown
- Drug- and toxin-induced
- PAH assoicated with
  - Collagen vascular disease
  - Congenital heart disease
  - HIV
  - Schistosomiasis
  - Portal hypertension
  - Chronic hemolytic anemia
- Persistent pulmonary hypertension of newborn
- Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

Group II: Pulmonary Hypertension due to left heart disease

- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

Group III: Pulmonary hypertension owing to lung disease and/or hypoxemia

- Chronic Obstructive Pulmonary Disease (COPD)
- Interstitial lung disease
- Other pulmonary disease with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group IV: Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Group V: Pulmonary hypertension with unclear multifactorial mechanisms

- Hematological disorders: Myeloproliferative disorders, splenectomy
- Systemic disorders: Sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- Metabolic disorders: Glycogen stroage disease, Gaucher disease, thyroid disorders
- Others: Tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

CLINICAL FEATURES

Presenting symptoms of PH are nonspecific; include fatigue, dyspnea, worsening exercise limitation, sporadic chest pains, abdominal distention and pedal edema. With progression of disease, the right ventricle starts to fail and cardiac output falls. This phase may manifest with worsening symptoms progressing to presyncope or even syncope.[7] As this process progresses unabated, it may lead to right heart failure, shock and death.

TABLE 125.2: Hemodynamic Classification of Pulmonary Hypertension

Pulmonary hypertension	*Mean PAP ≥ 25 mm Hg*	*All groups*
Precapillary pulmonary hypertension	Mean PAP ≥ 25 mm Hg PCWP ≤ 15 mm Hg Cardiac output normal or reduced	Group I – PAH Group III – PH due to lung disease Group IV – CTED Group V – PH multi-factorial etiology
Postcapillary pulmonary hypertension	Mean PAP ≥ 25 mm Hg PCWP > 15 mm Hg Cardiac output normal or reduced/increased	Group II – PH due to left heart disease

Physical examination: Physical findings will depend upon whether patient is in a compensated or a decompensated cardiovascular state. In early compensated phase, physical examination may be nonspecific. Accentuated second heart sound (P2) may be heard indicating elevated PAP. Presence of midsystolic murmur caused by turbulent flow across the pulmonary artery, left parasternal heave, right-sided S4 gallop and prominent jugular "a wave may be seen".[7] As disease progresses, hepatojugular reflex and inspiratory augmented tricuspid murmur (Caravallo's sign) may become apparent. Signs of right heart failure include pulsatile liver, marked distention of jugular veins, ascites and peripheral edema develop.[8] Cold extremities and systemic hypotension may be present when cardiovascular collapse ensures.

Signs of chronic lung disease, such as those of emphysema, interstitial lung disease (ILD) or chest wall abnormalities (e.g. kyphoscoliosis) are present in cases of chronic cor pulmonale.

Stigmata of Collagen Vascular Disease (CVD) can provide clues to the presence of CVD associated PH. These include skin changes of scleroderma (skin thickening/tightening, nail fold changes, telangiectasias), butterfly rash of lupus, heliotrope rash of dermatomyositis/polymyositis. The incidence of PAH is higher in patients with mixed connective tissue disease and reported as high as 38%.[9] Human Immunodeficiency Virus (HIV) infection has been associated with an increase prevalence of PAH up to 0.5%.[10]

DIAGNOSTIC EVALUATION

Diagnostic evaluation is aimed at two components: A) Diagnosis of the presence and severity of pulmonary hypertension and B) Etiological diagnosis. Pulmonary

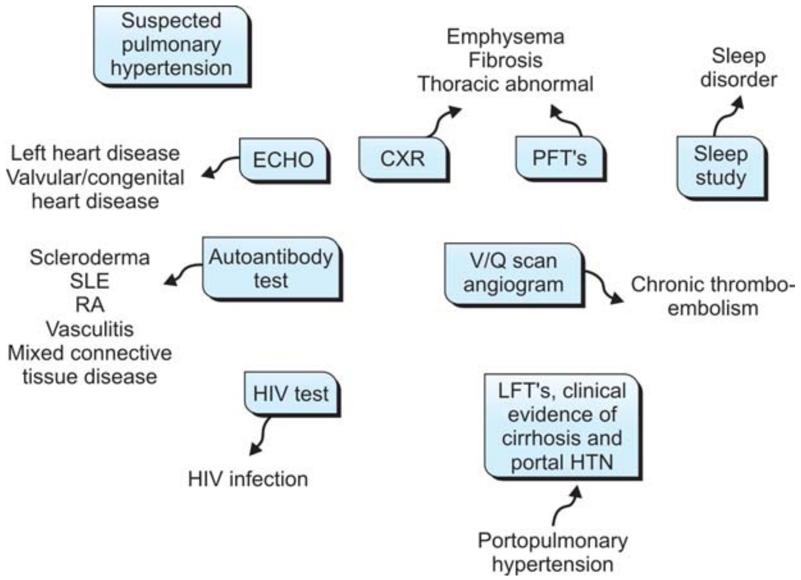
Suspected pulmonary hypertension
Emphysema
Fibrosis
Thoracic abnormal
Sleep disorder
Left heart disease
Valvular/congenital heart disease
ECHO
CXR
PFT's
Sleep study
Scleroderma
SLE
RA
Vasculitis
Mixed connective tissue disease
Autoantibody test
V/Q scan angiogram
Chronic thrombo-embolism
HIV test
HIV infection
LFT's, clinical evidence of cirrhosis and portal HTN
Portopulmonary hypertension

Fig. 125.1: Evaluation of pulmonary hypertension

hypertension occurring as a complication of chronic lung, chest wall, cardiac or collagen vascular disorders is discussed in individual chapters.

A number of diagnostic tests are required to be undertaken when PH is suspected in a new patient (Fig. 125.1). Suspicion for pulmonary hypertension, based on the history and physical examination, necessitates an echocardiogram that is a useful screening tool (Table 125.3). However, right heart catheterization is required to confirm the diagnosis.

Electrocardiogram (ECG): Electrocardiogram is a poor screening tool to diagnose pulmonary hypertension. Suggestive ECG findings include right-axis deviation; RSR pattern in lead V1, tall R wave and small S wave with R/S ratio > 1 in lead V1, qR complex in lead V1, large S wave and small R wave with R/S ratio < 1 in lead V5 or V6; or S1, S2, S3 pattern. ST-T segment wave depression and inversion may be present in the right precordial leads. Right atrial enlargement manifests as a tall P wave (>2.5 mm) in leads II, III, and aVF and frontal P-axis of 75°.[7]

Chest Radiography (CXR): CXR may reveal the following suggestive findings: Enlarged main and hilar pulmonary arterial shadows with attenuated peripheral pulmonary vascular markings (pruning), right ventricular enlargement seen on the lateral films as impingement of the anteriorly situated right ventricular silhouette into the retrosternal clear space.[8] Chest Radiography will also show the evidence of emphysema, other lung parenchymal diseases or chest wall deformity in case of chronic cor pulmonale.

TABLE 125.3: Pulmonary Hypertension Work-up

PH suspicion	Symptoms, history and physical examination
PH screening test	Echocardiogram
PH confirmation	Right heart catheterization
PH classification	Group I – Pulmonary arterial hypertension Group II – PH due to left heart disease Group III – PH due to lung disease Group IV – CTED Group V – PH multifactorial etiology
PH severity	6MWD Echocardiographic assessments NYHA/WHO FC

Echocardiogram (ECHO): This is a commonly used screening tool for evaluating pulmonary hypertension (Table 125.3). It is a simple, noninvasive test that can provide detail assessment of biventricular function and anatomy. Doppler ECHO can be used to calculate the Right Ventricle Systolic Pressure (RVSP) in the presence of tricuspid regurgitation jet. Presence of tricuspid jet is crucial to this measurement.

Pulmonary artery pressure approximately equals to right ventricular systolic pressure in the absence of pulmonary artery outflow obstruction or stenosis. The RVSP is approximated by the modified Bernoulli equation as $4v^2$, in which v is the velocity of the tricuspid jet in meters per second. Right Ventricle Systolic Pressure is obtained by adding right atrial pressure (RAP) to the RVSP.[7] Right Atrial Pressure estimate is based on either the height of jugular venous pulse or echocardiographic features of inferior vena cava.

$$\text{RVSP} = 4v^2 + \text{RAP}$$

Fisher et al. compared echocardiographic estimate of PAP with right heart catheterization, ECHO was performed within one hour of the RHC, and PAP was inaccurate (> 10 mm Hg variability) in 48% of cases.[11] Overestimation and underestimation were noted and the magnitude of underestimation was considered more prominent. This study elucidates the inadequacy of ECHO in both identifying and quantifying PAP.[11]

Ventilation-Perfusion Scan: This is an important test to determine the presence of chronic thromboembolic disease (CTEPH). Chronic thromboembolic disease is a potentially curable by patients undergoing pulmonary endarterectomy. In various studies, $\dot{V}/\dot{Q}$ scan has shown a sensitivity of 90 to 100% and specificity of 94 to 100% in differentiating between patients with idiopathic PAH and CTEPH. $\dot{V}/\dot{Q}$ scan is also useful to look for the presence of an underlying lung disease that will be evident as ventilation defects.

Computerized tomography of the chest: This is an emerging diagnostic modality in pulmonary hypertension. Advances in CT technology have led to improved imaging of heart and pulmonary vasculature. In one study, main PA diameter of 3.32 cm had 58% sensitivity and 95% specificity for the presence of PAH.[12] However, mean PAP used in this study was lower than the accepted definition of PH. Multidetector-row CT with three-dimensional volume rendering can elucidate pulmonary vein anatomy in the thorax. Abnormalities in the pulmonary venous drainage can prompt evaluation for structural anomalies causing PH.[13] Contracter et al. evaluated the role of helical CT chest in diagnosing right ventricule (RV) dysfunction after acute pulmonary embolism. Right ventricular dilation and deviation of interventricular septum towards left ventricle (LV) were the criteria used to define RV dysfunction. The sensitivity of CT chest for detecting RV dysfunction was 78% and specificity 100%, with a positive predictive value of 100%.[14]

Computed tomography chest is of particular help to diagnose a chronic lung disease, such as the bronchiectasis, COPD or interstitial lung disease.

Pulmonary function tests: Isolated reduction in the diffusion capacity of the lung for carbon monoxide (DLCO) is strongly suggestive of pulmonary vascular disease. In the absence of other lung pathology, isolated reduction in DLCO may be the only abnormal finding in lung function testing. Spirometry is particularly useful to assess the presence of severity of airflow obstruction.

Serological evaluation: A complete serological evaluation should be undertaken early in patients with PAH (as noted above). This should include testing for serological markers of systemic lupus erythematous, scleroderma, rheumatoid arthritis, polymyositis/dermatomyositis and mixed connective tissue diseases. Up to 40% of patients with PAH may have elevated antinuclear antibodies.[15]

Right heart catheterization (RHC): This remains the gold standard to diagnose of pulmonary hypertension. Right heart catheterization provides accurate measurement of mean PAP, right atrial pressure and cardiac output, and pulmonary capillary wedge pressure to determine the presence of pulmonary arterial vs. pulmonary venous hypertension.[7] Pulmonary vascular reactivity is assessed during catheterization and presence of reactivity has important therapeutic and prognostic implications in the treatment of PAH.[16]

Agents commonly used for vasoreactivity testing are inhaled nitric oxide, adenosine and intravenous epoprostenol. The definition of a positive vasodilator response is reduction of mean PAP equal to or more than 10 mm Hg and absolute reduction in the mean PAP to less than 40 mm Hg.[16] Unfortunately, less than 10% of patients elicit a positive vasodilator response and only 50% of initial responders remain responsive on repeated vasodilator testing.[17] Patients with a positive vasodilator response exhibit a better prognosis when treated with long-term calcium channel blocker therapy.[16]

Six-minute walk test: Exercise capacity in a PH patient is assessed by a six-minute walk test. It is a nonencouraged walk test that is conducted according to American Thoracic Society guidelines.[18] Several studies have demonstrated the prognostic ability of a six-minute walk distance (6MWD), which was the primary end point in several randomized clinical trials that led to the FDA approval of these drugs to treat PAH in USA. In a study by Miyamoto, PAH patients that walked < 332 meters had worse survival than patients who walked further. In addition, the distance walked significantly decreased in proportion to the severity of New York Heart functional class.[19]

World Health Organization/New York Heart Association (WHO/NYHA FC) Functional Class: It is determined at every clinic visit in PAH patients as outlined in Table 125.4 and has prognostic implication. Untreated patients who were in FC III or IV status had worse prognosis as compared to patients in FC I or II [2]. Goal of therapy is to improve FC. Patients that were treated with epoprostenol and remained in FC III or IV after three months of therapy had a 33% probability of survival over three years whereas patients in FC I or II had 88% probability of survival over three years.[20]

TABLE 125.4: World Health Organization/NYHA Classification of Functional Status in Pulmonary Hypertension Patients

Class	Description
I	Patients with PH in whom there is no limitation of usual physical activity; physical activity does not cause increased dyspnea, fatigue, chest pain or presyncope.
II	Patients with PH who have mild limitation of usual physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain or presyncope.
III	Patients with PH who have marked limitation of usual physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain or presyncope.
IV	Patients with PH who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

PATHOPHYSIOLOGY

Under normal conditions, pulmonary vasculature is a low resistance, high flow and high capacitance system. In pulmonary hypertension, pulmonary vasculature resistance (PVR) increases, leading to resistance to the flow of blood through the pulmonary vasculature. This may exhibit as RV strain and when the RV cannot overcome the increased resistance, right heart failure ensures.

The pathophysiology of PAH in Diagnostic Group I has been studied in much greater detail than in other diagnostic groups II to IV. However, similar pathology may exist in these groups also. PAH involves pulmonary arteries of less 500 µm. It is characterized by intimal proliferation, medial hypertrophy and adventitial hyperplasia. The muscularization of the small pulmonary arteries leads to decreased vascular lumen. Endothelial dysfunction has a main role in PH. There is increased production of endothelin-1, the most potent vasoconstrictor known to mankind, in the diseased pulmonary vasculature. In addition, there is increased production of vasoconstrictor thromboxane and decreased production of vasodilator, such as prostacyclin and nitric oxide (NO), which is recognized as an important endothelium derived vasodilator playing a major role in maintaining vascular tone in normoxemic pulmonary vasculature.[21] Increased shear may contribute to the increase in vascular tone in the presence of reduced NO production.[22] In addition to excessive vasoconstriction, both endothelin and thromboxane has vascular remodeling effects that lead to muscularized pulmonary arterioles.

In addition to medial hypertrophy, and intimal fibrosis, pulmonary hypertension is associated with thrombi *in situ* in small muscular pulmonary arteries.[1] The increased platelet aggregation may be due to abnormal arachidonic acid metabolism as shown by an elevated urinary metabolite of thromboxane (TXA_2) and reduced urinary metabolite of protacyclin (PIG_2) in pulmonary hypertension.[23,24]

MANAGEMENT

Treatment of the etiological cause constitutes the cornerstone of management of PH associated with chronic lung or heart diseases. The objectives of treatment of chronic cor pulmonale, for example consist of management of hypoxemia and airway obstruction. Pulmonary arterial pressures will fall with satisfactory management of the underlying etiology. The role of pulmonary pressure lowering drugs is neither established nor recommended in PH associated with left heart failure, lung disease or chronic thromboembolic disease (Diagnostic Group II-V).

Avoidance of Airway Irritants

Tobacco smoke is the most common cause of COPD. Multiple studies have reported improvement in functional markers, symptoms, morbidity and mortality in COPD with smoking cessation. Smoking cessation is an integral part of COPD management. All smokers irrespective of symptoms should be counseled on the deleterious effects of smoking and cessation strategies implemented.

Oxygen Therapy

Hypoxic vasoconstriction plays an important role in the pathophysiology of pulmonary hypertension. Oxygen therapy is a cornerstone in management of hypoxemia in these patients. Two seminal trials documented survival benefit with long-term oxygen therapy in COPD. Nocturnal Oxygen Treatment Trial (NOTT) included subjects with arterial PaO_2 55 mm Hg or less or arterial PaO_2 59 mm Hg or less with coexisting peripheral edema, hematocrit at least 55% or pulmonale. This trial demonstrated a survival benefit of continuous supplemental oxygen therapy over nocturnal oxygen use, and the average duration of treatment was 19.3 months. Pulmonary vascular resistance and hematocrit reduced more in subjects that were on continuous oxygen therapy.[25] The Medical Research Council (MRC) trial included patients with severe COPD, PaO_2 between 40 and 60 mmHg, hypercapnia and history of congestive heart failure.[26] Subjects received either oxygen for at least 15 hours per day, usually at 2 L per minute or no oxygen. A survival benefit with the use of continuous oxygen was noted after 500 days. In this study, subjects on room air showed increase PAP whereas subjects on oxygen therapy showed no such increase.

Anticoagulation

In situ thrombosis is a part of the pathology of pulmonary hypertension.[27] Improved survival has been demonstrated in patients with idiopathic pulmonary arterial hypertension who were treated with oral anticoagulation.[28] Therefore, anticoagulation is recommended in idiopathic PAH patients with no contraindication for anticoagulation.

Diuretics

In the presence of signs of right heart failure (peripheral edema, ascites, hepatomegaly) use of diuretics is strongly encouraged. Patients should be advised to maintain near-normal intravascular volume and monitor salt and water intake. Diuretics commonly used are furosemide (loop diuretic) and spironolactone (aldosterone receptor antagonist). Aggressive diuresis should be avoided to prevent systemic hypotension, acute renal failure and hemodynamic compromise.

Digoxin

Digoxin has not been extensively studied in PAH. Digoxin acts by decreasing the function of Na^+/K^+ ATPase pump in the myocardium, thereby increasing the myocardial contractibility. It also increases Central Nervous System (CNS)- mediated vagus activity thus decreasing AV nodal conduction. Digoxin may be useful in refractory right heart failure to augment RV function and increase cardiac output in PAH.[23]

Vasodilator Therapy

Multiple pharmacological agents modulate vascular remodeling in addition to their pulmonary vasodilatory effects. Several drugs are now available to treat PAH associated with Group I diseases. Three major pathways [endothelin pathway, prostacyclin pathway and nitric oxide pathway] have been implicated in the pathogenesis of PAH. Eight drugs targeting these pathways are currently Food and Drug Administration (FDA) approved to treat PAH (Diagnostic Group I classification) in United States. These include epoprostenol,[4] treprostinil,[5] inhaled treprostinil,[24] iloprost,[6] bosentan,[7] ambrisentan,[8] sildenafil and tadalafil.[22,9] Studies in PAH have shown the effectiveness of these agents on pulmonary hemodynamics, however, these are not indicated to treat pulmonary hypertension related to left heart disease, lung disease or chronic thromboembolic disease. More studies are needed before the available PAH medication can be recommended for use for these indications.

Endothelin Pathway: Endothelin-1, a peptide produced in endothelial cells and vascular smooth muscle cells, binds and activates 2 G protein–coupled receptors, ET_A and ET_B. ET_A is located predominantly on smooth muscle cells, whereas ET_B is found on both endothelial and vascular smooth muscle cells.[1,29-31] Activation of the ET_A receptor on smooth muscle cells causes sustained vasoconstriction and proliferation of these cells. However, activation of ET_B on endothelial cells induces clearance of endothelin-1 from the circulation and mediates vasodilation through the activation of NO and prostacyclin. Endothelin-1 is over expressed in PAH and is thought to be important in the pathogenesis of the disease. [12] Therefore, antagonists to endothelin receptors were developed as targeted PAH therapeutic agents.

Endothelin receptor antagonists: Bosentan was the first ERA to be available to treat PAH. It is considered a nonselective competitive antagonist of ET_A and ET_B receptors and ambrisentan is referred to as an ET_A-selective antagonist. Bosentan and ambrisentan have a relative affinity for ET_A over ET_B of 20:1 and 77:1, respectively based on in vitro competitive receptor binding assay.[32-34] According to one theory, ambrisentan should selectively block vasoconstrictive effects of ET_A

while maintaining vasodilatory and endothelin-1–clearing properties of the ET_B receptor. Despite an apparent receptor selectivity advantage for ambrisentan, a clinically meaningful difference in efficacy between agents has not been demonstrated.[31] Hence, factors, such as adverse events and drug interactions may be more relevant when considering treatment with an ERA agent.

Phosphodiesterases: Phosphodiesterases are a super family of enzymes that inactivate cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate, the second messengers of NO and prostacyclin, respectively.[1] Production of NO is impaired in patients with PAH,[35] resulting in decreased production of cGMP. One advancement in PAH therapy was to prolong the circulation of existing cGMP by inhibiting its inactivation by phosphodiesterases. PDE-5 is the predominant and selective phosphodiesterase in the pulmonary tissue.[36] PDE-5 inhibitors increase cellular cGMP levels causing preferential pulmonary vasodilation with less significant reductions in systemic blood pressure.

Phosphodiesterase 5 inhibitors: Sildenafil and tadalafil are PDE-5 inhibitors that have similar mechanisms of action.[37] Both sildenafil and tadalafil have higher selectivity for PDE-5 than for PDE-1, PDE-2, PDE-3 and PDE-4, at a level of 80- to >1000-fold for sildenafil and >10,000-fold for tadalafil. Currently, approved therapies for the treatment of PAH function through different pathways. These pathways are not distinct and are thought to interact with one another in a complex manner that has yet to be fully elucidated. Prostacyclin and NO are also known to reduce the release of endothelin-1, thus controlling the signaling for endothelin receptors.[29] Together these complex interactions promote aberrant cellular growth, vasoconstriction and thrombosis within the pulmonary arteries.

Prostanoids: Endogenous prostacyclins, produced by endothelial cells of blood vessels, are decreased in patients with PAH.[38,39] There are 4 prostanoid receptors in the lung that are considered to be involved in regulating vascular tone, platelet activation, and immunological cell responses.[40] Hence, prostanoids (prostacyclins and prostacyclin analogues) are a rational choice for the treatment of this disease. Current guidelines recommend the use of prostanoids in patients with PAH functional class II-IV.[41] In addition, sequential combination therapy with prostacyclin analogs, PDE5-i and ERA's should be considered if adequate response with monotherapy is not achieved or if patients deteriorate with monotherapy;[41] however, data supporting the use of combination therapy are limited and these therapies are the focus of current research.[42]

Prostanoids Agonist

Prostanoids have been used in routine clinical practice in PAH patients since the 1990s, although their investigational use was reported in 1980s.[43,44] Currently, there are several different prostanoids available in different formulations [for intravenous (IV) use, as a subcutaneous (SC) injection, and for inhalation].[45]

Epoprostenol: Epoprostenol, also known as synthetic prostaglandin I_2, was the first therapy approved in 1995 by the United States (US) FDA for the treatment of PAH.[46,47] Derived from the metabolism of arachidonic acid, it is a potent pulmonary and systemic vasodilator, an inhibitor of platelet aggregation,[47,48] and may modulate pulmonary vascular remodeling.[49]

The systemic half-life ($t_{1/2}$) of epoprostenol is 2 to 3 minutes. Epoprostenol metabolism in humans results in 2 major metabolites, which are primarily excreted via the kidneys.[48,50-52]

Clinical studies in PAH patients demonstrated improvement in hemodynamic parameters, functional status and exercise capacity (6-minute walk distance [6MWD]) with epoprostenol treatment.[48,51,53-59] Dose-dependent decreases in several parameters were observed with IV epoprostenol therapy, including total pulmonary resistance, pulmonary vascular resistance (PVR) and mPAP, and increases in cardiac index and stroke volume.[48,51,55] The hemodynamic effect of epoprostenol is similar in the acute and chronic settings.[48,51,52] Intravenous epoprostenol improved survival and the only PAH medication to have an indication for survival in its prescribing information.[48,50,55] However, in patients with scleroderma associated pulmonary hypertension, no significant improvement in survival was observed with epoprostenol therapy relative to conventional therapy.[54]

Treprostinil: Treprostinil is a synthetic prostanoid that is stable at room temperature and has a neutral pH.[60,61] Similar to epoprostenol, treprostinil is a potent pulmonary and systemic vasodilator, and an inhibitor of platelet aggregation.[60-62] Parenteral treprostinil is available as a branded product only (Remodulin®; United Therapeutics Corp.).[61] The manufacturer recommends that treprostinil be administered via a continuous SC infusion, with IV infusion used only in the event of intolerance to SC administration (e.g. severe injection site pain/reactions).[61]

Treprostinil is metabolized by the liver into five metabolites, which are primarily excreted in the urine. Treatment of patients with PAH with IV or SC treprostinil improves hemodynamic parameters and exercise capacity.[63-68] The effects of treprostinil on hemodynamics have been variable.[63,65-68] In a study comparing IV treprostinil with epoprostenol, the hemodynamic changes were similar for both of these agents.[65] Bioequivalence of IV and SC treprostinil was shown in a study in healthy volunteers.[69] In animal studies, the use of treprostinil reduced ventricular afterload (both right and left) and increased stroke volume and cardiac output.[61]

Iloprost: Iloprost is a synthetic prostaglandin I_2 analogue. Like epoprostenol and treprostinil, iloprost is a systemic and pulmonary vasodilator that also has antiplatelet properties.[70] Iloprost is available as a mixture of the 4S and 4R stereoisomers; with respect to vasodilation, the 4S isomer is more potent than the 4R isomer.[71] Iloprost is marketed under the brand name Ventavis® (Actelion Pharmaceuticals US, Inc.) in the US.[71] The systemic $t_{1/2}$ of inhaled iloprost is 20 to 30 minutes; Iloprost is metabolized via oxidation to produce one major metabolite, which is primarily excreted in the urine.[71]

Inhaled iloprost improves hemodynamic parameters, functional status and exercise capacity.[72-79] In addition, iloprost added to stable ongoing bosentan therapy significantly delayed the time to clinical worsening.[80] Hemodynamic effects of iloprost in humans include decreases in PVR and mPAP and increases in cardiac output and oxygen saturation after 12 weeks and 2 years of treatment.[75,79] Unlike the parenteral prostanoids, the effect of inhaled iloprost on mean systemic arterial pressure has been variable; some studies show no effect,[78,81-83] whereas others see significant reduction.[75] It has also been shown that patients receiving inhaled iloprost do not experience rebound symptoms during the night, which may occur with interruption of parenteral infusion of epoprostenol or treprostinil.[84]

Inhaled Treprostinil: The inhaled formulation of treprostinil is the most recent prostacyclin to be approved by the US FDA (July 2009). It is marketed under the brand name Tyvaso™ by United Therapeutics.

Systemic exposure of inhaled treprostinil was found to be proportional to the administered dose in a single-dose study in healthy volunteers;[85] in one study, including patients with PAH, 30 mcg/dose (4x/day) and 45 mcg/dose (4x/day) caused a maximum blood concentration of 0.33 ng/mL and 0.96 ng/mL, respectively, time to maximum concentration was 15 minutes and 45 minutes, respectively, and $t_{1/2}$ was 44 to 52 minutes.[86] Similar dose-proportionality in patients with PAH was reported in a second study.[87] Hemodynamic effects of inhaled treprostinil included decreases in mPAP and PVR.[86,87]

Clinical studies of inhaled treprostinil have been conducted in patients already receiving the endothelin receptor antagonist bosentan or the phosphodiesterase type-5 inhibitor sildenafil, and have shown that inhaled treprostinil significantly improved hemodynamics, functional class, and exercise capacity when added to oral therapy.[85-87] However, in one study (TRIUMPH-I), inhaled treprostinil when added to oral therapy significantly improved exercise capacity (6MWD) and did not improve the functional class.[86]

Oral Prostanoids

Oral formulations of prostanoids and one prostacyclin agonist are currently in development. An oral formulation of treprostinil has been developed by United Therapeutics; however, this formulation has not yet been approved in the US and is currently undergoing assessment in clinical trials.[45,88-90] Similarly, the prostacyclin analog beraprost has launched in Japan and Korea by Kaken Pharmaceuticals and is also undergoing assessment in the US.[91-102] In addition, there is a long-acting nonprostanoid prostacyclin receptor agonist prodrug, ACT-293987 (also known as NS-304), in the development for treatment of PAH by Actelion Pharmaceuticals.[103,104]

SUMMARY

Pulmonary Hypertension is a serious disease that carries a high mortality. Although echocardiogram is a good screening tool, a right heart catheterization is required to confirm this diagnose. Correct diagnosis is important as treatment options will depend upon these results. The currently available therapies are indicated to treat patients in PAH (Diagnostic Group I). Use of these agents to treat pulmonary hypertension in other Diagnostic Group [Diagnostic Group II-IV] is not recommended.

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Pulmonary Thromboembolism

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INTRODUCTION

Pulmonary thromboembolism (PTE) commonly called pulmonary embolism (PE) and deep vein thrombosis (DVT) are different manifestations of the same disease. PE is a disorder that holds the interest of a wide variety of medical practitioners, including the general physicians, pulmonologists, cardiologists, surgeons, obstetricians, radiologists, nuclear physicians, pathologists and others. For long, despite an improved understanding of the pathogenesis and consequently the use of preventive measures, morbidity and mortality from PE remained unchanged. The recent advances in the diagnostic strategies, pharmacotherapeutics and surgical management have decreased mortality from venous thromboembolic disease significantly in the past few decades.[1] Although there have been technological advances in management, for most clinicians in the third world countries, like India, the tests such as ventilation-perfusion lung scanning and spiral CT are not readily available.

EPIDEMIOLOGY

In most cases, PE is a consequence of DVT, of whom about 50% have an associated, usually clinically asymptomatic PE at lung scan.[2] In about 70% of patients with PE, DVT can be found in the lower limbs, if sensitive diagnostic methods are used.[3, 4] Although DVT and PE are manifestations of a single disease, PE has features that are distinct from DVT. The risk of death related to the initial acute episode or to recurrent PE is greater in patients who present with PE than in those who present with DVT.[5] According to prospective cohort studies, the acute case fatality rate for PE ranges from 7 to 11%.[6] Also, recurrent episodes are about three times more likely to be PE after an initial PE than after an initial DVT (60% vs 20%).[6] The overall age and sex-adjusted annual incidence of venous-thromboembolic disease is approximately 1 to 2 cases per 1000 persons and is considered strongly age dependant as the incidence rises to about 1% per year in persons greater than 75 years of age.[7, 8]

A recent epidemiological study confirmed that venous thromboembolism (VTE) is a major public health burden with an estimated 370,000 related deaths in 2004 in six European countries.[9] Moreover, PE may lead to chronic thromboembolic pulmonary hypertension, which can be severely disabling.[10, 11] PE has been shown by autopsy studies to be the cause of mortality in 10% of all hospital deaths, and contributing to mortality in a further 10%. Two thirds of the cases were unsuspected and unconfirmed antemortem. Furthermore, it is well known that only one third of cases suspected as PE on the basis of clinical symptoms are confirmed by investigations to be so (Fig. 126.1).

PATHOPHYSIOLOGY

The pathophysiology of PE includes the formation of DVT and subsequent embolization into the pulmonary arteries. Current evidence confirms that the factors related to clot formation, i.e. venous stasis, increased blood coagulability and injury to the vein wall (Virchow's triad) are the most important factors in the pathogenesis of VTE. The most common source of pulmonary emboli

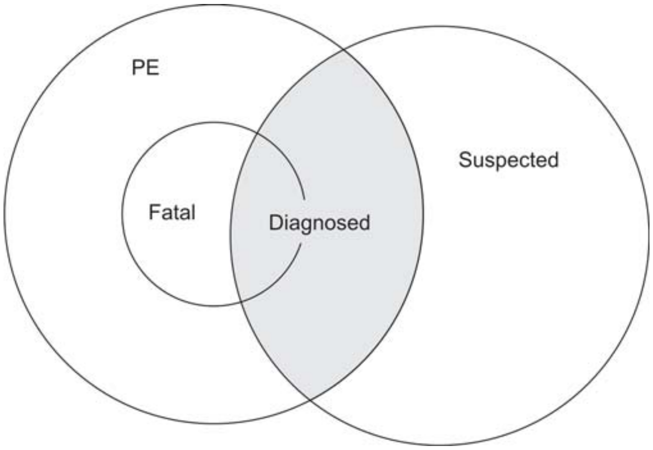


Fig. 126.1: Relationship between diagnosed and suspected PE

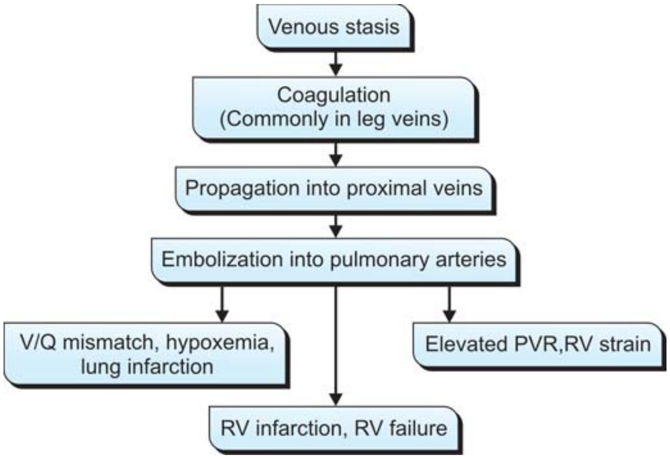

Venous stasis
Coagulation (Commonly in leg veins)
Propagation into proximal veins
Embolization into pulmonary arteries
V/Q mismatch, hypoxemia, lung infarction
Elevated PVR,RV strain
RV infarction, RV failure

Fig. 126.2: Pathophysiology and cardiovascular consequences of PE

is thrombosis in the deep veins of the lower limbs, particularly between the knee and the inguinal ligament. PE is infrequently due to thrombosis of the pelvic veins, veins of the upper extremities or other organ systems (e.g. hepatic and renal veins). The thrombus dislodges and travels through the venous circulation and lodges in one of the pulmonary arteries. The embolism results initially in an area of the lung that is ventilated but under perfused, resulting in an alveolar dead space. Release of vasoactive substances, like serotonin from the platelets and the blockade of the pulmonary artery by the clot, cause an elevation of pulmonary vascular resistance. This results in an increase in right ventricular workload, leading to a redistribution of blood flow and increase in right ventricular workload which, if excessive, may result in right ventricular failure (Fig. 126.2). Once this occurs there is a fall in the pulmonary blood flow and reduction of left ventricular filling, causing systemic hypotension.

Airway obstruction resulting from the reflex bronchoconstriction further contributes to the ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch. After about 24 hours, there is depletion of surfactant which may result in atelectasis and edema of the affected area. Pulmonary infarction itself is an uncommon consequence of PE, because the pulmonary parenchyma has three potential sources of oxygen, namely—the pulmonary arteries, the bronchial arteries and the alveoli. Generally, two of these sources need to be compromised before infarction develops and this usually happens only in patients with coexisting cardiopulmonary disease. Also, complete occlusion of the pulmonary artery is infrequent. Although the site of the clot and the extent of obstruction determine the severity of the disease and the outcome, in the presence of pre-existing cardiopulmonary disease, a small embolic event in the pulmonary artery may result in serious consequences. Conversely, a major occlusion in one of the main pulmonary arteries may have lesser consequences in a person with a normal pre-existing cardiopulmonary status.

RISK FACTORS

Venous thromboembolism is currently considered to be the result of an interaction between patient-related and setting-related risk factors.[12] Patient-related predisposing factors are usually permanent; whereas setting-related risk factors are more often temporary (Table 126.1). However, the predictive values of these factors are not equal and VTE can occur in patients without any identifiable predisposing factors.

Surgery and Fractures

Recent surgery and fractures, particularly of the femur and tibia, pose an increased risk. In surgical patients, the high risk groups are those that have major high-risk operations performed for abdominal or pelvic malignancy, major orthopedic surgery and any surgery requiring intensive care. The likely causative factors are immobility and liberation of clotting factors.

Malignancy

Although the exact mechanism is unknown, abnormalities of homeostasis occur in patients with neoplastic disease. A well known example is the association of thrombophlebitis migrans with

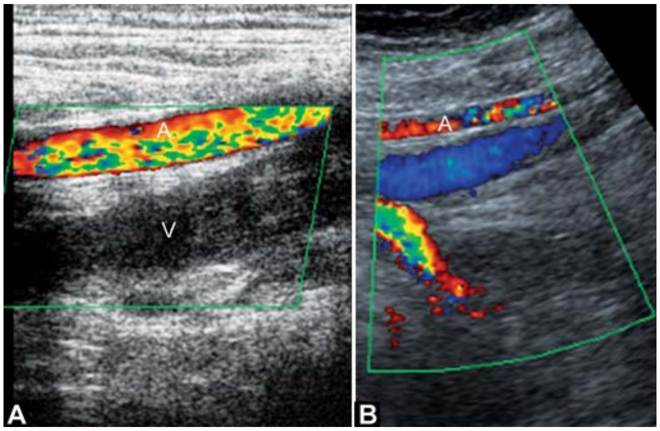
TABLE 126.1: Risk factors for pulmonary thromboembolism

Major risk factors		*Minor risk factors*
Surgery and bone fractures	• Abdominal/pelvic surgery • Hip/knee replacement • Postop ICU care • Bone fractures especially of tibia and femur	• Oral contraceptive use • Hormone replacement therapy • Myocardial infarction • Congestive cardiac failure • Congenital heart disease • Superficial venous thrombosis • Indwelling central vein catheter • Chronic obstructive airway disease • Increasing age • Occult malignancy • Thrombotic disorders • Long distance sedentary travel • Obesity
Malignancy	• Pancreatic • Bronchial • Genitourinary • Stomach and colon • Breast • Advanced/metastatic	
Obstetrics	• Pregnancy (late) • Peurperium • Cesarian section	
Immobilization (especially lower limb)	• Plaster of Paris cast • Paralysis • Hospitalization • Institutional care	
Others	Previous proven VTE	

gastrointestinal tract malignant disease. The association of venous thromboembolism is seen most often with pancreatic cancer, followed in the order of frequency by carcinomas of the bronchial tree, genitourinary tract, colon, stomach and breast. In one series, cancer was found to be a risk factor in 22.3% of the patients with venous thromboembolism.

Pregnancy and Puerperium

Venous thromboembolism is one of the leading causes of maternal morbidity and mortality. About two thirds of these cases occur during pregnancy and one third during postpartum. A recent case-control study showed that the risk of VTE was increased fivefold (OR 4.6, 95% CI 2.7–7.8) during pregnancy and 60-fold (OR 60.1, 95% CI 26.5–135.9) during the first 3 months following delivery compared to non-pregnant females.[13] The risk was highest in the third trimester of pregnancy and during the first 6 weeks after delivery. In pregnancy and puerperium, the clot formation is probably due to venous stasis in the lower limbs resulting from decreased venous return due to direct pressure from the enlarged uterus. Increased levels of some of the clotting factors and possible reduction in fibrinolytic activity may also contribute. In pregnancy, Doppler ultrasound (Figs 126.3A and B) can help to diagnose deep vein thrombosis.



Figs 126.3A and B: Color doppler images of the external iliac artery (A) and external iliac vein (V) in a patient with DVT (image A) and in a patient with patent veins (image B). In 'image A', thrombosed external iliac vein (V) is dilated and shows echogenic intraluminal thrombus, without color uptake. In 'image B'; the patent vein (V) shows normal color uptake

Immobilization

Immobilization for more than a week is an important risk factor. Diminished muscle activity in the lower limbs reduces venous return, facilitating accumulation of activated clotting factors.

Oral Contraceptive Therapy

Most Oral Contraceptives (OCP) consist of a combination of oestrogen and progestogen. The reduction in dose of oestrogen has been reduced over time; this has reduced the risk of VTE in females. However, there is still a twofold to fivefold increased risk, with the risk being highest during first year of use.[14]

Cardiorespiratory Disorders

The source of the emboli in these diseases is also the veins of the lower limbs, rather than the heart itself. In these situations, the risk of clot formation in the leg veins is probably enhanced by the reduction in the peripheral blood flow. Venous thromboembolism has been reported to be over three times more common in patients with heart disease (aged 30 years or more) than in age matched controls.

Inherited Causes

Deficiencies of natural coagulation inhibitors, such as antithrombin, protein C and protein S, are strong risk factors for VTE, but these deficiencies are rare and account for only 1% of all cases of VTE. Factor V Leiden and prothrombin (factor II) G20210A mutations are two more common genetic variants that have been consistently found to be associated with VTE, but still explain only a small proportion of VTE cases.

Age

Age is an important risk factor. In one series, 88.5% of the patients diagnosed with PE were aged 40 years or more.

CLINICAL FEATURES

The clinical presentation of PE can vary widely from one patient to another. Evaluating the likelihood of PE in an individual patient according to the clinical presentation is of utmost importance, not only for the interpretation of the diagnostic test results but also for the selection of an appropriate diagnostic strategy.[15] In 90% of cases, suspicion of PE are raised by clinical symptoms, such as dyspnea, chest pain and syncope, either alone or in combination (Table 126.2). In several series, dyspnea, tachypnoea or chest pain were present in more than 90% of patients with PE.[16, 18]

The initial presentation usually falls into one of the following three categories:[17]

TABLE 126.2: Prevalence of symptoms and signs in patients with PE[18-20]

Symptoms	*% of patients*
Dyspnea	80
Chest pain (pleuritic)	52
Chest pain (sub-sternal)	12
Cough	37
Leg pain	26
Syncope	19
Hemoptysis	11
Signs	*% of patients*
Tachypnea	70
Tachycardia	26
Loud P2	23
Signs of DVT	15
Cyanosis	11
Fever	7

1. *Pulmonary infarction syndrome*: The patients who fall in this category present with dyspnea and pleuritic chest pain. The severity of PE is deemed to be mild. This is the most common mode of initial presentation. In one study, three-quarter of the patients presented this way.
2. *Isolated dyspnea*: In these patients, the only symptom is acute shortness of breath. These patients are often hypoxic, and PE in these patients is deemed to be moderate. This presentation is encountered in roughly one-fifth of the patients.
3. *Circulatory collapse*: Patients in this category present with circulatory collapse, characterized by shock or syncope. PE in these people is deemed to be severe.

It is good to keep the following factors in mind during clinical assessment of a patient with suspected PE:
- Pleuritic chest pain, with or without dyspnea, is one of the most frequent presentations of PE. Moderate-to-large embolism may be associated with retrosternal; angina-like chest pain, which may reflect right ventricular ischemia.
- The onset of dyspnea may at times be insidious in onset and progressive over several weeks, the diagnosis of PE is considered by the absence of other causes of dyspnea.
- Syncope, a rare presentation of PE, may indicate a severely reduced hemodynamic reserve.

On physical examination, tachypnea is the most common sign. Other signs include—tachycardia, crackles, fever, diaphoresis, cyanosis, parasternal heave, loud pulmonary component of the second heart sound, third or fourth heart sound, wheezes, pleural friction rub, hepatomegaly and hepatojugular reflux. These findings are common to several cardiopulmonary disorders and so have low specificity. Since lower limb DVT is the cause of PE in the majority of cases, it is prudent to look for local pain, tenderness, redness and warmth. Unfortunately, these signs are also non-specific and may even be misleading at times.

DIAGNOSIS

The diagnosis of PE requires the integration of a careful history and physical examination with laboratory testing and appropriate imaging modalities.

Routine Investigations

A chest radiograph is usually the first investigation ordered for patients presenting with symptoms of PE, followed by ECG. Routine investigations, like chest X-ray, ECG and 2D-ECHO, are of limited value in the diagnosis of PE. More importantly, they contribute in excluding many common conditions with similar clinical presentation like; acute myocardial infarction, acute aortic dissection, pneumonia, pneumothorax, cardiac failure. Chest radiographic abnormalities are common in patients with PE; but they are not diagnostic (Table 126.3). Abnormal electrocardiogram may be seen in patients with PE, quite frequently, but the ECG abnormalities are also not specific for PE (Table 126.4).

D-dimer Testing

D-dimers are formed as a result of fibrin degradation and rise with intravascular coagulation. The levels in plasma reflect the fibrinolytic activity on pre-existing thrombi; and not necessarily the rate of thrombus formation. D-dimer levels are non-specific, which can be elevated in various conditions like cancer, inflammation, peripheral vascular disease, in hospitalized patients including obstetrics.[21, 22]

D-dimer levels have low specificity and positive predictive value;[23] elevated D-dimers cannot be used for the confirmation of diagnosis of PE,[15] nor a normal D-dimer test be used to overrule the clinical judgment of a physician in suspecting and performing further investigations for PE in patients with high clinical probability. However, the test has a high negative predictive value and reliably excludes PE in patients with low or intermediate clinical probability.[12]

TABLE 126.3: Radiological signs of PE[17]

Common	*Rare*
• Atelectasis	• Focal oligemia (*Westermark's sign*)
• Raised hemidiaphragm	• Wedge shaped density above the diaphragm (*Hampton's sign*)
• Focal infiltrate	• Enlarged right descending pulmonary artery (*Palla's sign*)
• Small pleural effusion	• Cardiomegaly

TABLE 126.4: Electrocardiographic findings in PE

Electrocardiography
• Sinus tachycardia
• T wave inversion in leads V1-4
• S1Q3T3 pattern
• New RBBB

Deep Venous Thrombosis Testing

Compression ultrasonography (CUS) is used as an indirect method for diagnosing PE. CUS has a sensitivity of over 90% for proximal DVT and a specificity of about 95%.[24, 25] It shows DVT in 30 to 50% of patients with PE[24, 25] finding a proximal DVT in patients suspected of PE is sufficient to warrant anticoagulant treatment without further testing.[15] The only validated diagnostic criterion for DVT is incomplete compressibility of the vein, which indicates the presence of a clot, whereas flow criteria are unreliable.[15] Proximal CUS can be performed and, when positive in patients with contraindications to contrast, CT can be avoided.[15]

Radioisotope Ventilation-Perfusion Scan ($\dot{V}/\dot{Q}$ Scan)

Ventilation-perfusion scintigraphy ($\dot{V}/\dot{Q}$ scan) is a well established diagnostic test for suspected PE (Fig. 126.4). It is non-invasive and safe to apply barring a few allergic reactions that have been described. The ventilation and perfusion phases of a $\dot{V}/\dot{Q}$ lung scan are performed together. A chest X-ray would be useful to have comparison and to look for other causes of lung disease. A defect in the perfusion images requires a mismatch in the ventilation scan, implying normal ventilation in the corresponding area, to be deemed as suggestive of PE. In the ventilation phase of the test, a gaseous radionuclide xenon, ^{133}Xe or Tc-99 m-labeled aerosols or Tc-99 m-labeled carbon microparticles (Technegas) is used. The perfusion phase of the test involves the intravenous

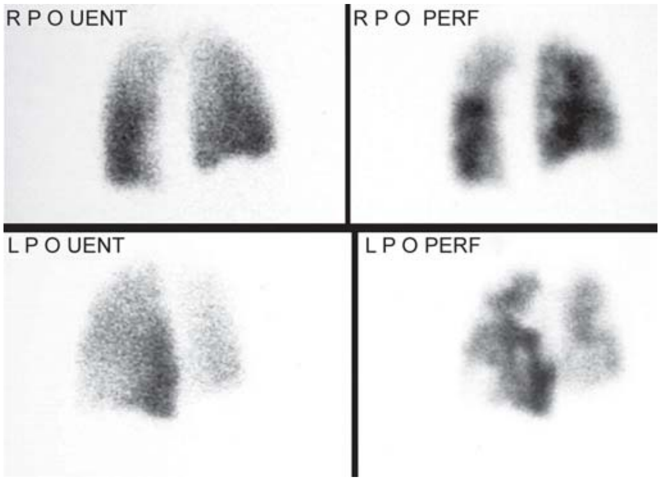


Fig. 126.4: Ventilation-perfusion lung scan shows a number of unmatched ventilation-perfusion defects; consistent with pulmonary thromboembolism

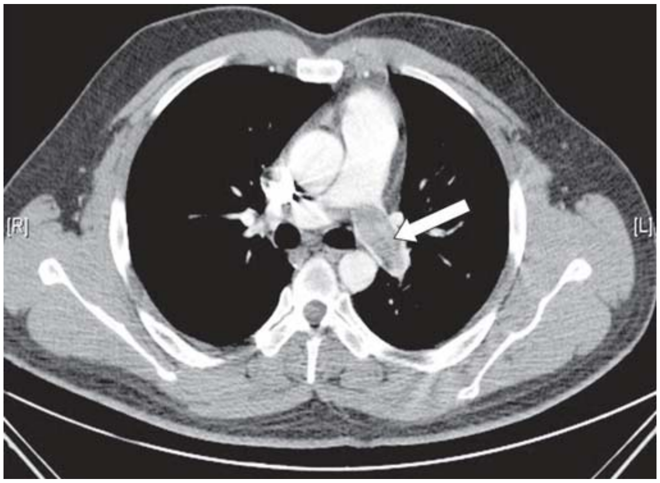


Fig. 126.5: CT-PA showing filling defect (arrow) in the main pulmonary artery at the origin of the left main pulmonary artery, suggesting thromboembolism

injection of radioactive technetium macroaggregated albumin (Tc99m-MAA), which blocks a small fraction of pulmonary capillaries and thereby enables scintigraphic assessment of lung perfusion at the tissue level. Where there is occlusion of pulmonary arterial branches, the peripheral capillary bed will not receive particles, rendering the area 'cold' on subsequent images.

Diagnostic accuracy of the $\dot{V}/\dot{Q}$ scan is greatest when the test is combined with clinical probability.[26] The value of the test could be summarized as follows:

- Patients with high clinical probability of PE and a high-probability $\dot{V}/\dot{Q}$ scan had a 95% likelihood of having PE.
- Patients with low clinical probability of PE and a low-probability $\dot{V}/\dot{Q}$ scan had only a 4% likelihood of having PE.
- A normal $\dot{V}/\dot{Q}$ scan virtually excludes PE.

In patients whose reports do not fall in the above categories, other confirmatory tests need to be done. $\dot{V}/\dot{Q}$ scan involved little risk for most people. The amount of radiation used together for ventilation and perfusion are about the same as the amount a person is naturally exposed to in a 1 year period. Although rare, the radioisotopes may cause allergic reactions.

Computer Tomography Pulmonary Angiography

Computer tomography-pulmonary angiography (CT-PA) is being increasingly used as a diagnostic modality for patients with suspected PE. In the past few years, it has become the procedure of choice for diagnosing PE (Fig. 126.5). One of the most commonly cited benefits of CT-PA is its ability to detect alternative pulmonary abnormalities that may explain the patient's clinical presentation.[27, 28] With spiral CT, the location and the magnitude of the thrombus is demonstrated and both mediastinal and parenchymal structures are evaluated, which may provide important alternate or additional diagnoses.

The main impediment for spiral CT has been the limitations of this modality for the accurate detection of small peripheral emboli.[29-31] Early studies comparing conventional single slice spiral CT with selective pulmonary angiography demonstrated high accuracy of spiral CT for detecting PE from the main pulmonary artery to the segmental arterial level,[32, 33] but they also concluded that sub-segmental emboli may be missed. Limitations in view of the inability to make a reliable diagnosis of small peripheral emboli, with a reported miss rate of upto 30% with single-slice spiral CT, have prevented the unanimous embrace of spiral CT as the new standard of reference for imaging PE.[34]

Although the accuracy of conventional single-slice spiral CT for the detection of isolated peripheral emboli may be limited, encouraging data are accumulating on the high negative predictive value of a normal spiral CT study.[28, 35-44] According to these studies, patient outcome is not adversely affected if anticoagulation is withheld on the basis of a negative spiral CT study. The high negative predictive value of a normal spiral CT study compares very favorably with catheter pulmonary angiography,[45] approaches 98% regardless of whether underlying lung disease is present.[39, 40] The frequency of a subsequent clinical diagnosis of PE or DVT after a negative spiral CT pulmonary angiogram is low, and much lower than that after a negative or low-probability $\dot{V}/\dot{Q}$ scan.[35, 37] Thus, even a single slice spiral CT appears to be a reliable imaging tool for excluding clinically relevant PE.

Lingering concerns about the accuracy of spiral CT for PE detection can be largely overcome by the advent of multidetector-row spiral CT (MDCT). With improved diagnosis of small peripheral emboli, MDCT is emerging as a preferred modality for imaging patients with suspected acute PE (Fig. 126.6). According to the Prospective Investigation of pulmonary embolism diagnosis (PIOPED) II study,[46] the sensitivity of MDCT was 83% and the specificity 96%. Positive predictive values were 96% with a concordantly high or low probability on clinical assessment, 92% with an intermediate probability on clinical assessment. Thus, new generation MDCT is now a challenge to catheter pulmonary angiography, the gold standard for the accurate detection of PE.[34]

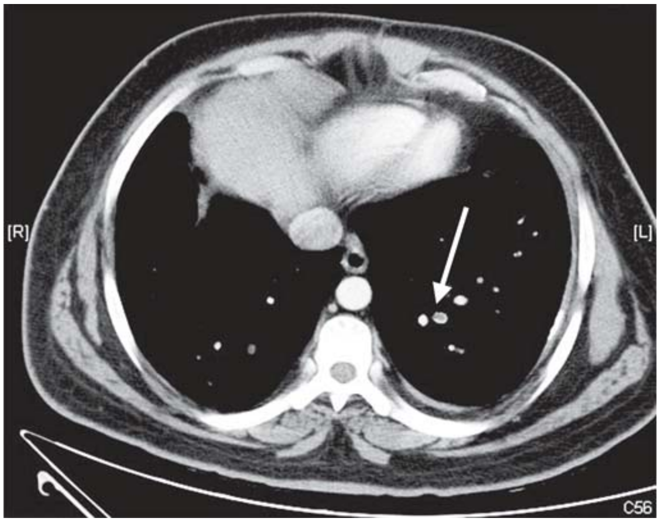


Fig. 126.6: Multidetector-Row Spiral CT (MDCT) showing filling defect (arrow) in a sub-segmental branches of the left descending pulmonary artery, suggesting thromboembolism

Pulmonary Angiography

Pulmonary angiography is still the gold standard investigation for the confirmation of PE (Fig. 126.7).[47] It is an invasive procedure with potential risks, therefore performed infrequently. It is indicated when cardiovascular collapse and hypotension are present, and when other investigations are inconclusive. The contrast is injected into the pulmonary artery via a catheter inserted through the femoral, internal jugular or the subclavian vein. The features indicating the presence of an embolus include intraluminal filling defect and abrupt vascular cut-off in pulmonary arteries. Fatal complications occur in 0.5 to 1.3% of the procedures and minor complications in 2% of patients.[17]

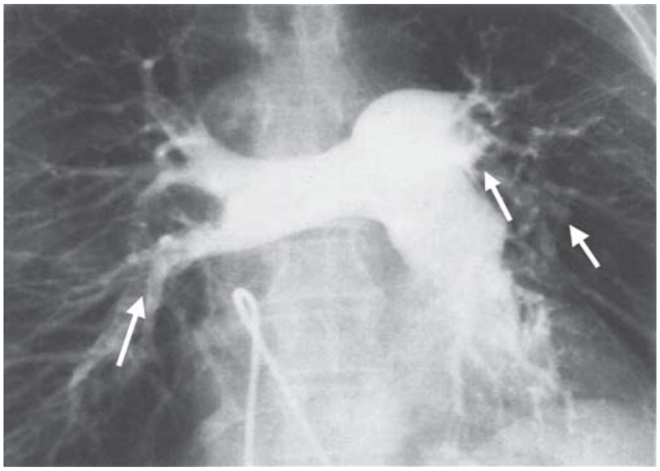


Fig. 126.7: Pulmonary angiogram showing several emboli obstructing pulmonary arteries (arrows)

CLINICAL PROBABILITY ASSESSMENT

In a patient with suspected PE, clinical probability assessment is considered as an essential step. The clinical pretest probability can be determined by taking into account the patient's clinical history, risk factors for VTE, clinical signs and the laboratory tests. The implicit evaluation of pretest probability was demonstrated to be relatively accurate in the PIOPED study.[48] Various clinical prediction rules are available for the diagnosis of PE, but the most widely used and validated in diagnostic studies are: (1) the Wells Score,[49] (Table 126.5) and (2) the Geneva Score.[50] The revised Geneva score proposed in 2006 (Table 126.6) is independent of the clinical judgement, chest radiographs and arterial blood gas analysis.[51]

Using one of the clinical prediction rules,[49, 51] the prevalence of confirmed PE is found to be 10% in low probability category, 30% in moderate category and 70% in high probability category.[52] Adopting one of these strategies may avert unnecessary investigations and may be cost saving. Therefore, we recommend its use in practice in resource limited settings like India. So far, these strategies have not been evaluated on clinical trials in developing countries.

TABLE 126.5: Wells score[49]

Variable		*Points*
Active cancer		+1
Hemoptysis		+1
Previous DVT or PE		+1.5
Heart rate > 100 beats/min		+1.5
Surgery or bed rest ≥ 3 days within 1 month		+1.5
Clinical signs of DVT		+3
No alternative diagnosis as more likely than PE		+3
Clinical probability	*Points*	*PE %*
Low	< 2	2–6
Intermediate	2–6	17–24
High	≥ 7	54–78
Clinical probability (dichotomized)		
PE unlikely	≤ 4	8–13
PE likely	> 4	37–56

TABLE 126.6: Revised Geneva score[51]

Variable		*Points*
Age > 65 yrs		+1
Active cancer		+2
Hemoptysis		+2
Previous DVT or PE		+3
Surgery or lower limb fracture within 1 month		+2
Unilateral lower limb edema and pain on palpation		+4
Spontaneously reported calf pain		+3
Heart rate 75–94 beats/min		+3
Heart rate ≥ 95 beats/min		+5
Clinical probability	*Points*	*PE %*
Low	≤ 3	7–12
Intermediate	4–10	22–31
High	≥ 11	58–82

DIAGNOSTIC STRATEGIES

Various combinations using clinical probability scores, D-dimer assays, lower limb imaging, ventilation perfusion lung scintigraphy and spiral CT have been evaluated in various studies to formulate diagnostic algorithms and for risk stratifications in patients with suspected PE. Recently, the European Society of Cardiology proposed diagnostic algorithms for patients with suspected high-risk (Fig. 126.8) and non-high-risk (Fig. 126.9) PE patients. Such algorithms need to be tailored to the needs of individual centers, based on the availability of investigative procedures and the resources.

TABLE 126.7: Features of right ventricular dysfunction

Echocardiography	• Rt Ventricular dilatation (without left heart disease) • Rt Ventricular free wall motion hypokinesia with sparing of apex (McConnell's sign) • Increased right ventricular after load • Pulmonary hypertension as tricuspid regurgitation with jet velocity > 2.8 m/sec
Right heart catheterization	• Impaired LV diastolic filling • Pulmonary arterial obstruction manifested as pre-capillary pressure > 20 mmHg and pulmonary capillary wedge pressure < 18 mmHg
Biomarkers	• BNP and pro-BNP

ASSESSMENT OF PROGNOSIS

Several strategies have been tried to prognosticate the out come in patients with PE. Some of them are as follows:

Clinical Assessment

Presence of hypotension and shock [defined as systolic blood pressure (SBP) less than 90 mm Hg or a drop of ≥ 40 mmHg for > 15 min] in patients with PE carries poor prognosis, and are the markers of high risk of death in acute PE.

Markers of Right Ventricular Dysfunction

Right ventricular dysfunction is related to intermediate risk of short-term mortality in acute PE. Echocardiographical findings suggesting right ventricular dysfunction have been reported to occur in at least 25% of PE patients.[53] More than a two fold increased risk of PE related mortality was found in patients with echocardiographic signs of right ventricular dysfunction.[54] Of various indices of right ventricular dysfunction (Table 126.7), there is lack of universally accepted criteria. However, a completely normal result should be considered as defining low risk PE. Right heart catheterization allows direct assessment of right ventricular filling pressures and cardiac output, but its routine use for risk stratification in acute PE is not recommended.

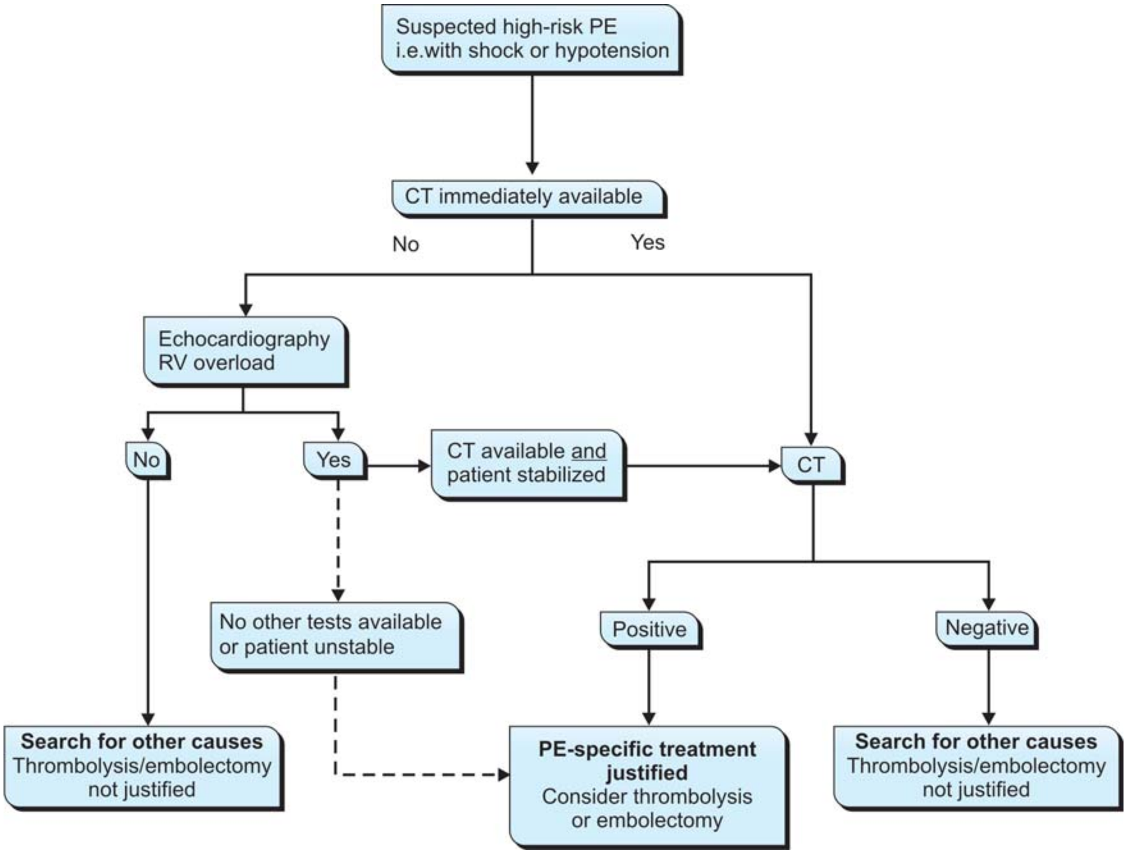

Suspected high-risk PE
i.e.with shock or hypotension
CT immediately available
No
Yes
Echocardiography
RV overload
No
Yes
CT available and patient stabilized
CT
No other tests available or patient unstable
Positive
Negative
Search for other causes
Thrombolysis/embolectomy not justified
PE-specific treatment justified
Consider thrombolysis or embolectomy
Search for other causes
Thrombolysis/embolectomy not justified

Fig. 126.8: Proposed diagnostic algorithm for patients with suspected high-risk pulmonary embolism (PE), with shock or hypotension. RV: Right ventricle; CT: Computed tomography. Reproduced from “Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008; 29:2288”, with permission of the Oxford University Press, Oxford

Ventricular dysfunction is associated with increased myocardial stretch which leads to the release of brain natriuretic peptide (BNP). Plasma BNP, released from myocytes of ventricles upon stretch, has been reported to differentiate pulmonary from cardiac dyspnoea. Different studies have shown that in acute PE, levels of BNP or N-terminal proBNP (NT-proBNP) reflect the severity of RVD and hemodynamic compromise.[55-58] BNP appeared to have better sensitivity and specificity than NT-proBNP in detecting right ventricular dysfunction.[59]

Although elevated BNP or NT-proBNP concentrations are related to worse outcome, their positive predictive value is low (12 to 26%).[15] On the other hand, low levels of BNP or NT-proBNP can be reliably used for identification of patients with a good prognosis regarding short-term mortality or a complicated clinical outcome (NPV 94 to 100%).[56, 60-64] A proBNP level less than 500 pg/ml was found to predict an uneventful hospital course in patients with acute PE.[65]

Markers of Myocardial Injury

Cardiac troponins T and I have both been reported to be elevated in acute PE in various observational studies. While right ventricular myocardium might not necessarily be its only source, elevated plasma troponin levels have been repeatedly reported as associated with worse prognosis in patients with PE.[66] It has also been observed that among patients with raised natriuretic peptide levels, increased serum troponins were associated with a further increase in the risk of adverse outcomes.[59] A cut-off value for troponin of greater than 0.09 ng/ml is a suitable predictor for death in hospital with a sensitivity, specificity, NPV and PPV of 80%, 92%, 99% and 34% respectively.[67]

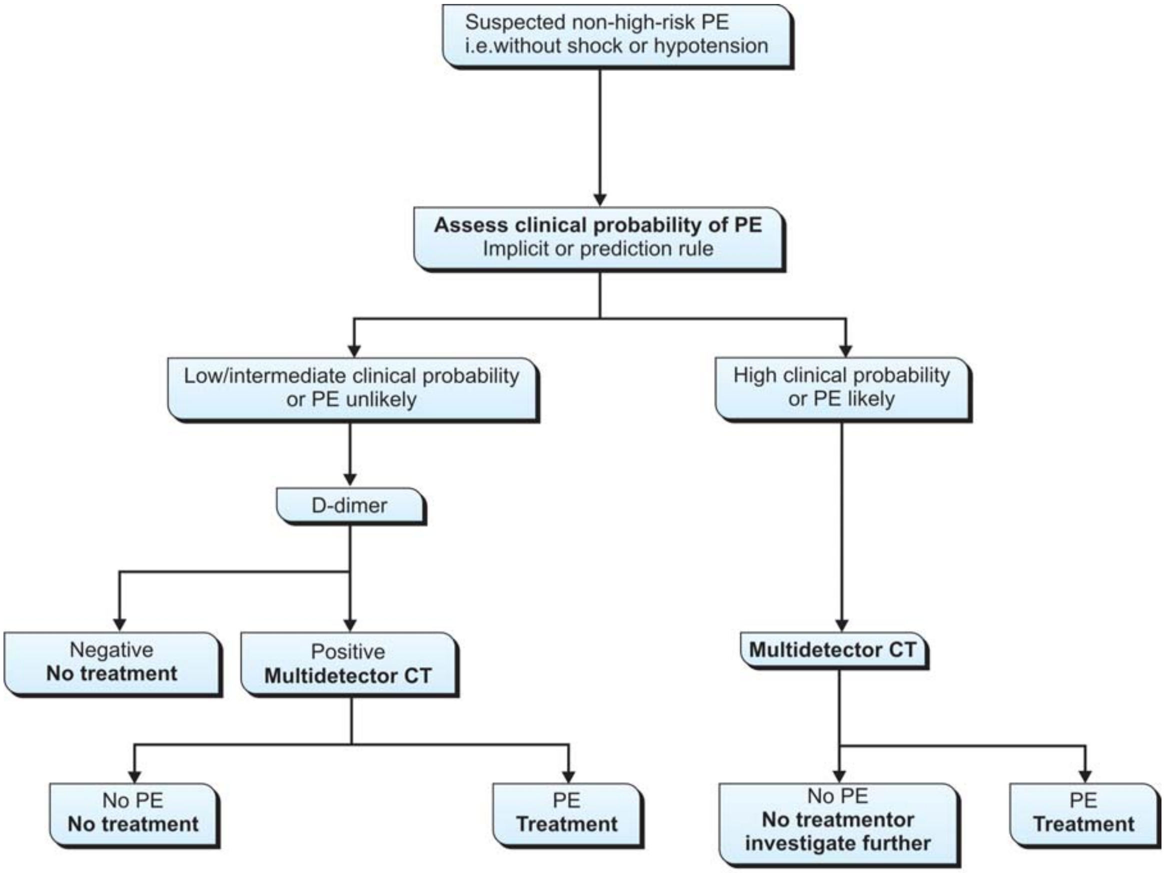

Suspected non-high-risk PE
i.e.without shock or hypotension
Assess clinical probability of PE
Implicit or prediction rule
Low/intermediate clinical probability or PE unlikely
High clinical probability or PE likely
D-dimer
Negative
No treatment
Positive
Multidetector CT
Multidetector CT
No PE
No treatment
PE
Treatment
No PE
No treatmentor investigate further
PE
Treatment

Fig. 126.9: Proposed diagnostic algorithm for patients with suspected non-high-risk pulmonary embolism (PE). MDCT: Multidetector-helical computed tomography. Reproduced from "Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008; 29:2289" with permission of the Oxford University Press, Oxford

New markers of myocardial injury are emerging; heart type fatty acid binding protein (H-FABP) is one of them. It is an early marker of myocardial injury, reported to be superior to troponin, NT-proBNP and myoglobin measurements for risk stratification of PE at admission. H-FABP greater than 6 ng/ml had a PPV and NPV for early PE-related mortality of 23 to 37% and 96 to 100% respectively.[68, 69] Growth Differentiation Factor (GDF-15) is another marker that has been found to be associated with complicated outcomes in patients with acute PE. The markers of myocardial injury, especially the newer ones, require further studies before they can be put to clinical use, establishing a role for the risk stratification of patients with PE.

MANAGEMENT

General Management

Analgesia should be given to patients with severe pleuritic pain, but opiates should be avoided in patients with incipient cardiovascular collapse since they cause vasodilatation. Hypoxemia should be treated with high percentage inspired oxygen, severe hypoxia may require ventilation. In hypotensive patients, colloids should be administered while monitoring central venous pressure; the right atrial pressure should be maintained high (15 to 20 mm Hg) to ensure maximal right ventricular filling. Use of ionotropic agents may be required to provide circulatory support. Diuretics and vasodilators are not indicated.[17]

Medical Treatment

Anticoagulation is the main stay of treatment for acute PE. The main objectives of anticoagulant therapy in the initial treatment of PE are to prevent thrombus extension while allowing endogenous fibrinolysis to proceed, and to prevent early and late recurrences of VTE. From the point of view of therapy patients suffering from PE can be classified into one of the following subsets:[70]

- *Stable PE:* Normotensive patients (when SBP ≥ 90 mmHg) and no evidence of right ventricular dysfunction.
- *Submassive PE*: Normotensive patients (SBP ≥ 90 mmHg) with evidence of right ventricular dysfunction.
- *Massive PE:* Patient is hypotensive or in cardiogenic shock (SBP < 90 mmHg) or cardiac arrest or there is fall in systolic BP by greater than 40 mm Hg; for at least 15 min.

Stable PE can be managed in hospital or on an outpatient basis with anticoagulation either with unfractionated heparin (UFH) or low molecular weight heparin (LMWH) or fondaparinux. Massive and sub-massive PE, however, carry high mortality; modalities to achieve early reperfusion of the pulmonary arteries may be life saving by reversing the right ventricular dysfunction. The various options available are thrombolysis, surgical embolectomy and percutaneous catheter embolectomy.

Anticoagulant Therapy

Anticoagulant treatment: It plays a critical role in the management of patients with PE and is required universally, regardless of whether they have undergone re-perfusion therapy for massive and sub-massive PE. Anticoagulants help in preventing formation of new thrombus, death and recurrent events with an acceptable rate of bleeding complications. The agents that are used for anticoagulation are as follows:

1. Unfractionated Heparin (UFH): UFH acts by binding to antithrombin and catalyzing the inactivation of thrombin factor Xa and other clotting factors. Besides, it also binds with other plasma proteins resulting in unpredictable pharmacokinetic and pharmacodynamic properties which can lead to non-hemorrhagic side effects, such as heparin-induced thrombocytopenia (HIT) and osteoporosis. Since the anticoagulant effect of UFH can rapidly be reversed, it is the agent of choice for patients with PE who are at high-risk of bleeding.

TABLE 126.8: Regimens of heparin therapy[70-73]

Intravenous route	*Subcutaneous route*
• 5,000 U bolus followed by 32,000 U/day infusion OR • 80 U/kg bolus followed by 18U/kg/hr infusion	• IV bolus of 5,000 U followed by 250 U/kg twice daily OR • Initial dose of 333 U/kg subcutaneously followed by 250 U/kg twice daily

Different regimens of heparin therapy[71-74] are practised by intravenous and subcutaneous routes (Table 126.8).

For the intravenous regimen, the bolus dose followed by continuous infusion is titrated to a target activated partial thromboplastin time of 1.5–2.5 times of control (approximately 60–80 seconds). The first measurement of APTT should be performed 4–6 hours after starting treatment to ensure adequate anticoagulation and repeated 3 hours after every change of dose and subsequently at least daily after target therapeutic dose is reached. Dosing based on patient's body weight is preferred to a standard regimen; it causes fewer fluctuations in APTT and achieves a therapeutic level more quickly with a shorter warfarin overlap. Subcutaneous heparin does not require frequent monitoring, unlike with IV dosing schedule, and is found to be as safe and effective as weight adjusted LMWH.[74]

The important complications associated with heparin use are bleeding, immune mediated platelet activation leading to HIT and osteoporosis. Sometimes uncommon dermatological side effects such as necrosis, alopecia and hypersensitivity are encountered. HIT is usually seen 4–14 days after heparin therapy, and can lead to major bleeding and thrombotic complications. HIT does not respond to platelet transfusion, heparin must be stopped. HIT may respond to plasmapheresis.

2. Low molecular weight heparin: Low molecular weight heparins are derived from UFH by chemical or enzymatic depolymerization. LMWH preparations have more predictable pharmacokinetic and pharmacodynamic properties have a longer half-life than heparin, and a lower risk of non-hemorrhagic side effects. Trials have confirmed the efficacy of LMWH administered subcutaneously, it has the advantages of a simple subcutaneous administration, without requiring laboratory monitoring. Low molecular weight heparins should be given with care in patients with renal failure. Intravenous unfractionated heparin may be the preferred mode

of initial anticoagulation for patients with severe renal impairment (creatinine clearance < 30 ml/min), and with severe risk of bleeding. For all other cases of acute PE, unfractionated heparin can be replaced by LMWH given subcutaneously at weight-adjusted doses without monitoring[15] (Table 126.9).

3. Fondaparinux: It is a synthetic polysaccharide with anti-Xa activity. It has been shown to be as effective as heparin and is not associated with HIT. Dosage given once daily is calculated for the body weight. It is contraindicated in severe renal failure (creatinine clearance < 30 ml/min).

Rapid anticoagulation can be achieved with parenteral anticoagulants such as intravenous UFH, fixed dose subcutaneous UFH, subcutaneous LMWH or subcutaneous fondaparinux. Anticoagulation should be initiated without delay in patients with confirmed PE and those with a high or intermediate clinical probability of PE, while awaiting definitive diagnostic confirmation (in the absence of any contraindication).[15] Treatment with parenteral anticoagulants along with (in confirmed cases of PE) or followed by (in patients with high clinical probability, after confirmation), vitamin K antagonists (VKA) (warfarin) are safe and effective therapeutic options for patients with PE. Parenteral anticoagulants should be given for oticast, 5 days and until the adequate maintenance anticoagulation with warfarin is achieved, i.e. international normalized ratio (INR) between 2 and 3 for greater than 24 hours.[75]

Long-term anticoagulation: Long-term anticoagulation to prevent clot recurrence is usually achieved by oral VKA—warfarin or acenocoumarol. Long-term treatment should be initiated once PE has been reliably confirmed. Oral anticoagulation with warfarin is instituted with dose between 5 mg and 10 mg preferably on the first treatment day, along with parenteral anticoagulants with subsequent dosing based on the INR values.

Studies performed in hospitalized patients showed that starting warfarin at a dose of 5 mg was associated with less excessive anticoagulation compared with 10 mg, although therapeutic INR (> 1.9) was achieved 1.4 days sooner with 10 mg protocol.[76,77] Clot recurrence, bleeding events and morbidity profiles did not differ in two groups. Taken together, these data suggest that warfarin can usually be started at a dose of 10 mg in younger patients (e.g. ≤ 60 years), and otherwise healthy outpatients and at a dose of 5 mg in older patients and in those who are hospitalized. Subsequent doses should be adjusted to maintain the INR at a target of 2.5 (range 2.0 to 3.0).[15] We practice a specific recommended dosage schedule to initiate warfarin with 5 mg/day[78] (Fig. 126.10). Similar dosage schedule is also available for 10 mg per day.[77]

TABLE 126.9: Dosage schedule for subcutaneous administration of low molecular weight heparins and fondaparinux

LMWH	*Dosage*
enoxaparin	1.0 mg/kg every 12 hr or 1.5 mg/kg once daily
tinzaparin	175 U/kg once daily
daltaperin	200 U/kg once daily
fondaparinux	5 mg (body weight ≤ 50 kg) once daily dosage 7.5 mg (body weight 50–100 kg) 10 mg (body weight > 100 kg)

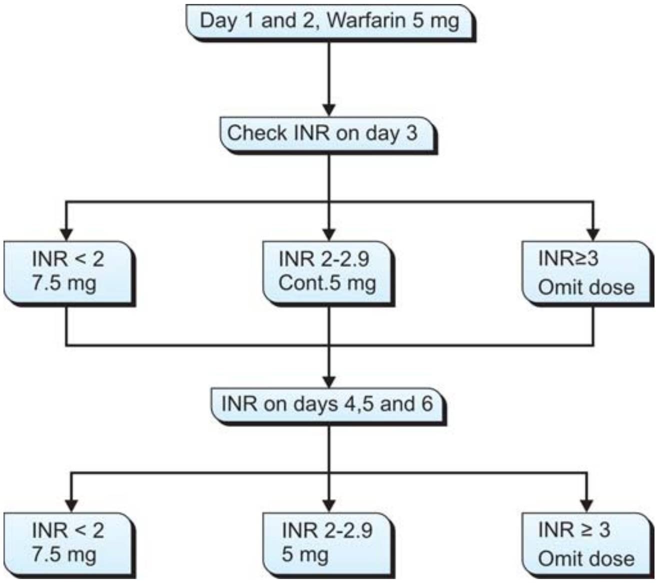


Fig. 126.10: Dosage schedule for initiation of warfarin therapy with 5 mg per day (as practiced in the department of Pulmonary Medicine, Christian Medical College Hospital, Vellore, India)

Monitoring of Oral Anticoagulants

In patients beginning VKA therapy, INR should be monitored after the initial two or three doses of oral anticoagulation therapy. For patients who are receiving a stable dose of oral anticoagulants, monitoring should be done at an interval of no longer than every four weeks.[79]

Duration of Anticoagulation Therapy

Duration of anticoagulant treatment in a particular patient should be ascertained depending on the risk benefit assessment between the estimated risk of recurrence after treatment discontinuation and the risk of bleeding complications, while on treatment. When there are transient risk factors for venous thromboembolism, such as the postoperative period, recurrence during and after treatment is unusual. Recurrent embolism in the absence of a recurrent or new risk factor should be treated with long-term anticoagulation. In patients with persisting underlying risk factors, such as deficiency of antithrombin III, protein C or protein S, the anticoagulation is usually prolonged to several years, possibly lifelong. Specific recommendations on the duration of anticoagulation are based on the onset of and conditions associated with PE (Table 126.10).[15]

Thrombolytic Therapy

Thrombolytic therapy is recommended as the first line treatment for patients with massive PE (hemodynamic compromise/imminent cardiac arrest). Thrombolytic therapy should be instituted at the earliest in such patients provided there are no contraindications,[80] pertaining to risk of bleeding (Table 126.11). The therapy not only helps in achieving rapid resolution of PE; but also rapid hemodynamic improvement. It has no role in the management of haemodynamically stable patients, except perhaps in the subgroup of patients with right ventricular dysfunction but normal systemic arterial pressure, where there is some evidence for its efficacy. Thrombolytic treatment is most effective when administered soon after PE, but benefit may extend for up to 14 days from the onset of symptoms.[17] While thrombolysis may be life saving in massive and submassive PE, the extent of long-term survival and reduction in mortality at 90 days remains unclear.[81] There are several thrombolytic agents with different dosage schedule which are commonly used (Table 126.12). Drawbacks of thrombolytic therapy are high cost, risk of severe and often fatal bleeding and allergic reactions (specifically to streptokinase).

Surgical Management

Surgical Embolectomy

Surgical embolectomy has been reserved for a selective group of patients who have massive PE with hemodynamic instability requiring cardiopulmonary resuscitation or who have failed thrombolytic therapy or have contraindications to its use. It may also be performed in patients with patent foramen ovale and intra cardiac thrombi.[82, 83] However, this procedure should be attempted only at centers with the necessary skills and experience.

Catheter Embolectomy

Catheter embolectomy or fragmentation of proximal pulmonary arterial clots may be considered as an alternative to surgical treatment in high-risk PE patients when thrombolysis is absolutely contraindicated or has failed or if patient is unwilling for surgical embolectomy.[15]

Inferior Vena Caval Filters

Inferior Vena Caval (IVC) filter devices placed in the inferior vena cava protect the pulmonary circulation from emboli. The routine use of IVC filters in patients with PE is not recommended, since they are associated with complications and late sequelae, including recurrent DVT episodes and development of the post-thrombotic syndrome. The two main indications for the use of filters are absolute contraindications to anticoagulation and high risk of VTE recurrence.

TABLE 126.10: Recommendations for long-term anticoagulation[15]

Thromboembolism	*Duration*
PE secondary to a transient (reversible) risk factor	3 months
Unprovoked PE	At least 3 months
First episode of unprovoked PE and low risk of bleeding, and in whom stable anticoagulation can be achieved	May be considered for long-term anticoagulation
Second episode of unprovoked PE	Long-term anticoagulation
PE and cancer	LMWH should be considered for the first 3 to 6 months. After this period, anticoagulant therapy with VKA or LMWH should be continued indefinitely or until the cancer is cured

TABLE 126.11: Contraindications for thrombolytic therapy[15]

Absolute	*Relative*
• Hemorrhagic stroke or stroke of unknown origin at anytime • Ischemic stroke in preceding six months • Central nervous system damage or neoplasm • Recent major trauma/surgery/ head injury (with in preceding three weeks) • Gastrointestinal bleeding within the last month • Known active bleeding	• Transient ischemic attack in preceding six months • Oral anticoagulant therapy • Pregnancy or within one week postpartum • Non-compressible punctures • Traumatic resuscitation • Refractory hypertension (systolic blood pressure > 180 mmHg) • Advanced liver disease • Infective endocarditis • Active peptic ulcer

TABLE 126.12: Thrombolytic agents and dosage schedule

Thrombolytic agent	*Dosage schedule*	*Advantages/Disadvantages*
Streptokinase	250000 IU as a loading dose over 30 min, followed by 100000 IU/h over 12–24hr *Accelerated regimen*:1.5 million IU over 2hr	• Cheap • Antigenic and hypotensive • Risk of allergic/anaphylactoid reaction on re-exposure
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg/h over 12–24hr *Accelerated regimen*:3 million IU over 2hr	• Fewer complications • Unlike streptokinase, no risk of inactivation by antibodies
Recombinant tissue plasminogen activator (rtPA)	100 mg over 2 hour or 0.6 mg/kg over 15 min (maximum dose 50 mg)	• Short infusion time • Not associated with allergic reactions or hypotension • Expensive

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127

Pulmonary Vascular Malformations

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INTRODUCTION

The diagnosis of pulmonary vascular malformations (Table 127.1) has revolutionized with the advent of multidetector computed tomography (MDCT).[1] The focus of this chapter is on pulmonary arteriovenous malformation (PAVM). Though PAVMs are not very common, they constitute an important differential diagnosis in patients presenting with hypoxemia, paradoxical embolism and nodules on chest radiographs. A high level of the index of suspicion is therefore required while evaluating patients with pulmonary symptoms.

PAVM are also known as pulmonary telangiectasias, cavernous angiomas of the lung, pulmonary arteriovenous fistulae or aneurysms.[2] Most PAVMs are congenital in nature. However, these abnormalities can also develop later in life as acquired conditions. PAVMs occur more frequently in women as compared to men (Table 127.2). The male:female ratio is 1:2. In neonates, there is male preponderance.[2,3]

Hereditary Hemorrhagic Telangiectasias or Rendu-Osler-Weber syndrome

This syndrome is named after three physicians (Rendu-Osler-Weber) who first described hereditary hemorrhagic telangiectasias (HHT) in the early 19th century. Almost every three in four cases of PAVMs have associated HHT. Conversely, approximately one in every four cases of HHT has PAVM.

HHT is a syndrome encompassing arteriovenous malformations in nose (>95%), skin (>80%), lungs (>30%), gastrointestinal tract (>30%), liver (>30%), and brain (>10%).[4,5] Diagnosis is generally established on the basis of Curacao criteria[6] (Table 127.3). HHT has an autosomal dominant inheritance with an age-related penetrance; all patients manifest the disease by the age of 40 years.[7] It is important to appreciate that arteriovenous malformation (AVM) in HHT (though present from birth) manifest clinically only in adult life after the AVM vessels have been exposed to pressure in the initial decades of life. The early clinical features include the appearance of

TABLE 127.1: Pulmonary Vascular Malformations

Congenital
Congenital pulmonary artery stenosis
Congenital pulmonary artery aneurysms
Pulmonary arteriovenous malformations (PAVM)
Bronchopulmonary sequestration (BPS)
Congenital pulmonary airway malformation (CPAM)
Hybrid lesions of BPS and CPAM
Anomalous pulmonary venous return
Pulmonary venous varices
Acquired
Pulmonary artery pseudoaneurysm
Pulmonary emboli

TABLE 127.2: Acquired Conditions Presenting with PAVM

Hepatic: Cirrhosis
Cardiovascular: Mitral stenosis
Infections: Actinomycosis, Schistosomiasis
Malignancy: Metastatic thyroid carcinoma
Postoperative congenital cyanotic heart disease patients
Trauma

TABLE 127.3: Curacao Criteria for the Diagnosis of Hereditary Hemorrhagic Telangiectasia

i. History of epistaxis
ii. Superficial telangiectasias in nose, lips, oral cavity and fingers
iii. Visceral arteriovenous malformations in pulmonary, gastrointestinal, brain or spinal cord
iv. Family history of first degree relative fulfilling the diagnostic criteria for HHT#

Definite diagnosis requires 3 out of 4 criteria
Possible diagnosis requires 2 out of 4 criteria

#Hereditary hemorrhagic telangiectasia

cutaneous telangiectasia or epistaxis. Later on, the patients may present with dyspnea, pulmonary hemorrhage or obscure gastrointestinal bleeding.[2]

Genetic testing is an important adjunct in the diagnosis of HHT. Most patients show mutations in one out of three genes: ENG (endoglin) associated with HHT type 1 and ACVRL1 with HHT type 2. ENG is a transforming growth factor beta (TGF-beta) binding protein that has been identified on chromosome 9. ACVRL1 or activin receptor-like kinase 1 has been mapped to chromosome 12. Mutations in MDAH4 encoding SMAD4 resulting in overlap juvenile polyposis/HHT syndrome and an HHT locus on chromosome 5 has also been described. TGF-beta has a role in modulating vascular phenomena like angiogenesis, induction of endothelial mitogens response in cells to vascular insults. Therefore, aberrations in TGF-beta result in anatomical arteriovenous malformations.[2,4,8,9]

PATHOGENESIS

By definition, telangiectasia is a localized tortuous enlargement of the postcapillary venule with perivascular lymphocytic infiltration and smooth muscle proliferation. AVM is a direct association between the pulmonary artery and the pulmonary vein with aneurysmal enlargement of the feeding artery.[10] It has been hypothesized that in PAVM, there is incomplete resorption of vascular septae, which demarcate arterial and venous plexuses during fetal development.[11] Other investigators have postulated a defect in the terminal arterial loop, which results in dilatation of thin-walled capillary sacs.[12]

Almost two out of three PAVM occur in the lower lobes, and three out of four patients have unilateral disease. Approximately, one in three patients has multiple PAVM and half of those with multiple lesions have bilateral disease. Most PAVMs are of 1–5 cm in dimensions and involve the pleura.[2,13] They are classified as simple or complex depending on the number of feeding arteries and the draining veins.[14] Simple PAVMs have single feeding artery and a single vein, whereas complex PAVMs have multiple feeding arteries and draining veins. Almost 90% PAVM are of simple type, supplied by the pulmonary artery and PAVM drain into the left atrium. Simple PAVM predominantly occur in the lower lobe, while the complex PAVM occur in the lingula and the right middle lobe.[10]

Anatomically, PAVMs have one of the three characteristic appearances: (a) large single sac; (b) plexiform mass of dilated vascular channels; or (c) direct tortuous communication between artery and vein.[11,13] Pathologically, they consist of two elements —vascular channels lined with endothelium form the first element and the connective tissue stroma with no connection with lung parenchyma form the second element. Most PAVMs have paper thin walls, similar to the AVMs occurring in other parts of the body. Occasionally, PAVM may become calcified or contain a thrombus.[11,13,15]

CLINICAL FEATURES

In early life, patients with PAVM are asymptomatic or may present with cyanosis, cardiac failure or respiratory failure. Most patients become symptomatic in the fourth or the fifth decade. Symptoms occur more frequently in patients with PAVM and HHT than in patients with PAVM alone.[16] Moreover, symptoms correlate with the size and number of PAVM. Single and less than 2 cm PAVM are asymptomatic. Patients with multiple PAVMs have a higher probability of presence of symptoms.[16]

Epistaxis is the most common symptom in PAVM. Epistaxis may precede the development of external telangiectasia by 10 to 30 years in HHT.[17] Epistaxis may occur spontaneously or result from minor trauma to the nasal telangiectasia present. One in two patients with HHT develop epistaxis in the first two decades of life with almost all the patients developing it by the fifth decade.[16] The presence of lung nodules (PAVM) and the history of recurrent epistaxis should raise the suspicion of HHT.[4]

Dyspnea is the next common symptom after epistaxis. It is most frequently observed with large or multiple PAVM. Platypnea is another characteristic pulmonary symptom, although it is also observed in other conditions. Hemoptysis is the third most common symptom after epistaxis and dyspnea.[18,19] Gastrointestinal hemorrhage occurs in 20 to 30% patients. This symptom manifests in later life with 50% patients developing between 30 and 58 years and the remaining after the age of 58 years.[17] Infrequently, occult bleeding from extrapulmonary sources, including from superficial telangiectasias over skin and mucosa may result in iron-deficiency anemia.[20] Many nonspecific symptoms may occur from complications, such as hypoxemia, polycythemia or cerebrovascular accidents due to the presence of AVM in the brain.

On general physical examination, superficial telangiectasia present on face, oral cavity, chest and upper extremities are the sole findings in these patients. The predominant skin lesions are found on the lower lip, tongue, nose, and skin. The HHT lesions of 1 to 3 mm size are slightly rounded with dendrite-like projections, ruby-colored and sharply demarcated from adjacent skin and mucosa. Unlike the flat and readily blanchable spider nevi in chronic liver disease, the telangiectasia of HHT are papular and do not completely blanch with pressure.[21,22] PAVM patients with significant hypoxemia develop cyanosis and clubbing, almost all patients with PAVM and dyspnea manifest clubbing.[2,18,19]

On chest examination, murmurs or bruits increasing on inspiration are heard in almost one out of two patients with PAVM.[19] The murmurs also increase when the PAVM assumes a gravitationally dependent position. Though the triad of dyspnea, clubbing and cyanosis is considered specific for PAVM, it is observed in only 10% cases.[23]

INVESTIGATIONS

On arterial blood gas analysis, hypoxemia especially orthodeoxia (decrease in saturation from supine to sitting position) are observed in PAVM. Pulmonary function tests have no role in the diagnosis.

Chest radiography is the initial investigation raising the suspicion of PAVM in a patient. It may reveal a lobulated and sharply defined pulmonary nodule in the lower lobe. The size of the nodule which is usually single, varies from 1 to 5 cm. Smaller PAVM may reveal only a nonspecific increase in pulmonary vascular markings, which may wax and wane over a period of time.[24,25] On fluoroscopy, PAVM lesions in the lung reveal pulsations during Valsalva maneuver.[26] Contrast echocardiography is an excellent tool for the evaluation of intrapulmonary shunts. The contrast bubbles injected in the peripheral vein are visualized in the left atrium after a delay of three to eight cardiac cycles (2–5 seconds) as compared to an intracardiac shunt when they are visualized in the left atrium within one cardiac cycle of appearing in the right atrium.[27,28]

MDCT has become the investigation of choice. The high-resolution volumetric images can be attained with a single breath hold. Moreover, three-dimensional reconstruction of the lesion on MDCT assists in the characterization of the vascular lesions.[1] Smaller lesions missed on the chest radiograph can be diagnosed by MDCT. This modality also helps in the differentiation of PAVM from other vascular lesions of the lung (Table 127.1). The use of contrast as a timed bolus, can help to delineate the arterial and venous phases to further characterize the feeding arterial supply and venous drainage.[29]

Magnetic resonance imaging has a limited sensitivity and specificity for PAVM due to the overlap of signals with the adjacent lung parenchyma.[30] Prior to the availability of advanced MDCT, conventional pulmonary angiography was necessary to confirm the diagnosis of PAVM. Over the years, digital subtraction angiography has replaced conventional angiography.[31]

Central nervous system involvement is the most commonly reported complication in patients with PAVM (Table 127.4). Paradoxical embolism is the most plausible mechanism for noninfectious cerebrovascular accidents.[32,33]

MANAGEMENT

One in four PAVM slowly enlarge in size, whereas the remaining lesions are unchanged over years.[16,17] The

TABLE 127.4: Complications of Pulmonary Arteriovenous Malformation

Central nervous system
- Infective: Brain abscess
- Vascular: Migraine, transient ischemic attack, cerebrovascular accidents
- Seizure

Pulmonary
- Hypoxemia/orthodeoxia
- Hemothorax
- Massive hemoptysis
- Pulmonary hypertension

Cardiac
- Congestive cardiac failure
- Infective endocarditis

Hematological
- Anemia
- Polycythemia

TABLE 127.5: Indications for therapy in Pulmonary Arteriovenous Malformation

Paradoxical embolization
Symptomatic hypoxemia
Feeding vessel more than 3 mm or larger
Progressive enlargement

growth rate varies from 5 to 10 mm every 5 to 15 years. It has also been observed that enlargement is more common in patients with HHT compared to patients without HHT. The main modalities of therapy include surgery and embolotherapy[34,35] (Table 127.5).

Till the late 1970's, surgery was the mainstay of treatment of PAVM. The various procedures included local excision, segment resection, lobectomy or pneumonectomy. In patients unfit for surgery, the transaction of pulmonary artery was also used as a treatment modality.[36] Video-assisted thoracoscopic surgery is a preferred choice.[37]

Embolization of the feeding artery was first used in the year 1977. The embolic material includes vascular plugs, coils, balloons and alcohol. Currently, embolotherapy is the modality of choice.[38,39] It avoids general anesthesia and there is no loss of pulmonary parenchyma. It is also the procedure of choice in multiple and/or bilateral PAVM. As compared to surgery, periprocedural mortality and morbidity with embolization is almost negligible.[40,41] There is no role of hormonal therapy, unlike anecdotal reports in patient with AVM of other regions.[2] The role of antibiotic prophylaxis to avoid the chances of cerebral abscess needs emphasis before dental and surgical procedures in these patients.[2]

OTHER PULMONARY VASCULAR MALFORMATIONS

Many congenital and acquired abnormalities may affect the pulmonary arteries in adults.[42-51] Congenital stenosis of pulmonary arteries (proximal interruption, anomalous origin of the left pulmonary artery or pulmonary artery sling) may be discovered incidentally during chest radiography or MDCT. Acquired anomalies may generally include the diffuse or focal enlargement of pulmonary arteries. The acquired abnormalities commonly result from causes, such as pulmonary hypertension, pulmonary artery aneurysm and intravascular pulmonary metastasis.[42]

Congenital Pulmonary Artery Aneurysm and Pseudoaneurysm

Most pulmonary artery aneurysms and pseudoaneurysms are caused by trauma (including the iatrogenic causes, such as the malpositioned Swan-Ganz catheters, and chest tube insertion), infection (fungal, tuberculosis, pyogenic) and vasculitis (Behçet's syndrome). The pulmonary artery aneurysms due to tuberculosis known as Rasmussen aneurysms generally occur in the upper lobe. Pulmonary artery aneurysm and pseudoaneurysm may sometimes occur in the presence of pulmonary hypertension, congenital pulmonary stenosis, neoplasm (bronchogenic carcinoma) and connective tissue disease (Marfan syndrome). The recognition of pulmonary artery aneurysms and pseudoaneurysms is important because of the high risk of rupture related morbidity and mortality.[43]

Anomalous Pulmonary Venous Return

Total anomalous pulmonary venous return (TAPVR) is a congenital disorder characterized by total mixing of systemic venous and pulmonary venous blood within the heart. This complete mixing of venous blood produces cyanosis. In contrast, partial anomalous pulmonary venous return (PAPVR) is usually an acyanotic condition. Anatomically, these are vascular malformations of the pulmonary circuit. However, as a matter of convention both these entities are considered as congenital heart diseases.

Bronchopulmonary Sequestration

Bronchopulmonary sequestration (BPS) is a solid or cystic mass of nonfunctioning lung tissue with an anomalous systemic blood supply. There is no tracheobronchial connection with the sequestrated lobe/segment. Both the intrapulmonary (more common) and extrapulmonary forms are commonly seen on the left side (intrapulmonary occurring more frequently in left lower lobe). In fact, a high index of suspicion is required to suspect these conditions to enable an early diagnosis on MDCT.[52,53]

Congenital Pulmonary Airway Malformation

Congenital pulmonary airway malformation (CPAM), earlier known as congenital cystic adenomatoid malformation (CCAM), is an uncommon developmental abnormality of the lower respiratory tract. The patient may present with respiratory distress in the neonatal period or remain asymptomatic until later in life. Many cases are now detected by routine prenatal ultrasound examination, more recently by fetal magnetic resonance imaging. CPAMs result from abnormalities of branching morphogenesis of the lung. The different types of CPAMs are postulated to originate at different levels of the tracheobronchial tree and at different stages of lung development, possibly influenced by in utero airway obstruction and/or atresia. Surgical resection is the only definitive treatment.[54-57]

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Section

16

RESPIRATORY SLEEP DISORDERS

Ashutosh Aggarwal

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Approach to Respiratory Sleep Disorders

Ahmad Abdelwahed, Jeremy A Weingarten

INTRODUCTION

Disorders of respiration during sleep are common in the general adult population. The clinical spectrum of respiratory sleep disorders includes obstructive sleep apnea, central sleep apnea, nocturnal hypoventilation and hypoxemia, and nocturnal manifestations of general pulmonary diseases such as asthma and chronic obstructive pulmonary disease. The evaluation of an individual suspected of a respiratory sleep disorder includes an extensive sleep history, physical examination and diagnostic testing. Controversy exists regarding the utilization of in-lab (laboratory) versus home nocturnal polysomnography; however, in-lab sleep studies remain the diagnostic "gold standard". Screening questionnaires may add information to the sleep evaluation, but findings must be confirmed with other diagnostic modalities. The clinical manifestations and issues related to obstructive airways disease and alveolar hypoventilation syndromes during sleep are discussed at the end of the chapter.

SLEEP HISTORY

Sleep complaints are varied and can often be attributed to respiratory sleep disorders. A common complaint of individuals presenting to a sleep clinic is insomnia, characterized as difficulty in initiating sleep, maintaining sleep, or a generalized nonrestorative sleep; the prevalence of comorbid insomnia in patients with obstructive sleep apnea (OSA) ranges from 39 to 55%.[1] Although insomnia is often related to comorbid psychiatric disease, medical disease or an idiopathic etiology, patients with respiratory sleep disorders often perceive their inability to sleep as insomnia and do not make the connection between their complaints and breathing abnormalities during sleep. Poor sleep quality, often described as unrefreshing and restlessness, is another common complaint of individuals with respiratory sleep disturbances; frequent nocturnal arousals due to respiratory events result in poorly consolidated sleep in these individuals. Excessive daytime sleepiness, a cardinal manifestation of OSA and other primary sleep disorders, is a major reason for seeking out a sleep specialist; frequent nocturnal arousals and poorly consolidated sleep, despite at times prolonged time in bed, can account for this common complaint. Changes in cognition associated with disrupted sleep include deficits in vigilance, executive function and coordination.[2] Finally, disruption of a bed partner's sleep due to the nocturnal activities of the patient is a common reason for individuals to undergo sleep evaluation; loud snoring, restlessness, choking sounds and limb movements/kicking are all common complaints of bed partners of individuals with respiratory sleep disorders (Table 128.1).

When directly queried, specific events reported by the patient may be clues to a diagnosis of a respiratory disorder during sleep. Snoring is a near universal complaint in people with OSA and can often be quite disruptive to individuals who sleep in close proximity to the patient. Although snoring is present primarily during sleep, patients can often perceive snoring resulting in a respiratory effort-related arousal (RERA) and also complain of loud breathing and snoring while awake. Choking and gasping during nocturnal arousal is caused by frank obstructive events; the patient

TABLE 128.1: Common complaints of patients and bed partners

Common sleep complaints	*Common bed partner complaints*
Snoring	Disruptive/crescendo snoring
Excessive daytime sleepiness	Restlessness
Poor sleep quality	Choking/gasping
Frequent nocturnal arousals	Limb movements/kicking bed partner
Insomnia	Concern of breathing cessation
Morning dry mouth	
Morning headache	
Nocturia	
Palpitations	
Cognitive deficits	

increases respiratory effort against a subtotally or totally occluded glottis, with subsequent opening of the glottis on arousal resulting in a loud snort. Morning dry mouth is attributed to increased airflow through the oropharynx. Morning headache is often a manifestation of sleep-related hypercapnia in individuals whose respiratory sleep disorder is associated with nocturnal alveolar hypoventilation. Nocturia has been associated with OSA and is felt to be due to intrathoracic pressure changes and consequent release of natriuretic hormones during obstructive events.[3] Sympathetic surges during respiratory events result in frequent heart rate accelerations on electrocardiogram and symptomatic palpitations. Finally, limb movements during sleep are common physical manifestation of the arousal response associated with respiratory events and does not necessarily represent an alternate primary sleep disorder such as periodic limb movement disorder.

It is crucial during the sleep history to ascertain sleep positioning of the patient and its relationship to respiratory complaints during sleep. In imaging studies of individuals with OSA, the retropalatal and retroglossal space has been shown to be the major site of obstruction;[4] gravitational effect on the tongue base and palate while the patient is in the supine position functionally reduces the cross-sectional area of the upper airway and often exacerbates symptoms of OSA, particularly snoring and obstructive events. Although patients often do not realize the reasons, they prefer to sleep in the nonsupine position. It is likely that in individuals with OSA, sleep in the nonsupine position is a protective mechanism to reduce the likelihood of obstruction.

As patients present with varied and sometimes bizarre sleep complaints, it is important to have a working knowledge of the manifestations of other sleep disorders in order to differentiate these problems from more typical respiratory sleep disorders. While limb movements during sleep may be a part of the arousal response to obstructive respiratory events, they may also represent a primary sleep disorder, such as periodic limb movement disorder or a seizure disorder. The differential diagnosis of hypersomnia, one of the primary complaints seen in sleep clinic, is varied and includes any disorder that increases the frequency of nocturnal arousal (respiratory sleep disorders, limb movement disorders), narcolepsy, idiopathic hypersomnia and insufficient sleep syndromes (behaviorally-induced, related to psychiatric or medical disease, circadian rhythm disorders). Complaints associated with some of these alternative diagnoses elicited during the sleep history include sleep paralysis, dream enactment, somnambulism, hypnagogic and hypnopompic hallucinations, and restless legs during wakefulness/periodic limb movements during sleep.

A complete medication history is essential in evaluating the patient with sleep complaints. Respiratory suppressants, such as narcotics and benzodiazepines, may increase the risk of OSA in individuals who are at risk for this disorder. Narcotic medication is additionally associated with opioid-induced central sleep apnea syndrome.[5] The use of REM-suppressant medication may decrease the severity of an individual's sleep-disordered breathing. Individuals with OSA are especially vulnerable to obstructive events during REM sleep; therefore, the use of REM-suppressant medication decreases an individual's opportunity to have obstructive events. The most common REM-suppressants are antidepressant medications. Selective serotonin reuptake inhibitors (SSRIs), in addition to being potent REM-suppressants, are known to increase the frequency of limb movements during sleep, further complicating the individual's diagnostic evaluation.

PHYSICAL EXAMINATION FOR RESPIRATORY SLEEP DISORDERS

Examination of the upper airway is an essential component of the evaluation for respiratory sleep disorders. Although complete evaluation of the upper airway requires endoscopic visualization of structures and radiologic imaging (X-ray cephalometry, computed tomography, and magnetic resonance imaging), a general physical examination in the pulmonologist or sleep specialist's office often provides important clues to the diagnosis of respiratory sleep disorders and will guide future diagnostic modalities. The Mallampati classification system was initially developed in the anesthesia literature to predict the difficulty of direct laryngoscopy; this scoring system has been shown to be an independent predictor of the presence and severity of OSA in patients with suspected respiratory sleep disorders.[6]

The Mallampati grade (I–IV) is determined by asking the patient to open the mouth and protrude the tongue without emitting sound. The grading is as follows:

I. Soft palate and entire uvula visualized.
II. Soft palate and portion of the uvula visualized.
III. Soft palate visible only (base of the uvula may be seen).
IV. Soft palate not visualized (hard palate only visible structure).

While visualizing the posterior pharynx, assessment of the size of the tonsils and presence of macroglossia may be made. Examination of the nose to determine the presence of septal deviation, external nasal deviation, inflamed mucosa and patency of nares should be performed to determine the contribution of decreased nasopharyngeal airflow to respiratory symptoms. Craniofacial features should be evaluated such as the presence of retrognathia or micrognathia. Finally, evaluation of the neck should be performed to determine the presence of thyroid disease and measure neck circumference; increasing neck circumference has been associated with greater risk of OSA.[7]

While the upper airway examination is an essential component in the evaluation of the potential risk of OSA, other clues to the diagnosis of a respiratory sleep disorder and the clinical sequelae of such disorders can be discerned by a more general physical examination. Cardiac evaluation is essential to determine the presence of signs of right heart failure (right ventricular heave, loud P2) and left heart failure (S3, S4, displaced PMI, murmur due to valvular disease). Respiratory examination may demonstrate coexistent obstructive airways disease or neurologic disease (diaphragmatic paralysis) that may contribute to nocturnal hypoventilation and subsequent gas exchange abnormalities during sleep. Abdominal examination may suggest congestive hepatopathy due to cor pulmonale. Extremity examination may demonstrate peripheral edema, clubbing and/or cyanosis, which may lead to further cardiopulmonary evaluation. Finally, neurologic evaluation is important to determine the risk of nocturnal hypoventilation from neuromuscular disease and central sleep apnea from cerebrovascular disease (as manifested by focal neurologic deficits). Although the findings on physical examination are nonspecific, they are essential for complete evaluation of the patient presenting to sleep clinic.

NOCTURNAL POLYSOMNOGRAPHY

Although clinical prediction models used to estimate the presence of OSA in various populations have been evaluated, in-laboratory nocturnal polysomnography (PSG) remains the “gold standard” diagnostic method in determining the presence of a sleep-related breathing disorder. In its most recent practice parameters,[8] the American Academy of Sleep Medicine (AASM) stated that PSG is routinely indicated for the diagnosis of sleep-related breathing disorders (Table 128.2). Multiple sleep latency testing (MSLT), an adjunct in-laboratory test during which an individual takes several naps throughout the day to objectively measure daytime sleepiness, is not indicated in the evaluation of sleep-related breathing disorders.

In-laboratory polysomnography is a complex medical procedure that enables recording and analysis of a wide spectrum of physiologic processes during sleep; the complexity of this test provides important cardiopulmonary and electromyographic information in the context of electroencephalographically derived sleep stages and body position. For a type 1 study (in-laboratory, technician supervised study), several physiologic components are monitored and recorded (Table 128.3). In addition, audiovisual recording is usually performed.

Although PSG is considered the “gold standard” for diagnosing sleep-related breathing disorders, it is not infallible. Data loss, artifacts and measurement errors may affect the analysis of the raw data. Scoring of sleep studies is performed by sleep technicians; intra- and inter-rater event recognition errors and differences in

TABLE 128.2: Indications for Polysomnography

- Obstructive sleep apnea syndrome (OSA)
- Central sleep apnea syndrome (CSA)
- Cheyne-Stokes respiratory pattern (CSR)
- Alveolar hypoventilation syndromes

Additional high level indications (2005 Statement and supported by strong evidence-based medicine)

- Positive airway pressure titration in patients with sleep-related breathing disorders
- Preoperative evaluation to determine the presence of OSA in patients before they undergo upper airway surgery for OSA
- Follow-up evaluation after upper airway surgery or utilization of an oral appliance
- Follow-up after significant weight gain or loss (10% of body weight) or when clinical response is sub-optimal
- Individuals with systolic or diastolic heart failure with nocturnal symptoms
- Those who remain symptomatic despite optimal medical therapy.

TABLE 128.3: Components of Type 1 (In-lab, technician supervised) polysomnography study

- Electroencephalography
- Electrooculography
- Electromyography (chin, anterior tibialis)
- Electrocardiography
- Oronasal airflow (via nasal thermistor and nasal pressure transducer)
- Pulse oximetry
- Rib cage and abdominal wall movements (inductance plethysmography)
- Snoring

respiratory event definitions among different sleep laboratories (discussed below) can result in over- or underestimation of respiratory events. Night to night variability and the "first night effect," a well described phenomenon in which individuals evaluated in the sleep lab will have poorer sleep quality on the first night when compared with successive study nights, likely affects the accuracy of PSG.[9] Regardless of potential pitfalls of in-lab PSG, it remains the most comprehensive and accurate analysis of sleep currently utilized.

Based on objective findings, we are able to classify respiratory events into apnea (obstructive, central or mixed), hypopnea, respiratory effort-related arousal (RERA), hypoventilation, and Cheyne-Stokes breathing.[10] An apnea is defined as a reduction in the amplitude of the nasal thermistor by ≥ 90% for 10 seconds; if the event is associated with respiratory effort, it is classified as obstructive; if no respiratory effort is present, it is a central event; and if it starts out without respiratory effort but which resumes in the latter portion of the event, a mixed apnea. A hypopnea, which should not be classified as obstructive, central or mixed unless quantitative measures are utilized (calibrated respiratory inductance plethysmography, esophageal manometry, or diaphragmatic/intercostal EMG), is defined as a reduction in the nasal pressure transducer amplitude by ≥ 30% for 10 seconds with a concomitant oxygen desaturation of ≥ 4%.

The alternative definition of a hypopnea, which is utilized in some sleep centers, consists of a decrease in the nasal pressure transducer amplitude by ≥ 50% lasting for 10 seconds and with either concomitant ≥ 3% drop in oxygen saturation or an EEG arousal. The number of apneas and hypopneas that occur per hour of sleep are combined to provide an apnea-hypopnea index (AHI), which is utilized as a measure of severity of disease. A RERA is defined as a period of 10 seconds of increasing respiratory effort or flattening of the nasal pressure amplitude leading to an arousal from sleep that does not meet criteria for an apnea or hypopnea; diagnosis of a RERA should be made utilizing esophageal manometry or calibrated respiratory inductance plethysmography along with the flattening of nasal pressure waveform. Conceptually, a RERA is an obstructive event in which the individual is able to maintain airflow against increasing airflow resistance by concomitantly increasing respiratory effort. The respiratory disturbance index (RDI) is the total number of apneas, hypopneas and RERAs per hour of sleep, and an alternate index of disease severity.

In clinical practice in the United States, the AHI, not the RDI, is used by insurers to determine eligibility for treatment of sleep-related breathing disorders. Hypoventilation is scored if there is an increase of ≥ 10 mm of Hg in partial pressure of arterial carbon dioxide (P_aCO_2) when compared with wake state; end-tidal CO_2 and transcutaneous CO_2 are often used as surrogates for the P_aCO_2. Cheyne-Stokes respiratory pattern is present if there are at least three consecutive cycles of crescendo-decrescendo respiratory amplitude change (flow and effort) lasting at least 10 minutes or with an AHI ≥ 5 (central apnea and hypopnea).

PORTABLE MONITORING

In-laboratory nocturnal polysomnography is the "gold standard" for diagnosing and treating sleep-disordered breathing; however, it is also a resource-intense procedure with limited capacity and thus prolonged wait-times until individuals are successfully evaluated and treated. A recent analysis evaluated the time from referral until CPAP initiation in five regions throughout the world: the United States, England, Belgium, Australia and Canada.[11] The average wait time was 2 to 60 months, with wide variability among these regions; England had the longest (range 7–60 months) and Belgium the shortest wait time (2 months). Although these data do not evaluate average wait times in other regions of the world, which may in fact have longer wait times with limited availability, it is clear that the need for decreased time to treatment for respiratory sleep disorders is a major challenge in sleep medicine.

Portable monitoring encompasses a wide spectrum of diagnostic technology utilized to determine the presence or absence of sleep-disordered breathing outside of a formal in-laboratory study. Four types of sleep monitoring devices have been defined;[12] these designations are currently used for research as well as clinical purposes. Type 1 studies are standard, attended in-laboratory polysomnography measuring all physiologic parameters described previously. Type 2 studies record the same variables as Type 1 studies (EEG, EOG, chin EMG, EKG, airflow, respiratory effort and oxygen saturation) but do not require the presence of sleep technician, nor do they require that the patient spend the night in a sleep laboratory. Type 3 studies are required to measure at least four physiologic parameters, including ventilation (respiratory effort/airflow), heart rate or EKG and oxygen saturation. Type 4 studies previously were defined as requiring 1 channel measurement (pulse oximetry, most commonly); however, the definition of a type 4 study has been changed from its original description and now requires at least three physiologic parameters, although these parameters are not fully defined.[13]

Advantages of using portable monitoring include decreased time to diagnosis of sleep-disordered breathing, improved comfort due to the patient being able to be studied in a comfortable and familiar environment, and decreased costs associated with diagnostic testing. Using a mathematical model to simulate head to head comparison of multiple diagnostic and therapeutic strategies to determine the presence of and treat OSA under various assumptions, Trikalinos and colleagues found that using a strategy of in-laboratory PSG followed by in-laboratory full night CPAP titration versus a strategy of portable monitoring followed by a full night in-home CPAP auto titration resulted in a decrease in time to diagnosis of 11.5 weeks using portable monitoring (13.6 weeks versus 2.1 weeks) and a decrease in time to CPAP titration of 22.5 weeks (27.3 versus 4.8 weeks).[14] Although the portable monitoring group had a markedly decreased total time until diagnosis and treatment, the simulation found that the false-negative rate in this group was 9% while the false-positive rate (individuals in whom CPAP titration was offered despite the absence of clinically diagnosed OSAHS) was 15% among middle aged individuals and 30% among older adults (70 years old). In the standard group (in-lablaboratory PSG and titration), the false-positive rate and false-negative rates were zero; this is an expected finding, as this modality is the "gold standard" method.

The false-positive and false-negative rates cited in the above study demonstrate a major limitation of portable monitoring. As type 3 and type 4 studies are the most common portable monitoring techniques, fewer physiologic parameters are measured and the data may underestimate or overestimate the presence and/or severity of disease. Type 3 and 4 studies do not measure electroencephalographic data, thereby preventing sleep staging; thus, total time in which the apnea-hypopnea index is determined is the total recording time instead of total sleep time. For example, if an individual has 100 respiratory events during the night, is studied by a portable device and the total recording time is 8 hours, the calculated AHI is 12.5 events per hour (mild sleep-disordered breathing); however, if the same individual has 100 respiratory events but has a complete in-laboratory study demonstrating 5 hours of total sleep time by EEG criteria despite a total recording time of 8 hours, then he/she would have a calculated AHI of 20 events per hour (moderate sleep-disordered breathing).

Another limitation of portable monitoring is the fact that data loss is likely to occur as the leads frequently fall off a patient during the course of a study; without the availability of the technical staff in the home to monitor this problem, a variable amount of data will not be captured. Although a presumptive diagnosis of a respiratory sleep disorder may be made, treatment cannot be carried out with portable monitoring, thereby limiting its clinical utility. Finally, portable monitoring has not been thoroughly studied in disorders other than obstructive sleep apnea, again limiting its utility.

The Portable Monitoring Task Force of the American Academy of Sleep Medicine has recently published clinical guidelines for the use of unattended portable monitoring for the diagnosis of obstructive sleep apnea.[15] Based on a review of the literature evaluating type 3 devices (stated as the most commonly used device in the outpatient setting), the Task Force reported that portable monitoring is indicated for the diagnosis of OSA in individuals with a high pretest probability of moderate to severe OSA in conjunction with a comprehensive sleep evaluation. Populations that should not be evaluated with portable monitoring include those with significant comorbid medical disease (including pulmonary disease, neuromuscular disease and congestive heart failure) and those suspected of having other sleep disorders (central sleep apnea, a limb movement disorder, etc.). The guidelines also made exceptions for individuals who do not meet the above criteria but cannot undergo in-laboratory polysomnography due to problems of safety, immobility, or critical illness. While there may be a role for portable monitoring in the diagnosis of OSA in high risk populations without comorbid disease, its limitations in the diagnosis and management of respiratory sleep disorders lead many to believe that it remains a suboptimal testing modality.

SLEEP QUESTIONNAIRES

Sleep questionnaires, which quantify the severity of symptomatic daytime somnolence and/or screen for the presence of OSA, assist the sleep physician in determining an individual's risk for primary sleep disorders. The Epworth Sleepiness Scale (ESS), a self-administered tool to measure subjective daytime sleepiness, is one of the most commonly utilized questionnaires in sleep medicine due to its simplicity and brevity. The original research article describing the ESS demonstrated that the severity of OSA was significantly correlated with the ESS score.[16] The ESS evaluates an individual's sleep propensity by assigning the likelihood of falling asleep on a 4-point scale (0–3) in each of eight situations, which include the following as examples: sitting and reading, watching television, sitting and talking to someone, etc. Although the ESS is a widely used measure of subjective sleepiness and an integral component of an initial sleep evaluation, it has been shown to not correlate with objective measures of sleepiness (MSLT)[17] and not be able to differentiate between primary snoring and OSA,[18] thereby limiting its usefulness in screening individuals for respiratory sleep disturbances.

A recent systematic review analyzed the accuracy of screening questionnaires in determining the presence or absence of obstructive sleep apnea diagnosed by nocturnal polysomnography (Table 128.4).[19] Potential studies were screened and determined to be eligible for the study if they utilized patient-based questionnaires as screening tools for OSA in individuals of over 18 years of age, the questionnaire's accuracy was compared with PSG results as the "gold standard" for diagnosing OSA, the definition of OSA was clearly defined as an AHI, apnea index, or RDI ≥ 5. Ten studies met inclusion in this systematic review, evaluating 1,484 subjects. The Berlin Questionnaire, Wisconsin Questionnaire and STOP and STOP-Bang questionnaires were the most frequently studied; in individuals without a history of sleep disorders, the Wisconsin Questionnaire had the highest sensitivity in determining the presence of mild OSA (95%, AHI ≥ 5) while the STOP-Bang Questionnaire, which was used in a surgical population only, had the highest sensitivity (93%) in those with moderate OSA (AHI ≥ 15). Although screening tests in general are most useful when they demonstrate high sensitivity, the tests described above are not perfect discriminating tools; the specificities of the above questionnaires are 64 and 43%, respectively. Caution, when interpreting the results of screening questionnaires for OSA, should be employed.

RESPIRATORY DISORDERS DURING SLEEP

Although sleep apnea syndromes are the most commonly diagnosed and treated disorders in a sleep medicine practice, many disease entities seen in a general pulmonary practice manifest with significant nocturnal symptoms.

Asthma

Nocturnal asthma, which is defined by a drop in forced expiratory volume in 1 second (FEV_1) of at least 15% between sleep and awake states associated with increased airway hyperresponsiveness and inflammation,[20] has gained increased awareness and is likely under-reported. In a large cross-sectional survery of nocturnal asthma symptoms in France, 81% of 13,493 patients had nocturnal symptoms;[21] although this study did not measure pulmonary function parameters, the high prevalence of subjective symptoms of individuals diagnosed with asthma remains a significant finding. Several pathophysiologic mechanisms are proposed as contributing to the etiology of nocturnal asthma symptoms, including circadian increases in inflammatory mediators (eosinophils, macrophages, $CD4^+$ lymphoctyes and leukotrienes), positional changes in lung volume and airways resistance with supine positioning for sleep, changes in the β-adrenergic receptors controlling airway tone, alterations in glucocorticoid receptor binding affinity and the association of OSA with nocturnal asthma symptoms.[20]

Genetic polymorphisms in the β-adrenergic receptor are of recent interest; it is postulated that genetic substitution of glycine for arginine at locus 16 may result in increased presence of nocturnal asthma. In a study of 47 Chinese asthmatics (25 nocturnal asthma, 22 non-

TABLE 128.4: Questionnaires as a screening test for OSA

Questionnaire (Study Author)	*Sensitivity*	*Specificity*
ASA	0.79	0.37
Berlin (Chung)	0.79	0.50
Berlin (Netzer)	0.54	0.97
STOP	0.74	0.53
STOP-Bang	0.93	0.43
Wisconsin	0.87	0.40

ASA, American Society of Anesthesiologist's checklist; STOP, Snoring, Tired, Observed apnea, Pressure elevation; STOP-Bang, STOP and BMI, age, neck circumference, gender

Adapted from: Abrishami A, Khajehdehi A, Chung F. Can J Anaesth 2010 May; 57(5):423-38.

nocturnal asthma), the presence of gly/gly genotype at locus 16 was 72% in the nocturnal group and 32% in the non-nocturnal group (p=0.022).[22] In a meta-analysis that included five studies of nocturnal asthma, the presence of the glycine allele at locus 16 more than doubled the risk (OR 2.2, p<0.001) of nocturnal asthma,[23] although this polymorphism was not found to increase the overall risk of asthma in both this study and other meta analyses.[24]

Prior to focusing on the specific treatment of nocturnal symptoms of asthma, it is imperative that the patient has adhered to standard asthma therapy which ideally manages asthma symptoms throughout the course of a 24-hour period. Thus the first step in controlling nocturnal asthma symptoms includes avoidance of allergens, adequate evaluation and treatment of comorbid conditions that may potentiate asthma severity and the use of appropriate pharmacologic therapy.[25] Altering the timing of medication administration may be helpful in individuals with significant nocturnal asthma symptoms. Administration of oral prednisone at 3 PM improved morning FEV_1 and decreased blood eosinophil counts and bronchoalveolar lavage cell line counts when compared with alternately timed dosing.[26] Long-acting β-agonist therapy likely improves nocturnal symptoms and has been shown to improve quality of life measures in individuals with nocturnal asthma in a randomized controlled trial.[27] Other timed therapies may be useful in nocturnal asthma; further studies are needed.

COPD

Chronic obstructive pulmonary disease (COPD) and sleep apnea syndromes are both common disease entities in the general adult population. The presence of both COPD and OSA has been termed the "overlap syndrome" and denotes worsened nocturnal gas exchange parameters compared with either disease entity alone. Although early studies suggested that individuals with COPD had higher prevalence of OSA and vice versa, subsequent studies with improved methodologic quality proved this supposition false. The Sleep Heart Health Study (SHHS), which evaluated a large cohort of individuals sampled from several ongoing cohort studies of cardiovascular health, enrolled 5,954 subjects who underwent ambulatory PSG and spirometry.[28] After adjusting for body mass index, there was no significant difference in the presence of sleep apnea among those with and without obstructive airways disease; therefore, the presence of OSA or COPD did not increase the risk of the other disease entity to be present. Further findings from the study included:

1. In those without OSA, there was no difference in ESS, sleep latency, sleep efficiency, and sleep architecture among those with and without airways obstruction, although there was a small difference in total sleep time.
2. Individuals with the "overlap syndrome" had lower sleep efficiency than those with OSA or airways obstruction alone.

Oxygen saturation of hemoglobin is significantly affected by the presence of OSA, airways obstruction, and the "overlap syndrome". In individuals without OSA in the SHHS[28], an FEV_1/FVC ratio of 60 to 65% had a 2-fold increased risk of oxygen saturation of <90% for greater than 5% of total sleep time (OR 1.92; CI 1.1–3.34) after adjusting for potential confounders. In those with the "overlap syndrome", the odds ratio of spending >5% total sleep time below 85% oxygen saturation as compared with subjects without OSA and airways obstruction was 30, while the odds of OSA alone (without airways obstruction) was 15; thus, the "overlap syndrome" connotes a much greater degree of gas exchange abnormality when compared with OSA or airways obstruction alone. Potential pathophysiologic mechanisms for the degree of oxyhemoglobin desaturation in the overlap syndrome include altered respiratory mechanics due to lung disease, ventilation/perfusion abnormality and pulmonary parenchymal abnormalities due to underlying lung disease. Management of the overlap syndrome includes positive airway pressure (continuous or bilevel mode), pharmacologic management of airways obstruction and oxygen supplementation when indicated.

Hypoventilation/Hypoxemia Syndromes

The International Classification of Sleep Disorders

Diagnostic and Coding Manual defines sleep related hypoventilation/hypoxemia as P_aCO_2 >45 mm Hg, an oxyhemoglobin saturation of <90% for more than five minutes with a nadir of ≤85% or >30% of total sleep time with an oxygen saturation of <90%.[29] While gas exchange parameters are important for the diagnosis of hypoventilation/hypoxemia syndromes, the causes of these gas exchange abnormalities is comprised of a heterogenous group of disorders that affect the ability of the respiratory system to compensate for sleep-related changes in ventilatory control mechanisms and respiratory mechanics. This group includes neuromuscular, pulmonary and chest wall disorders and various idiopathic disorders (congenital central alveolar hypoventilation). The primary pathophysiology of nocturnal hypoxemia relates to the inability of the respiratory system to maintain adequate ventilation, resulting in an elevation of alveolar partial pressure of carbon dioxide and a subsequent reduction of alveolar oxygen, consistent with the alveolar gas equation; an alternate cause of hypoxemia likely relates to increasing ventilation and perfusion mismatch in poorly ventilated lung regions.

Clinical features of alveolar hypoventilation include poor sleep quality, nocturnal and/or morning headache, daytime sleepiness and loss of energy, decreased intellectual performance, loss of appetite and weight loss, and features of progressive right heart failure/cor pulmonale.[30] Treatment for sleep-related hypoventilation/hypoxemia syndromes is disorder specific, although noninvasive ventilation in the bilevel mode is often a necessary adjunctive measure utilized in all of these disorders; short-term improvement in clinical symptoms and the suggestion of a mortality benefit, particularly in individuals with neuromuscular disease, is present when noninvasive ventilatory support is utilized.[31]

Neuromuscular disorders that may result in nocturnal hypoventilation/hypoxemia include amyotrophic lateral sclerosis (ALS), spinal cord injury, diaphragmatic paralysis, myasthenia gravis, Eaton-Lambert syndrome, post-polio syndrome, myopathic disorders and Charcot-Marie-Tooth syndrome.[32] Individuals with ALS, a neurodegenerative disorder characterized by loss of motor neurons with resultant progressive weakness and atrophy of skeletal muscles including accessory muscles of respiration, are at risk for both diurnal and nocturnal hypoventilation/hypoxemia. In a prospective observational study of 38 patients with ALS, the forced vital capacity (FVC) decreased by a mean of 10% after six months and 71% of patients developed chronic hypoventilation by 26 months;[33] the criteria to define chronic hypoventilation included nocturnal desaturation of oxyhemoglobin saturation <88% for five consecutive minutes. Although this study did not specifically evaluate hypoventilation during sleep, it can be assumed that all patients who developed chronic hypoventilation were affected during sleep since the normal physiologic response to sleep is a mild elevation of P_aCO_2 even in the absence of disease,[34] compounding the disease related hypoventilation.

Although the diminished function of respiratory muscles is the primary defect in neuromuscular disorders during sleep, individuals with chest wall disorders (kyphoscoliosis, ankylosing spondylitis, trauma, pleural disease, history of thoracoplasty and obesity) and pulmonary disease (COPD, asthma, IPF, CF) are at risk for nocturnal hypoventilation/hypoxemia due to several additional mechanisms. During REM sleep, bursts of rapid eye movements are associated with inhibition of accessory muscles of respiration;[35] ventilation and gas exchange thus depend solely on the diaphragm. Individuals with chest wall and/or pulmonary disease may already have gas exchange abnormalities due to their underlying disease when awake; normal increases in P_aCO_2 associated with sleep onset compounds the underlying gas exchange problems, resulting in worsening hypoxemia. Obesity results in reduced chest wall compliance due to the mass load placed on the thoracic cage; the reduction in compliance is further exacerbated in the supine position, worsening ventilatory function during sleep by increasing the work of breathing.[36]

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129A

Obstructive Sleep Apnea-Hypopnea Syndrome—A Developing Countries' Perspective

Harmanjit Singh Hira

A syndromic presentation mimicking first recognized in the 19th century when Charles Dickens (1837) gave literacy description of a sleepy red-faced fat boy "Joe".[1] Burwell et al.[2] described a medical description of a Pickwickian syndrome as "obesity, somnolence, cyanosis, polycythemia, right heart failure" in 1956. It was 1964 that Gastaut et al.[3] provided the polygraphic recording of pickwickian patients' "presence of apneas during sleep". Introduction of the term "Sleep Apnea Syndrome" (SAS) in patients presenting with clinical picture as different from the pickwickian syndrome was coined by Guilleminault in 1976.[4]

An apnea is a period of time during which the breathing stops or slows to <25% of a normal breath for a period that lasts for 10 seconds or more. Hypopnea is a decrease in breathing from 69% to 26% of normal and is associated with a 4% or greater drop in the saturation of oxygen in the blood. Sleep apnea syndrome (SAS) is diagnosed when these frequent interruptions occur up to 30 times or more in an hour. Natural history of sleep apnea syndrome may be listed as: Pure snoring → snoring with occasional apneas → overt SAS → sleep apnea with daytime hypoventilation → Pickwickian syndrome.

Obstructive sleep apnea-hypopnea (OSAH) is characterized by recurrent episodes of upper airway collapse and obstruction during sleep. These episodes of obstruction are associated with recurrent oxyhemoglobin desaturations and arousals from sleep. OSAH associated with excessive daytime sleepiness (EDS) is commonly called Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS). Despite being a common disease, OSAHS is under recognized by most primary care physicians in India. Also, an estimated 80% of Americans with OSAHS are not diagnosed.[5] Central apnea syndrome occurs when the brain fails to signal the diaphragm and chest muscles to breathe. It is more common in the elderly persons.

Pathophysiology

Conceptually, the upper airway is a compliant tube, therefore, subject to collapse.[6] Most patients with OSAHS demonstrate upper airway obstruction at either the level of the soft palate (nasopharynx) or of the tongue (oropharynx) which are normally dilated as open airways (Fig. 129A.1A). Both anatomic and neuromuscular factors are important in causing obstruction. Anatomic factors (enlarged tonsils; larger volume of the tongue, soft tissue or lateral pharyngeal walls); length of the soft palate; abnormal positioning of the maxilla and mandible) decrease the cross-sectional area of the upper airway (Fig. 129A.1B) and/or increase the pressure surrounding the airway, both of which predispose the airway to collapse.[7,8]

Upper airway neuromuscular activity, including reflex activity, decreases with sleep, this decrease may be more pronounced in patients with OSAHS. Reduced ventilatory motor output to upper airway muscles is believed to be the critical initiating event leading to upper airway obstruction; this effect is most pronounced in patients with an upper airway predisposed to collapse for anatomical reasons.

Central breathing instability is a well-established factor contributing to the development of central sleep apnea, particularly in patients with severe congestive heart failure. Evidence also indicates that central breathing instability contributes to the development of OSAHS:

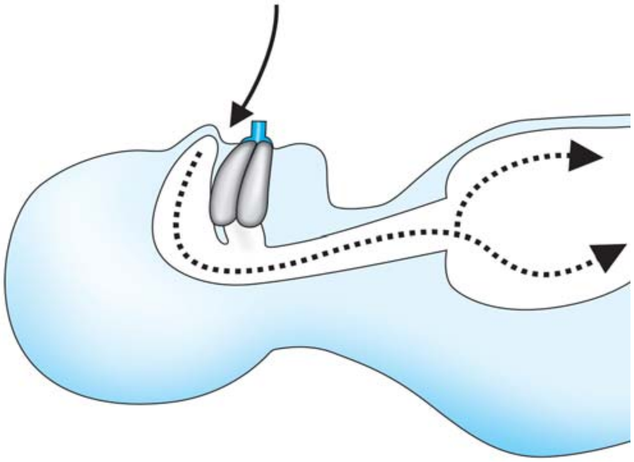

Fig. 129A.1A: Normal open upper airway (arrows). Obstruction occurs at either the level of the soft palate (nasopharynx) or at the level of the tongue (oropharynx)

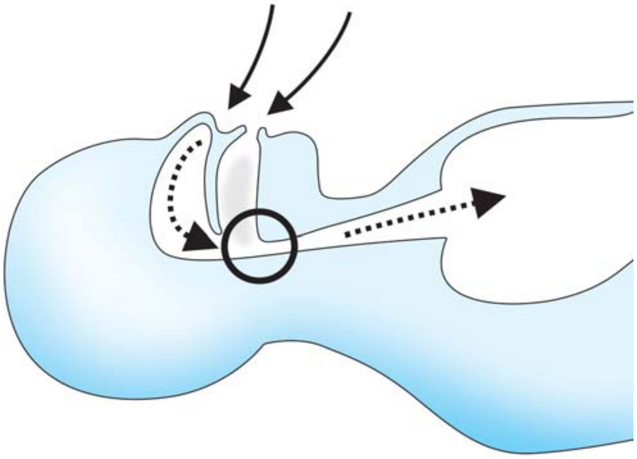

Fig. 129A.1B: Cross-sectional area of the upper airway and/or increase the pressure surrounding the airway, both of which predispose the airway to collapse to lead to closed airway marked as a black circle.

i. Upper airway obstruction in the absence of ventilatory motor output (central sleep apnea) has been observed.[9-11]

ii. Reduction in pharyngeal dilator activity has been associated with periodic breathing and hypocapnia in subjects with evidence of inspiratory flow limitation.

iii. Men have been shown to be more susceptible to the development of central sleep apnea and have a decreased responsiveness to carbon dioxide compared with women, a result consistent with the increased prevalence of OSAHS in men compared with women.

Systemic hypertension is observed in 50 to 70% of patients with OSAHS. It has been shown that patients with OSAHS had increased glucose levels and increased insulin resistance.[12] We have also observed that OSAHS is associated with increased production of reactive oxygen species and other oxidative stress biomarkers like uric acid and lactate.

Clinical Features

OSAHS is a common disease, globally and in India,[6] the estimated prevalence is 2% for women and 4% for men. The male-to-female ratio in community-based studies is 2–3:1. Three large epidemiologic studies have demonstrated that the prevalence of OSAHS in women appears to increase after menopause. The prevalence increases with age,[13] with an estimated rate as high as 65% in a community sample of people older than 65 years.[14]

Symptomatology

Symptoms of OSAHS generally begin insidiously and are often present for years before the patient is referred for evaluation. The common symptoms can be grouped as follows:

Nocturnal Symptoms

- Snoring, usually loud, habitual and bothersome to others
- Witnessed apneas, which often interrupt the snoring and end with a snort
- Gasping and choking sensations that arouse the patient from sleep
- Restless sleep, with patients often experiencing frequent arousals and tossing or turning during the night
- Increased frequency of mictuirition

Daytime Symptoms

- Not feeling refreshed upon awakening
- Morning headache, dry or sore throat
- Excessive daytime sleepiness that usually begins during quiet activities (reading, watching television). As the severity worsens, patients begin to feel sleepy during activities that generally require alertness (school, work, driving). It is the experience of the author that these patients generally sleep while waiting for their turn for examination in outpatient department.

  - EDS is most frequently assessed by a sleep physician using the Epworth Sleepiness Scale (ESS). This questionnaire is used to help determine how frequently the patient is likely to doze off in 8 frequently encountered situations.
  - An ESS score greater than 10 is generally considered sleepy. However, a 2003 study showed that an ESS score of 12 is associated with a greater propensity to fall asleep on the Multiple Sleep Latency Test (MSLT) suggesting that 12 would be a better cutoff.[15] The ESS is useful for evaluating responses to treatment; the ESS score should decrease with effective treatment.
- Daytime fatigue/tiredness: Most of the patients who do not report EDS, do complain of fatigue, having a lack of energy, or getting tired during the day. In one study of 190 patients with OSAHS, patients were more likely to report lack of energy (62%), fatigue (57%) and tiredness (61%) than sleepiness (47%).[16] When asked to choose their most significant symptom, 40% of patients chose lack of energy, compared with 22% for sleepiness.[16]
- Problems with memory, concentration and cognitive function, particularly executive functioning
- Impotence
- History of motor vehicle accident(s).

Physical Examination

The general physical examination is frequently normal, other than the presence of obesity (defined as a BMI >30 kg/m^2), an enlarged neck circumference and hypertension. Evaluation of the upper airway is required in all patients, particularly in nonobese adults with symptoms consistent with OSAHS. The following features have been associated with the presence of OSAHS:

- *Neck circumference:* A neck circumference greater than 43 cm (17 inches) in men and 37 cm (15 inches) in women has been associated with an increased risk of OSAHS.
- *Mallampati score:* This score has been used for many years to identify patients at risk for difficult tracheal intubation. Scoring is classified (Fig. 129A.2) as Class 1: Full visibility of tonsils, uvula and soft palate; Class 2: Visibility of hard and soft palate, upper portion of tonsils and uvula; Class 3: Soft and hard palate and base of the uvula are visible; and Class 4: Only hard palate visible.

The classification provides a score of 1 to 4 based on the anatomic features of the airway seen when the patient opens his or her mouth and protrudes the tongue. A 2006 study showed that for each 1 unit increase in the Mallampati score, the odds ratio of having OSAHS (defined by an AHI > 5) increased by 2.5, and the AHI increased by five events per hour.[17]

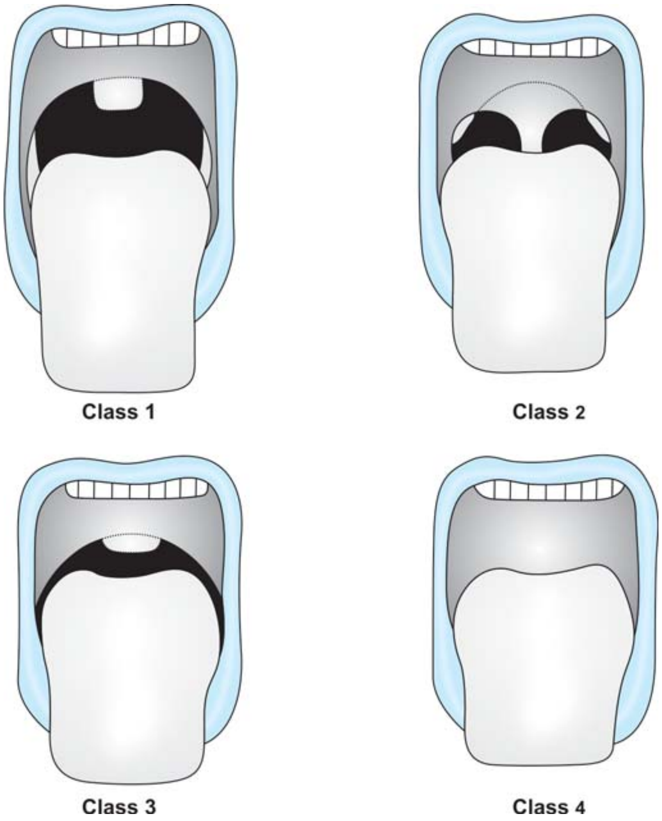

Fig. 129A.2: Shows the pictures of all four classes based on Mallampati score.

- Narrowing of the lateral airway walls, which is an independent predictor of the presence of OSAHS in men, but not women
- Enlarged ("kissing") tonsils (3^+ to 4^+) (Fig. 129A.3)
- Retrognathia or micrognathia
- Large degree of overjet
- High-arched hard palate

Causes

Obstructive sleep apnea syndrome is common in the presence of several known risk factors (Table 129A.1).

Other diseases associated with the development of OSAHS are as follows:

- *Hypothyroidism:* This has been associated with the development of OSAHS;[19] however, evidence indicates that the prevalence of hypothyroidism in

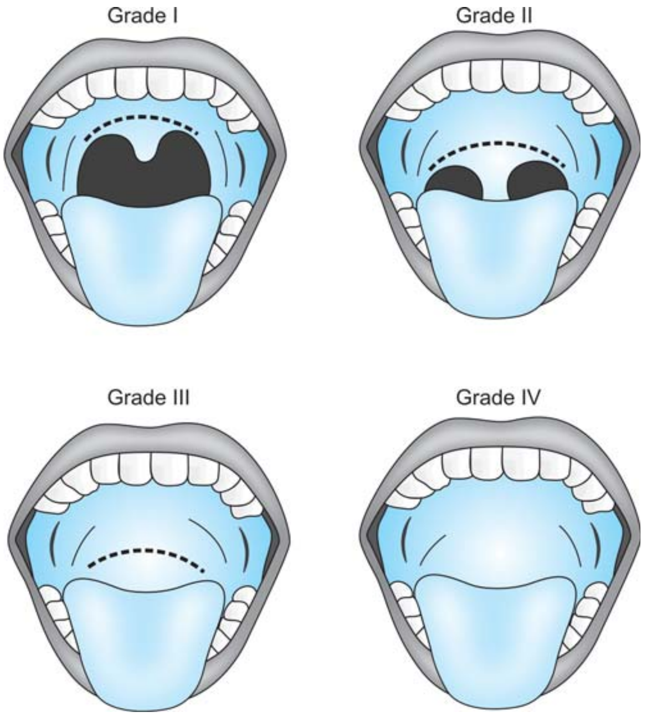

Fig. 129A.3: Grading of tonsil enlargement

TABLE 129A.1: Known risk factors for OSAHS

- Obesity
- Male sex
- Age
- Adenotonsillar hypertrophy, particularly in children and young adults
- Alcohol use
- Craniofacial skeletal abnormalities, particularly in nonobese adults and children
- *Family history:* Risk increases with each additional close family relative with OSAHS.[18]

patients with OSAHS is no higher than in the general population, therefore, patients with OSAHS need not be routinely screened for hypothyroidism, except possibly for the elderly women.

- Neurologic syndromes such as postpolio syndrome, muscular dystrophies, and autonomic failure syndromes such as Shy-Drager syndrome.
- *Stroke:* The relationship of OSAHS to cerebrovascular disease is still being determined. There is growing evidence that the prevalence of OSAHS is increased in patients who have had a stroke. However, whether OSAHS is a risk factor for stroke or stroke is a risk factor for developing OSAHS remains unclear.
- Acromegaly.

Laboratory Investigations

In addition to the routine clinical, radiological, hematological and biochemical assessments, investigations are required to establish the diagnosis and exclude other comorbidities and/or complications. Thyroid function tests should be performed on any patient with possible obstructive sleep apnea-hypopnea syndrome who has other signs or symptoms of hypothyroidism.

An arterial blood gas determination is needed in patients presenting with cor pulmonale, in order to rule out daytime hypoxemia or hypercapnia. Pulmonary function tests should be performed if the patient has evidence of cor pulmonale or if nocturnal symptoms are suggestive of nocturnal asthma (patient wakes up with shortness of breath that does not immediately resolve or is associated with wheezing).

An overnight sleep study or polysomnography is required to diagnose obstructive sleep apnea-hypopnea syndrome. During polysomnography, multiple body functions are monitored in asleep patient (Fig. 129A.4). Guidelines for the indications and performance of polysomnography are now available which include the following[20] (Figs 129A.5A to C):

- Sleep stages are recorded via an electroencephalogram, electrooculogram and chin electromyogram.
- Heart rhythm is monitored with a single-lead ECG.
- Leg movements are recorded via an anterior tibialis electromyogram.

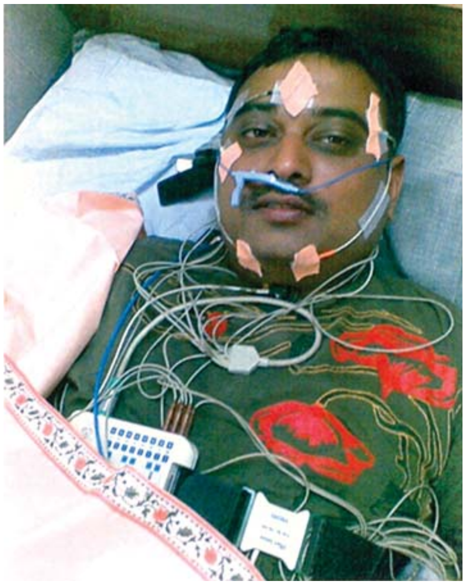

Fig. 129A.4: Shows the patient with all the sensors and recorder during polysomnography in sleep laboratory

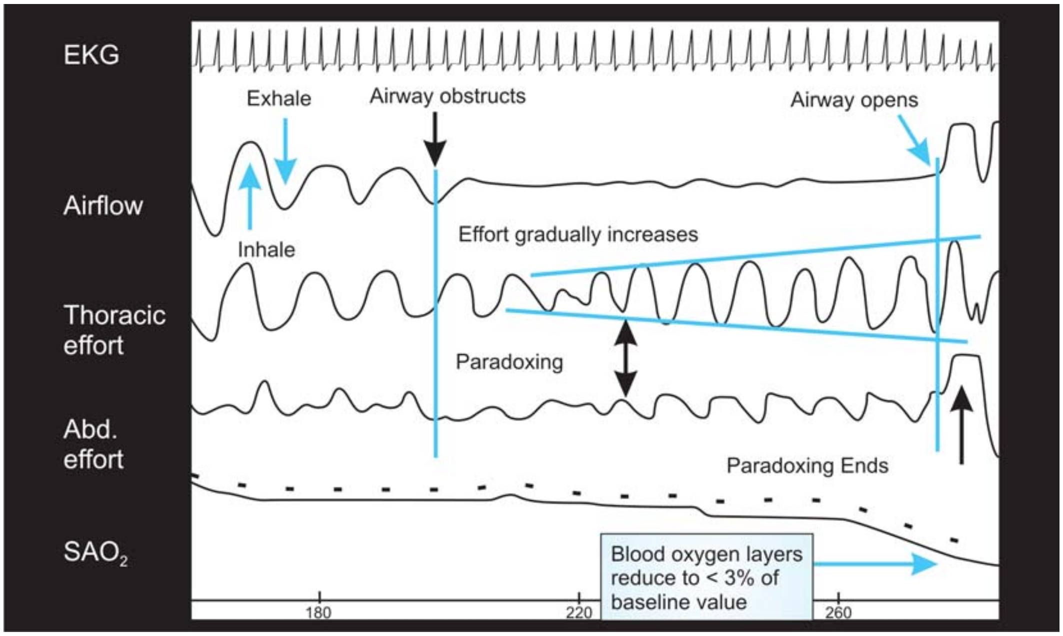

Fig. 129A.5A: Obstructive sleep apnea. Note the absence of flow despite paradoxical respiratory effort (blue arrows)

- Breathing is monitored, including airflow at the nose and mouth (using both a thermal sensors and a nasal pressure transducer), effort (using inductance plethysmography), and oxygen saturation.
- The breathing pattern is analyzed, for the presence of apneas and hypopneas. Definitions have been standardized by the American Academy of Sleep Medicine (AASM).[21]

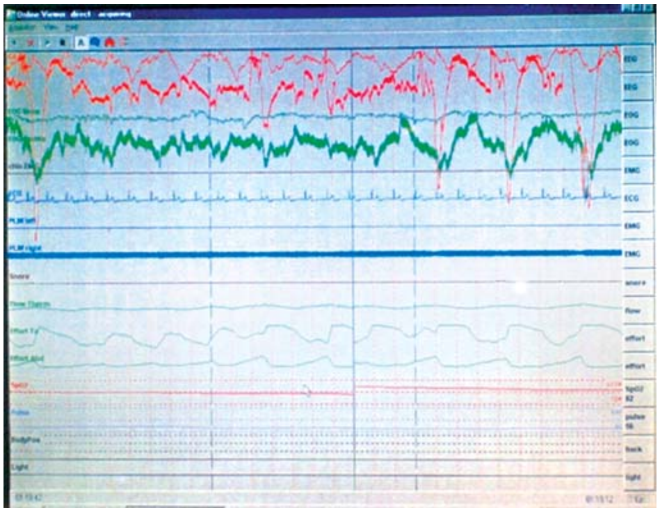

Fig. 129A.5B: All parameters during running polysomnography

- Obstructive apnea is the cessation of airflow for at least 10 seconds with persistent respiratory effort (Fig. 129A.6).
- Central apnea is the cessation of airflow for at least 10 seconds with no respiratory effort (Fig. 129A.6).
- Mixed apnea is an apnea that begins as a central apnea and ends as an obstructive apnea (Fig. 129A.7).
- The recommended definition of hypopnea is a 30% or greater decrease in flow lasting at least 10 seconds and associated with a 4% or greater oxyhemoglobin desaturation (Fig. 129A.8). An alternative definition is a 50% or greater reduction in flow lasting at least 10 seconds and associated with either a 3% or greater oxyhemoglobin desaturation or an arousal.
- Respiratory event-related arousal is an event in which the patient has a series of breaths with increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep that does not otherwise meet the criteria for an apnea or hypopnea.
- The AHI (apnea-hypopnea index) is derived from the total number of apneas and hypopneas divided by the total sleep time.
- A normal cutoff for AHI has never been defined in an epidemiological study of healthy people. Most sleep centers use a cutoff of 5–10 episodes per hour.[10]

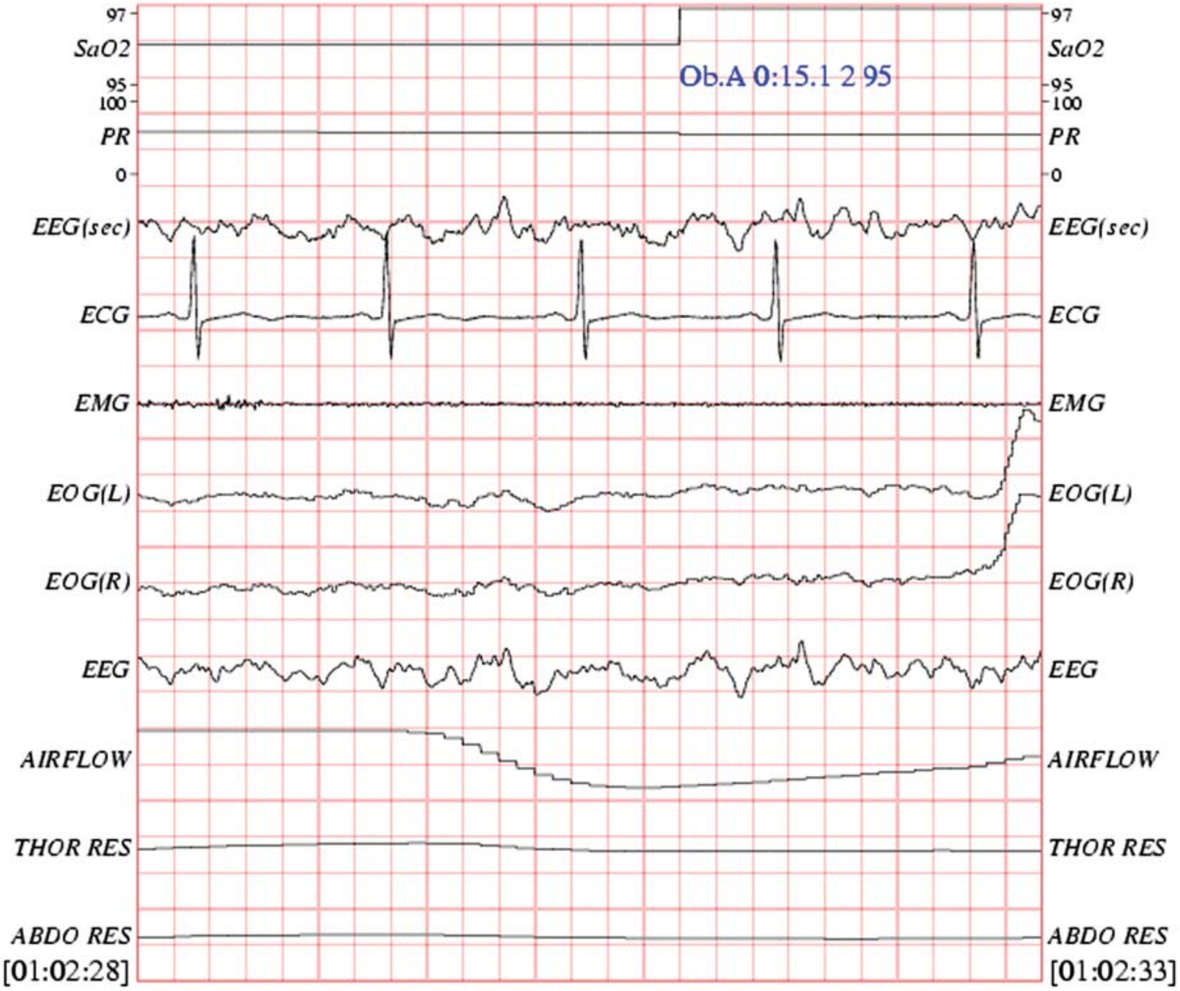
97
SaO2
95
100
PR
0
Ob.A 0:15.1 2 95
EEG(sec)
ECG
EMG
EOG(L)
EOG(R)
EEG
AIRFLOW
THOR RES
ABDO RES
[01:02:28]
[01:02:33]

Fig. 129A.5C: A print-out of parameters of polysomnograph

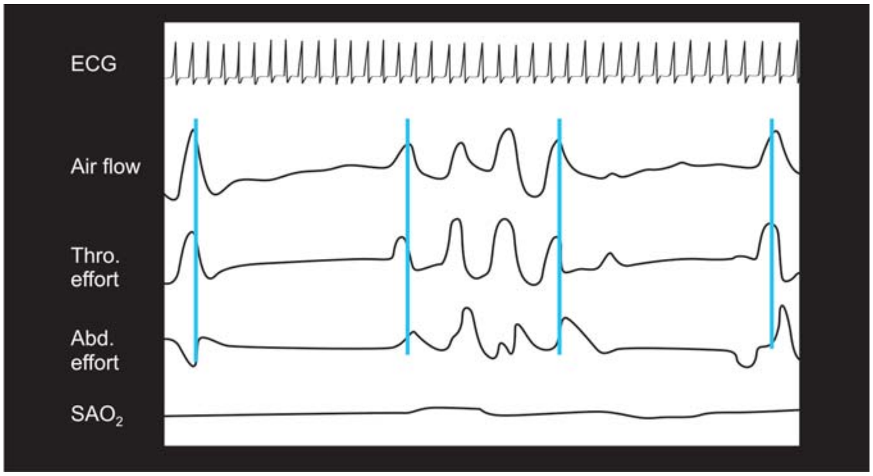
ECG
Air flow
Thro. effort
Abd. effort
SAO$_2$

Fig. 129A.6: Central apnea. These are central apneas (2) with minimal oxygen desaturation. Note there is no airflow and respiratory effort.

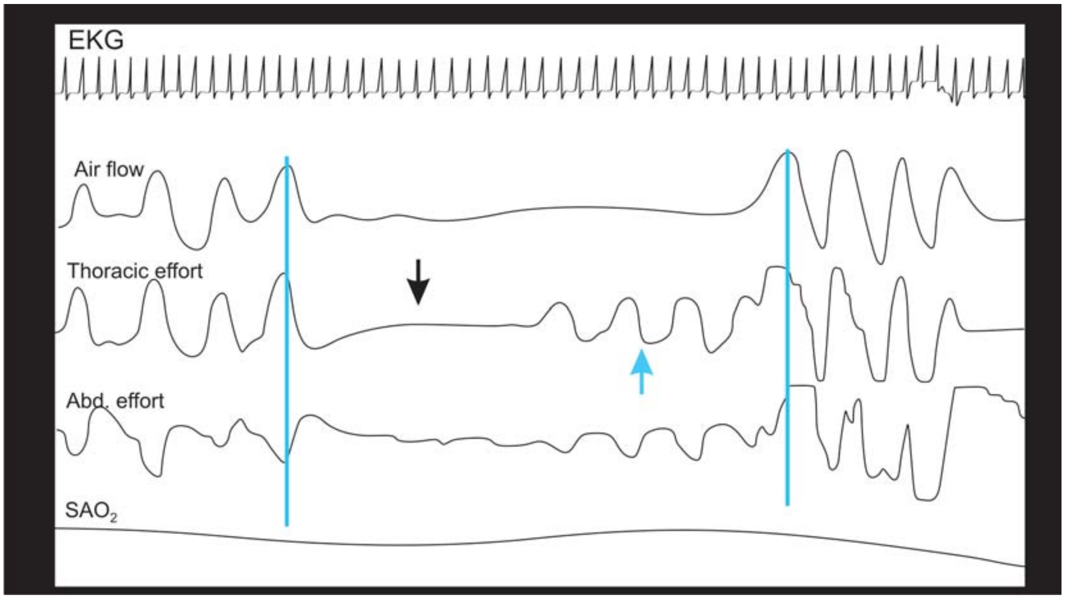

Fig. 129A.7: Mixed apnea, a complete absence of nasal and air flow. A total absence of respiratory effort at the beginning of the event (black thick arrow) is followed by gradual increase in effort (blue thick arrow) which eventually breaks the apnea. An oxygen desaturation is ≥3%

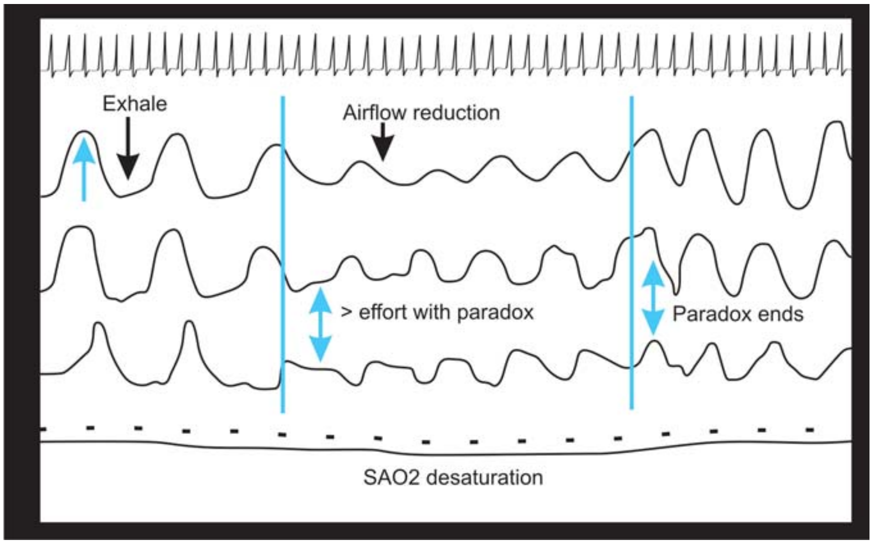

Fig. 129A.8: Hypopnea. This is an 18 sec hypopnea event. The airflow signal is reduced by 50% during this event (small black arrow)

- The severity of OSAHS is arbitrarily defined and differs widely between centers. Recommendations for cutoff levels on AHI include 5–15 episodes per hour for mild, 15–30 episodes per hour for moderate and more than 30 episodes per hour for severe.

The use of portable monitors for the in-home diagnosis of OSAHS is becoming more common. The American Academy of Sleep Medicine has published guidelines on the use of portable monitors. These guidelines recommend its use only in patients with a high probability of disease and in those without comorbidities (particularly congestive heart failure), and that negative studies be followed by a full, attended study.[21]

Polysomnography can be followed by a MSLT. The MSLT is considered an objective measurement of EDS. The MSLT consists of 4–5 naps of 20-minute duration every two hours during the day. The latency to sleep onset for each nap is averaged to determine the daytime sleep latency. Normal daytime sleep latency is greater than 10–15 minutes. OSAHS is generally associated with latencies of less than 10 minutes. The routine use of the MSLT in the evaluation of OSAHS has significantly decreased because sleep physicians generally treat OSAHS based on the subjective symptoms reported by the patient. The MSLT is generally used to confirm the diagnosis of narcolepsy in patients in whom narcolepsy is a consideration. As opposed to people without narcolepsy, narcoleptic patients have rapid eye movement sleep on at least two of the 4–5 naps during the day.

Treatment

The treatment of obstructive sleep apnea-hypopnea syndrome in part depends on the severity of the sleep-disordered breathing. People with mild apnea have a wider variety of options, while people with moderate-to-severe apnea should be treated with nasal CPAP.

Conservative measures include weight loss, avoidance of alcohol for 4–6 hours prior to bedtime and sleeping on one's side rather than on the stomach or back. These measures are included in the treatment of all patients with OSAHS, but uses as primary treatment in patients with very mild apnea whose main symptom is snoring. In a 2006 practice parameter, both weight loss and positional therapy were rated as "guidelines," indicating a patient care strategy with a moderate degree of evidence.[22]

Nasal Continuous Positive Airway Pressure (CPAP)

CPAP is the most effective treatment for OSAHS, and has become the standard of care. CPAP works by splinting the upper airway, and preventing the soft tissues from collapsing (Figs 129A.9A and B). By this mechanism, it effectively eliminates the apneas and/or hypopneas, decreases the arousals and normalizes the oxygen saturation.

Most sleep center physicians still titrates the CPAP level during a sleep study. This can be done on the second night of the study or during the second half of the diagnostic study, termed a split-night polysomnography. Guidelines for positive-pressure titration studies are available.[23-25]

Currently, CPAP devices are available that automatically change pressures based on the presence and/or absence of OSAHS (auto-positive airway pressure, or auto-PAP), where the need of titration is not required. The rationale for auto-titrating devices is based on the concept that the pressure required to treat OSAHS may vary over the course of the night and between different nights, sleep stages, and body positions with

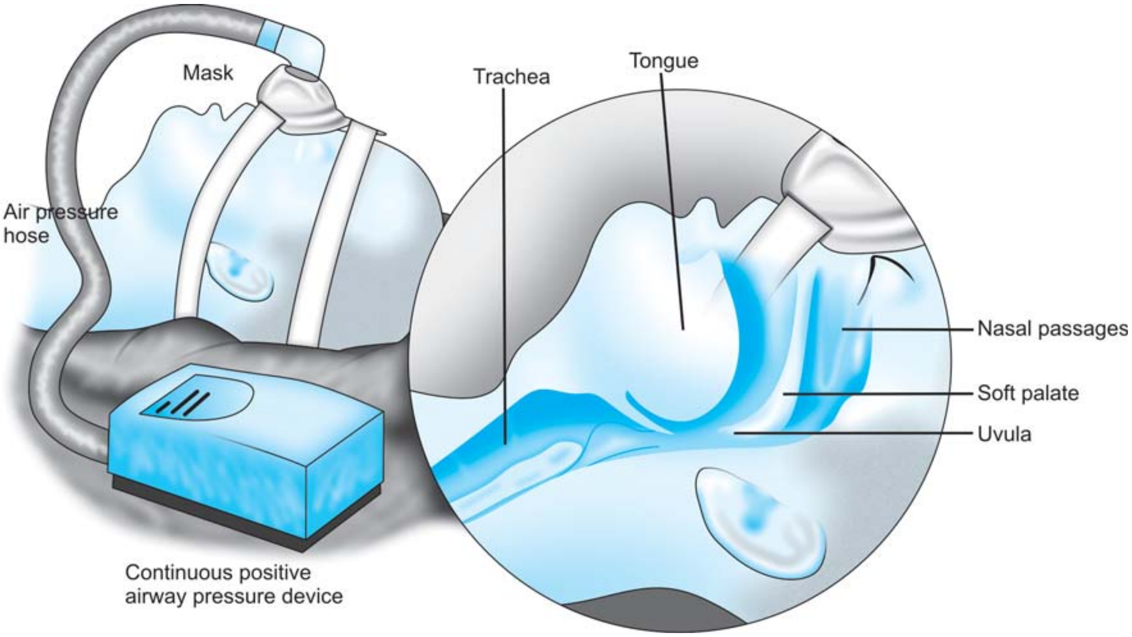

Fig. 129A.9A: CPAP device along with patient is seen. Left side shows the CPAP equipment with air flowing with supra-atmospheric pressure through the Air Pressure Hose and delivered to the patient through nasal mask (part of figure outside the circle). The continuous positive pressure acts as an air splint and keeps the closed airway during apnea as opened (part of figure in circle)

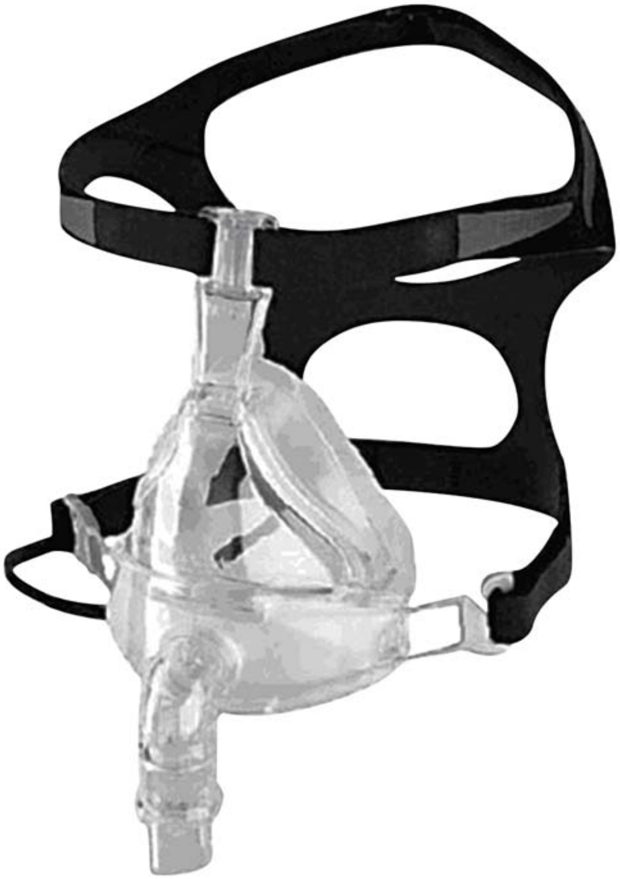

Fig. 129A.9B: Shows the nasal mask along with head gear. Latter keeps the mask tightened on the nose to prevent any air leak

the variations not captured by a one-night titration study. In theory, the mean pressure delivered by auto-PAP devices is lower than that delivered with fixed CPAP; however, no studies have shown increased patient compliance with auto-PAP devices.[26]

All patients with an AHI greater than 15 are considered eligible for CPAP, regardless of the symptomatology. For patients with an AHI of 5–14.9, CPAP is indicated only if the patient has one EDS or comorbidities (hypertension, cardiovascular disease or combination of them).

Continuous positive airway pressure has been shown to improve daytime sleepiness, mood, and cognitive function in people with both mild and moderate apnea.[27,28] It has also been shown to increase quality of life.[29.] Continuous positive airway pressure decreases blood pressure, primarily in patients with severe OSAHS, and may improve the left ventricular ejection fraction in patients with congestive heart failure and OSAHS.[30]

The most common adverse effects of CPAP are dry mouth, rhinitis and sinus congestion. These can be treated effectively with humidification and antihistamines and/or nasal steroids.

Many patients do not accept (or even initiate) CPAP therapy and up to 25% do not regularly follow-up with a sleep physician;[31] most of these patients are nonadherent to therapy. Continous positive airway pressure compliance may be determined as early as two weeks after CPAP is initiated. Patients who consistently use their positive airway pressure device at six months were, on an average using the device for more than 2 hours per night during the first two weeks, were more ready and confident to continue use. On the other hand, intermittent users were more likely to report general discomfort and adverse effects from the device, and that the device was too inconvenient. Compliance can be objectively measured.[32] Most modern positive airway pressure machines measure both “machine-on” and “mask-on” times, with the mask-on time used to measure compliance.

Some patients require the use of bi-level positive airway pressure (BiPAP). In BiPAP, a higher inspiratory pressure and a lower expiratory pressure are used. In patients with sleep apnea, the levels are set such that the expiratory pressure eliminates apneas and the inspiratory pressure eliminates hypopneas. BiPAP is generally used in patients who cannot tolerate high CPAP pressures (patients who experience difficult exhalations) or who have barotrauma complications (ear infections, bloating). Many physicians automatically place a patient on BiPAP if the CPAP level needs an increase above 15 cm water. Compliance with BiPAP has not been demonstrated to be better than the compliance with CPAP.[33]

Follow-up of Patients on CPAP Therapy

Once diagnosed with OSAHS and started on nasal CPAP, patients require regular follow-up with a sleep specialist. Most patients are seen within two months of initiating CPAP to determine if it has been effective in alleviating symptoms, to troubleshoot problems preventing the regular use of the CPAP, and to reinforce the importance of daily use. Further follow-up depends on whether the CPAP has been effective.

- If effective, the patient is generally seen at 6–12 month intervals to troubleshoot new problems, to reinforce daily use and to be certain the CPAP remains effective.
- If CPAP has not been effective, problems preventing use are identified, steps are taken to eliminate problems and the patient is seen at 2–3 month intervals until the use is regular and the CPAP is effective in alleviating symptoms. Repeat titration may be necessary.

- Routine repeat polysomnography is generally not indicated for patients who report improved symptoms. Repeat CPAP titrations are usually performed in patients without effective relief of their symptoms despite intervention or in patients who had relief of symptoms but present months to years later, reporting the return of symptoms, generally in association with weight gain.
- Residual EDS after treatment with CPAP is a commonly encountered problem.

Oral Appliances

These devices act by moving the tongue or mandible forward, thereby enlarging the posterior airspace (Figs 129A.10A and B). Multiple different devices are available. In 2006, the AASM published practice parameters and a review of the use of oral appliances in persons with OSAHS.[34,35]

Multiple small cohort studies have shown that these devices effectively lower the AHI in case of: Mild-to-moderate disease (AHI <30); lower BMI; increased mandibular protrusion with the device; and the presence of positional OSAHS. Guidelines recommend that oral appliances are indicated for patients with mild-to-moderate OSAHS who prefer oral appliances to CPAP devices; patients with mild-to-moderate OSAHS who do not respond to CPAP therapy; and patients with mild-to-moderate OSAHS in whom treatment attempts with CPAP devices fail. Oral appliances should not be considered effective therapy for patients with severe OSAHS.

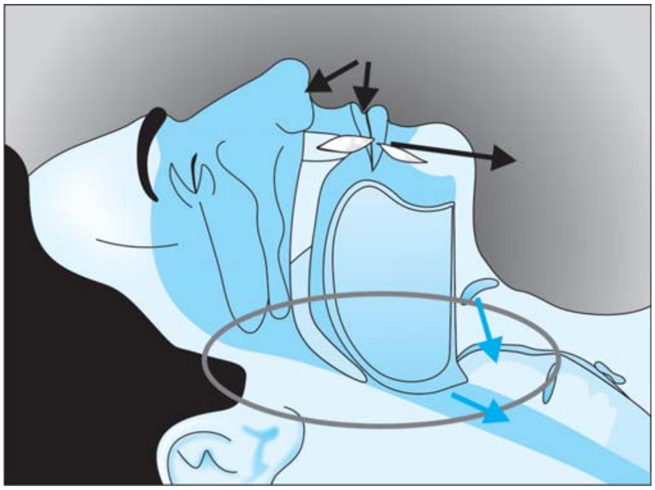

Fig. 129.10A: Shows the relaxed jaw position to cause tongue and throat tissue to collapse and narrow the airway (blue arrow)

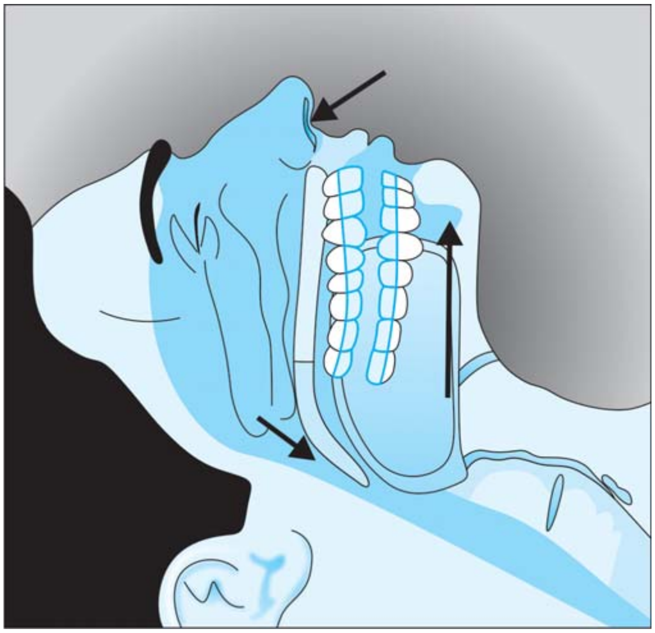

Fig. 129.10B: Shows the oral TAP (Thornton Adjustable Positioner) device that is worn over the teeth, much like an athletic mouth guard. The device gently moves the lower jaw slightly forward, opening airway (arrows) and improving nighttime breathing and alleviating snoring

Surgical Treatment

Surgical correction of the upper airway is still performed but is not considered primary therapy for OSAHS. The theoretic advantage of surgery if the patient is cured is that, compliance with CPAP or an oral appliance is no longer an issue. However, a primary reason that surgery has not become a standard therapy is the lack of long-term outcome studies that show that the surgical correction continues to be effective for five or more years after it is performed.

Factors that increase the likelihood of successful surgery include lower AHI, lower BMI, the location of collapse (surgeries targeted specifically to collapse at either the nasopharynx or oropharynx improve outcome), the degree of mandibular protrusion (better outcomes are achieved in patients with clear deficiencies), and the presence of fewer comorbidities.

Patients should be considered for surgery primarily if multiple attempts at therapy with CPAP have failed and if an oral appliance is not an option. If the patient opts for surgery, ensure that it should be performed by a qualified surgeon and the patient should be willing to undergo combination or multiple surgeries. Guidelines for the surgical treatment of OSAHS were last published in 1995.[36] Surgery procedures include the following:

- Uvulopalatopharyngoplasty (UPPP, Figs 129A.11A and B) is the resection of the uvula and soft palate. It is effective in approximately 40% of patients, but predicting which patients will benefit from the procedure, is problematic. Patients with treatment success often present with a recurrence of symptoms, especially if they continue to gain weight.
- Craniofacial reconstruction involves advancement of the tongue [geniohyoid advancement with hyoid myotomy (GAHM) or maxillomandibular bones osteotomy (MMO)]. These procedures should be performed only at centers with expert personnel. Short-term success rates are approximately 70% for GAHM and 95% for MMO. No good long-term studies have been performed to evaluate the success for either GAHM or MMO.
- Tracheostomy provides definitive correction because it bypasses the obstruction. It is recommended for patients with very severe OSAHS, especially if the patient does not tolerate CPAP or has cor pulmonale. In author's experience, the patients in India do not opt for tracheostomy.
- Bariatric surgery as therapy for OSAHS has been investigated in several nonrandomized, uncontrolled studies, with most showing a decrease in the AHI with weight loss. The 2006 practice parameter on medical therapies for OSAHS lists bariatric surgery as an option for OSAHS, although with limited evidence.[26]

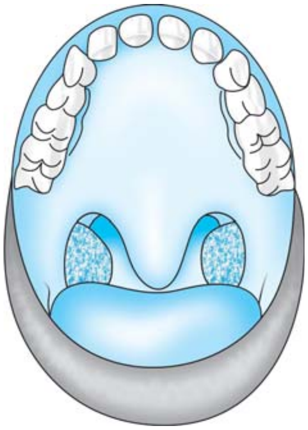

Fig. 129A.11A: Shows the oral cavity with narrow air space before UPPP

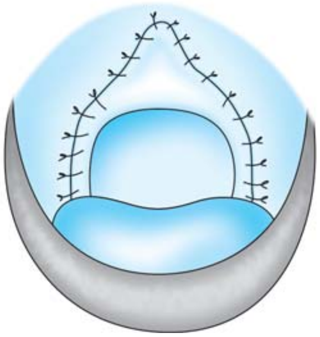

Fig. 129A.11B: Shows the oral cavity with widened air space following UPPP

Follow-up of Patient with Surgery/Oral Devices

If a patient chooses upper airway surgery or an oral appliance, he or she requires repeat polysomnography after surgery or with the device in place to be sure the OSAHS has improved.

Diet: All patients who are obese, should be counseled about the importance of diet and exercise, should be referred to a dietitian and/or a weight loss program.

Drug Therapy: The drugs have been used with no demonstrable effect. The AASM recently published a practice parameter and review of the medical therapies of OSAHS.

- Use of protriptyline for OSAHS was listed as a guideline (patient care strategy based on level 2 or 3 evidence).[37]
- The use of modafinil is recommended for the treatment of residual sleepiness in persons with OSAHS, is considered a standard treatment (generally accepted patient care strategy with level 1 or excellent level 2 evidence).
- Selective serotonin reuptake inhibitors, methylxanthines and estrogen replacement therapy should not be considered for the treatment of OSAHS.
- Central nervous system stimulants, nonamphetamine are used for treatment of fatigue without interfering with normal sleep architecture. They promote wakefulness.
- Concern exists that the use of modafinil (or other stimulants) in the management of OSAHS may result in decreased CPAP usage. This is important because stimulants do not control the sleep-disordered breathing, resulting in worsening symptom control and potentially increasing the risk of cardiovascular morbidity. The dose of modafil used is 100–200 mg PO qd; some patients may require as much as 300 mg PO qd. This is not recommended for children.

Prognosis

The short-term prognosis, in relation to symptoms such as daytime sleepiness and snoring, ranges from good to excellent with regular use of CPAP. The long-term prognosis is unknown because no randomized treatment studies investigating the effect of CPAP on preventing the development of cardiovascular squeal have been conducted.

Patient Education

All patients with obstructive sleep apnea-hypopnea syndrome should receive education about sleep and proper sleep hygiene, OSAHS, and the risks of driving while sleepy. They also should receive education regarding the role of nasal CPAP and the importance of its daily use.

Special Concerns

Motor Vehicle Accident Risk

Predicting accident risk in patients with obstructive sleep apnea-hypopnea syndrome is difficult because many individuals with OSAHS do not accurately perceive their level of drowsiness. A large body of work has been compiled on the influence of OSAHS on driving-simulator performance, with the majority of the studies indicating poor performance, similar to that seen with alcohol impairment while driving.[38] The regular use of CPAP improves the driving performance. At least two studies have shown improvement on a driving simulator after CPAP use.[39,40] Specifically, in one study, the number of off-road events decreased from 17.8 to 9 after one month of effective CPAP therapy, but no change was noted after a month of ineffective pressure set at 1 cm H_2O.

Geriatric Populations

The prevalence of OSAHS increases with age. However, the clinical significance of OSAHS in healthy, community-dwelling people has been questioned because these people do not show significant squeal (sleepiness). Elderly patients presenting to sleep centers for evaluation have similar symptomatology (including EDS) and polysomnographic results compared with patients who are not elderly, except that elderly patients under report snoring as a chief complaint, they tend to be less obese and they are less objectively sleepy based on MSLT results. Thus, all elderly people, particularly if overweight, should be questioned about snoring, witnessed apneas and daytime sleepiness and should be referred for evaluation if necessary. Age does not appear to influence compliance to CPAP therapy. Thus, all elderly patients with significant and symptomatic OSAHS should be offered therapy.

Pediatric Populations

OSAHS in children has an estimated prevalence of 2%, affecting boys and girls in equal numbers. Children most often present with loud snoring and symptoms and signs of adenotonsillar hypertrophy. EDS is not a common symptom in children with OSAHS. Instead, school-aged children often report problems with schoolwork. Studies have shown improvement in cognitive function and/or grades after adenotonsillectomy in children with OSAHS.[41]

Pregnancy

Several case reports associate intrauterine growth restriction (also termed intrauterine growth retardation) in pregnant women with concomitant untreated OSAHS. Complications such as hypertension, preeclampsia, low Apgar scores and intrauterine growth restriction were more common in habitually snoring pregnant women compared with nonsnoring pregnant women.[42] Habitual snoring was independently predictive of hypertension and growth restriction after correcting for other factors (weight, age, smoking status).

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129B

Obstructive Sleep Apnea

Macy MS Lui, Mary SM Ip

INTRODUCTION

Sleep-related breathing disorders have become a mainstream topic in clinical medicine in recent decades, when epidemiological studies clearly demonstrated the common occurrence of sleep apnea in various ethnic populations. With the growing recognition of the importance of Obstructive Sleep Apnea (OSA), research has been blooming to uncover its pathophysiology, neurobehavioral and cardiometabolic consequences, as well as effective therapeutic modalities.

EPIDEMIOLOGY AND RISK FACTORS

Obstructive sleep apnea is characterized by intermittent upper airway collapse during sleep, resulting in recurrent bouts of hypoxia and arousals. Obstructive Sleep Apnea Syndrome (OSAS) refers to the clinical manifestations, often excessive sleepiness, in the presence of significant OSA. Various prevalence studies have been undertaken across the continents and the reported prevalence rates range from 3 to 50%, indicating that it is a common disorder affecting worldwide populations (Table 129B.1). The heterogeneous rates can be explained by the highly diverse study populations of different ethnicity, age and cultural background, and the different study design or methodology, including diagnostic tools and event definitions. The rising body mass index surely contributes to the higher prevalence reported in the more recent studies and thus the figures quoted from studies done in 1990s are likely to be substantially underestimating the real time prevalence currently.

Age and Sex

Numerous studies support the increasing occurrence of OSA with advancing age and this plateaus after the age of 65.[1] In women, the prevalence of OSA starts to rise after menopause.

Obstructive sleep apnea has also been consistently found to be more common in men, with male:female ratios reported to range from 2:1 to 8:1. The male:female ratios with OSA in clinic-based studies appear to be considerably higher than in the community (approximately 5:1 to 8:1 versus 2:1 to 3:1).[2] The reasons for the gender difference in OSA prevalence have not been clearly defined, but the discrepancy of community versus clinic ratios suggest that women with OSA may present less than their male counterparts for clinical consultations. Although the exact underlying reasons for the under presentation of women have not been investigated, it is likely the situation would be worse in developing countries where access to medical facilities are limited and in some communities, where cultural perceptions may favor men as the priority gender in health care.

Body Habitus

The epidemic of obesity is sweeping worldwide and the impact is no less in the developing countries in concert with economic development, increased urbanization and increased consumption of high-calorie food. The prevalence of obesity ranges from 20 to 50% in recent studies, including mainly urban Indians and similarly high figures are also reported in many other developing countries.[3] Obesity is considered a major risk factor of

TABLE 129B.1: Prevalence studies of OSA in adults

Author/ year	*Subjects undergoing PSG/diagnostic tool*	*Age (Yrs)*	*BMI (kg/m²)*	*Findings*
Tufik et al. 2010[4]	1042 community dwelling Brazilian, by PSG	20 t0 80	64% had BMI ≥30	Prevalence of OSAS was 41% in men, 26% in women
Johansson et al. 2009[5]	331 community dwelling elderly in Sweden, by PSG	71 to 87	Mean ~27	55% with OSA (AHI ≥5), half of them had moderate-severe OSA
Reddy et al. 2009[6]	Q: 2505 community dwelling urban Indian PSG: 365	30 to 65	24.3 ± 4.6	Estimated population prevalences of OSA and OSAS were 9.3% and 2.8%, respectively
Sharma et al. 2006[7]	Q: 2150 semi-urban population in Delhi PSG: 150	30 to 60	24.6 ± 5.2	Prevalences of OSA and OSAS were 19.7% and 4.9% in men, 7.4% and 2.1% in women, respectively
Udwadia ZF et al.[8]	Q: 658 healthy urban Indian men 250 underwent home sleep study	35 to 65	24.6 ± 4.3	Estimated prevalence of OSA 19.5%, OSAS 7.5%
Ip et al. 2004[9]	Q: 854 community dwelling women in Hong Kong PSG: 106	30 to 60	22.4 ± 3.2	Conservatively estimated prevalence of OSA (AHI ≥5) were 3.7%; OSAS 2.1%
Ip et al. 2001[10]	Q: 784 community dwelling men in Hong Kong PSG: 153	30 to 60	23.9 ± 3.5	Conservatively estimated prevalences of OSA (AHI ≥5) were 8.8%; OSAS 4.1% Bixler EO
et al.[11]	Q: 12219 Caucasian women, 4364 Caucasian men PSG: 1000 women, 741 men	20 to 100	29.6 ± 7.5(women) 26.9 ± 4.2(men)	Prevalences of sleep disordered breathing (AHI ≥10 and daytime symptoms) were 3.9% in men, 1.2% in women
Ng et al. 1998[12]	2298 multi-ethnics in Singapore, by survey and symptoms criteria	40 to 59	24.0 (95% CI 23.6–24.4)	Prevalence of snoring: 6.8% (whole population), 6.2% (Chinese), 8.1% (Malay), 10.9% (Indian) OSA: 0.43% (whole population)
Ohayon et al. 1997[13]	Telephone interview survey: 2078 men, 2894 women	15 to 100	Not available	OSAS: 3.5% in men and 1.5% in women
Marin et al. 1997[14]	1222 community dwelling Spanish, 50% men, by night oximetry	18 to 88	About 24	Overall 11% had >10 desaturations/hour. OSAS in 3% men and 1.7% women
Olson et al. 1995[15]	441 community dwelling Australians, by PSG	35 to 69	Not available	Moderate OSA (AHI ≥15) was present in at least 5.7% men, and 1.2% women
Young et al. 1993[16]	Q: 3515 state employees in Wisconsin, USA PSG: 602	30 to 60	About 30	OSA (AHI ≥5): 24% in men, 9% in women OSAS: 4% in men, 2% in women

Q = Questionnaire respondents
PSG = Polysomnography
BMI = Body Mass Index
AHI = Apnea Hypopnea Index
OSA = Obstructive Sleep Apnea
OSAS = Obstructive Sleep Apnea Syndrome (OSA in the presence of excessive sleepiness)

OSA across various ethnic populations.[17] In a population-based cohort study in USA, a 10% weight gain predicted an approximate 32% increase in the AHI while a 10% weight loss predicted a 26% decrease in the AHI.[18] A similar trend was also observed in pediatric population.[19] Adipose tissue deposited around the upper airway reduces the airway size and increase its collapsibility, thus increasing neck circumference also predicts OSA.[20] Truncal obesity could adversely affect the ventilatory mechanic by reducing the functional residual capacity, increasing the chest compliance and work of breathing, and decreasing the efficiency of the compensatory mechanism in the body in face of hypoxemia or hypoventilation.[21]

Craniofacial Factor

Craniofacial structure comprises of bony component and soft tissue component. Bony factors are believed to be more important factor predisposing to OSA in lean subjects, both bony and soft tissue factors contributed in moderately obese subjects and the acromegalics, while soft tissue abnormalities dominate in obese or hypothyroid subjects.[22-24] Reversible sleep disorder breathing is common among subjects with primary hypothyroidism.[25] Cephalometric abnormalities have been described in a number of Caucasian as well as Asian studies, reduced dimension of anterior cranial base, reduced posterior and superior airway spaces, inferiorly displaced hyoid, increased soft palate dimension, other soft tissue enlargement were identified as the risk factors for OSA.[26-28] Other commonly described features include retrognathia and enlarged tongue. In addition to BMI and age, larger thyromental angle, higher Mallampati score, increased neck circumference were demonstrated to be predictors of OSA in both Chinese and Caucasian adults.[29]

Genetic Influence

Subjects with first degree relatives affected by OSA are noted to present at a younger age with snoring, with lower BMI, and smaller posterior airway space than their nonfamilial counterparts.[30] Genetic makeup and a number of the craniofacial syndromes determine the craniofacial morphology and the neuroventilatory mechanism governing the collapsibility and caliber of the upper airway, which directly predispose to OSA. The Angiotensin-converting enzyme gene insertion/deletion polymorphism was significantly associated with hypertension in OSA subjects.[31] Apolipoprotein E (APOE) is found in chylomicron and is essential for normal catabolism of triglyceride-containing lipoproteins.[32] The presence of dysfunctional APOE product, ApoE-ε4, was associated with higher risk of moderate to severe sleep disordered breathing, regardless of age, sex, BMI and ethnicity.[33] Apolipoprotein E4 was also linked to neurocognitive deficits in OSA.[34,35]

Ethnicity

Ethnicity may influence genetic, cultural or environmental factors, all of which could predispose to OSA. Craniofacial features differ across ethnicities, as well as the prevalence of obesity, which is heavily affected by socioeconomic environment in addition to genetic influence. Socioeconomic status also affects diet and exercise habits, access to health care and levels of health awareness, which could all influence the prevalence of OSA. In developing countries, even when the population is of the same ethnicity, continuing under-nutrition in the less developed areas and escalating over-nutrition associated with urbanization and economic development in other areas, have created double jeopardy to the health care systems.[16] Cultural differences could pose influence in perception, acceptance and threshold for reporting sleep complaints. European-Americans were found to report more sleep-related symptoms than other ethnic groups in a population-based studies, including 1,118 older adults in New York.[36] Among Caucasian and Asian adults matched for age, sex and BMI, there was no difference in the severity of reported symptoms, despite the significantly higher Respiratory Disturbance Index (RDI) and lower oxygen saturation in Asian adults.[37] It was plausible that Asian was more tolerant of the OSA symptoms with a tendency for late presentation.

Other Risk Factors

Smoking and alcohol consumption have been reported to be risk factors for OSA.[38] Both allergic and nonallergic rhinitis were shown to predispose to OSA in previous studies.[39]

PATHOGENESIS OF OSA

The pathophysiological mechanisms predisposing to OSA involve a complex interplay of multiple structural and functional factors, each of variable degree of significance in an individual. The pharynx can be viewed as a collapsible conduit that comprises of muscles, which serves the functions of speech, swallowing and respiration. It is prone to occlusion when the surrounding pressure is greater than the intraluminal pressure. Anatomical structures, such as redundant soft tissue or bony structures are factors that increase the collapsibility of the upper airway. Pharyngeal Critical Pressure (Pcrit) is the extraluminal pressure at which maximal inspiratory flow occurs. It provides an objective surrogate measure of the collapsibility of upper airway in human. It is measured by lowering the nasal pressure until the inspiratory airflow ceases. Pharyngeal Critical Pressure defines a spectrum of severity of upper airway obstruction from normal breathing (Pcrit <-10 cm H_2O) to snoring (Pcrit -10 to -5 cm H_2O), to obstructive hypopnea (Pcrit -5 to 0 cm H_2O) and obstructive apnea (Pcrit > 0 cm H_2O) during sleep.[40,41] Patients with the Upper Airway Resistance Syndrome (UARS), characterized by inspiratory flow limitation and respiratory effort-related arousals, typically have Pcrit levels that are between snoring and hypopnea.[42]

Upper airway patency is sustained throughout the respiratory cycle by both tonic activity (e.g. Tensor palatini) and phasic activity (e.g. Genioglossus) of pharyngeal muscles. The tones of the pharyngeal muscles are regulated by conscious states-related mechanisms, local mechanoreceptor reflexes and central ventilator control mechanisms. In face of a narrowed airway, elevated neuromuscular activities of the pharyngeal muscles, mediated by pressure sensing mechanism and negative pressure reflex, are observed as compensatory mechanism to sustain airway patency.[43] There are evidence that such local neuromuscular compensation is impaired in patients with OSA.[41]

Ventilatory control mechanisms influence the pharyngeal collapsibility during sleep. The central nervous system is affected by signals from central and peripheral chemoreceptors responding to hypercapnia or hypoxemia, and increases ventilatory drive to upper airway and diaphragm in a coordinated manner. Increased hypercapnic ventilatory responses, prolonged circulatory times or low oxygen stores within the body can lead to ventilatory instability with subsequent periodic breathing.[44] Of note, measurement of loop gain, a measure of ventilatory instability, was shown to be high in patient with severe OSA.[45] Therefore, a brisk ventilatory response to hypoxemia/hypercapnia after an arousal in the susceptible individual can result in hypocapnia that reach the apnea threshold and result in a hypopnea or apnea with reinitiation of sleep.[46] Such self perpetuating cycle results in recurrent sleep apnea.

CLINICAL FEATURES

The classical symptoms for OSA include excessive daytime sleepiness (EDS) and habitual snoring. A range of other symptoms (Table 129B.2) have also been reported in association with OSA.

Excessive sleepiness is believed to be the result of sleep fragmentation and the repetitive hypoxic disturbance to the brain. The presence of EDS is usually assessed with the use of structured scales, such as the Epworth Sleepiness Scale (in this scale, a score of 10 out of maximum of 24 indicates excessive daytime sleepiness),[47] or more objectively by multiple sleep latency test and multiple wakefulness test. Subjective EDS correlates poorly with the presence and severity of OSA. It is also subject to many influences, such as cultural factors, personal threshold of tolerating sleepiness and social stigmatization at workplace. Excessive Daytime Sleepiness and lack of concentration at work could lead to tremendous loss in productivity and economic loss. A recent systemic review has confirmed that untreated OSA is a significant contributor to motor vehicle crashes and characteristics that may predict crash in driver with OSA include BMI, apnea hypopnea index, oxygen saturation and daytime sleepiness.[48] Other conditions associated with OSA could also contribute to the sleepiness, such as depression and hypothyroidism.

Patients may complain of insomnia, which includes difficulties in initiating sleep, recurrent awakening from sleep or early morning awakenings.[49] The bed partners may also notice the obstructive breathing pattern, which includes snoring, snorting, choking, witnessed apnea and restless sleep behavior due to recurrent arousals and some may be so disturbed that they sleep in a separate room.

Obstructive Sleep Apnea subjects also commonly have comorbidities, such as hypertension, diabetes mellitus, hyperlipidemia, atherosclerotic vascular diseases and the metabolic syndrome.[50] Physical examination would likely reveal an overweight or obese subject often with comorbid cardiometabolic diseases. (Table 129B.2)

In less developed places, people may only present for medical opinion when there are florid and disabling features, such as gross obesity or marked daytime sleepiness, but as socioeconomic status of the community

TABLE 129B.2: Symptoms and signs of OSA

Symptoms
- Heavy snoring
- Sleep choking
- Witnessed apnea
- Daytime sleepiness, history of motor vehicle accidents
- Poor concentration, poor memory
- Insomnia
- Nocturia
- Morning headache

Physical signs
- Overweight or obese, truncal obesity
- Crowded pharyngeal airspace
- Receding chin
- Macroglossia
- Tonsillar hyperplasia
- Elevated Mallampati score

Associated conditions
- Hypertension
- Stroke
- Diabetes mellitus
- Metabolic syndrome
- Hypothyroidism
- Acromegaly
- Allergic rhinitis
- Pulmonary hypertension

advances and public health care information increases, one will begin to see patients presenting with more equivocal symptoms. It is also important to note that a minority of OSA subjects are lean.

DIAGNOSIS

Risk Stratification for Referral for Polysomnography

Snoring and daytime sleepiness are the most common relevant presenting complaints in primary care. Snoring has been reported to be present in 18% of urban middle-aged Indians in a community-based study.[3] In the same study, 33.6% of the habitual snorers also complained of excessive daytime sleepiness. Clinical assessment using a combination of symptoms, physical examination findings and other objective tools, has been utilized to triage patients for PSG referrals, and this strategy is particularly important in resource limited settings.

Habitual snorers are at a higher risk of having OSA as compared to nonsnorers, but the positive and negative predictive values of snoring for the presence of OSA were 63% and 56%, respectively. Male gender, advanced age, higher BMI and abdominal obesity were identified to be the predictors of presence of OSA.[4] Higher Mallampati score, tonsillar hyperplasia and lateral pertitonsillar narrowing were associated with OSA independent of obesity.[51,52] Modified Berlin questionnaire, which classified patients into high or low risk categories according to clinical domains, including snoring, sleepiness, obesity and hypertension, was validated as screening tool for the presence of OSA.[53] High-risk category predicted an AHI>5 with a sensitivity of 86%, specificity 95%, positive and negative predictive values of 96% and 82%, respectively. However, the Berlin questionnaire had a low diagnostic accuracy for a predominantly Chinese population.[54] This might be attributed to the use of a BMI obesity threshold, which is meant for Caucasians.

Portable Monitoring

Sleep recording devices are classified into four types: Type 1 is standard in-laboratory attended PSG, type 2 uses the same technology as type 1 but is unattended, type 3 records 4 to 7 physiologic parameters and at a minimum include two respiratory parameters (airflow and effort), a cardiac signal (pulse or electrocardiogram), and oxygen saturation. Type 4 devices measure only one or two parameters, including oxygen saturation. Portable devices are becoming more sophisticated but lack standardization.

Portable monitoring is increasingly used as alternative approach to PSG for the diagnosis of OSA in some countries including USA, following the statement by the US Centers for Medicare and Medicaid Services in 2008.[55,56] The use of unattended portable devices is typically recommended in populations at high-risk for OSA clinically without significant comorbid medical conditions.[57] Overnight oximetry is occasionally used as screening tools for OSA but the reported sensitivity and specificity were suboptimal.[58] The finding of frequent oxygen saturation dips in the presence of appropriate clinical settings can support the diagnosis of OSA.

The interpretation of oximetry could be difficult in subjects with underlying pulmonary or cardiac disorders associated with hypoxia. Oximetry frequently underestimates the severity of sleep disordered breathing, as arousals are not measured. The mechanism of desaturation, with regard to obstructive, central or mixed apnea, is not discernible with the use of oximetry. Sleep disorders, such as upper airway resistance syndrome, periodic leg movement syndrome and narcolepsy may not be diagnosed by oximetry. Despite such shortcomings, unattended home sleep studies or split night polysomnography (PSG) were found to be cost-effective alternatives to PSG in resource-limited settings.[59]

Actigraphy is a specific portable device that record body activity and movement, which is interpreted by computer algorithm as sleep versus wake periods. It is useful for diagnosis of circadian rhythm sleep disorders, and when it is combined with a validated way of monitoring respiratory events, use of actigraphy may improve accuracy in assessing the severity of obstructive sleep apnea compared with using time in bed.[60]

Polysomnography

Overnight in-laboratory attended PSG is the standard test for diagnosis of OSA, which comprises of recordings of sleep stages (electroencephalogram, electrooculogram, submental electromyogram), respiratory events (airflow, thoracoabdominal effort, oximetry), cardiac rhythm (electrocardiogram) and other relevant signals (leg movement, snoring, video recording).[61] Despite the fact of being the gold-standard, the high cost and long waiting list of PSG makes it less readily available than portable monitoring. The interpretation of PSG recordings would be technically suboptimal if subjects could not sleep long enough in-laboratory (≥ 4 hours). This is sometimes called first night effect, which also contributes to the night-to-night variation of the PSG recordings. The reduced sleep duration or quality would pose problem in the accuracy of diagnosing sleep-related disorders mainly affecting Rapid Eye Movement sleep (e.g. OSA, REM-related sleep behavioral disorder), which predominate in later part of the night with deeper sleep.

The various sleep stages experienced by the patient and the oximeter tracings are summarized on the hypnogram. Respiratory events are classified into apnea, hypopnea or Respiratory Effort-Related Arousals (RERA), which could be central or obstructive in mechanism (Table 129B.3). Obstructive events occur with upper airway partial/complete obstruction in the presence of respiratory effort, while no respiratory effort is found in purely central events. Definition of RERA varies across centers and it is commonly accepted to indicate a sequence of breaths over the duration of at least 10s with increasing respiratory effort, which results in an arousal. Respiratory Effort Related Arousals (RERAs) may not involve any oxygen desaturation and constitute the main events in the entity called Upper Aiway Resistance Syndrome (UARS), which is believed to be part of OSA disease spectrum with similar pathophysiology and clinical consequences. Apnea Hypopnea Index (AHI), the number of apnea or hypopnea per hour of sleep, is the most commonly used parameter to indicate severity of OSA. Respiratory Disturbance Index (RDI) refers to the sum of AHI and RERA.

Pragmatic Approach to Diagnosis in Developing Countries

The diagnosis of OSA carries important long-term therapeutic implications and therefore, one must attempt a reliable diagnosis within resource constraints.

In developed countries, full overnight polysomnography in the sleep laboratory is considered the gold standard, but this may not be applicable to developing economies. And even in well developed health care systems, there is a revisit to the diagnostic algorithm as there is an overwhelming demand with a long waiting list for sleep studies due to the escalating prevalence of obesity and OSA.[62]

For those presenting with typical OSA symptoms with no comorbidities to cause nocturnal desaturation, a combination of questionnaire (which may need local adaptation and validation) and limited sleep study may suffice, with further referrals for full sleep studies in those with significant symptoms but no definitive diagnosis.[63,64]

If one is suspecting other types of sleep apnea, there is a need of tests with more respiratory event channels for documentation and characterization of respiratory flow and efforts. If one is suspecting other less common sleep disorders, such as narcolepsy or REM behavioral disorders, full studies would be necessary.

TABLE 129B.3: Recommended definition of respiratory events*

Breathing Events	*Definition*
Apnea	Drop in the peak thermal sensor excursion by ≥90% of baseline, lasting at least 10s, at least 90% of the event's duration meet the amplitude reduction
Hypopnea	Nasal pressure signal excursion drop by ≥30% of baseline lasting at least 10s, with ≥4% desaturation from pre-event baseline, at least 90% of the event's duration meet the amplitude reduction
Respiratory Effort-related Arousals	Sequence of breaths lasting at least 10s characterized by increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep when the criteria for an apnea or hypopnea are not met
Types of Respiratory Events	
Obstructive	Continued thoracoabdominal respiratory effort throughout the entire period of reduced/absent airflow
Central	Absent thoracoabdominal respiratory effort throughout the entire period of reduced/absent airflow
Mixed	A respiratory event with both obstructive and central components, beginning with period of absent respiratory effort with resumption of respiratory effort towards the end of the event

*The AASM Manual for Scoring of Sleep and Associated Events 2007

It cannot be over-emphasized that the cost-effectiveness of a diagnostic test does not lie in the test device itself all test results need to be interpreted by someone who knows the test, who can decipher the pitfalls and inaccuracies, and the test results must be correlated with the clinical features for accurate definitive diagnosis and treatment plan in the individual.

MORBIDITIES ASSOCIATED WITH OSA

Neurocognitive and Neurobehavioral Dysfunction

A wide range of neurocognitive deficits are associated with OSA, which may lead to physical or social impairment, compromised quality of life or even depression.[65] Subjects with severe OSA often have impairment in vigilance, concentration, short-term memory and visuomotor skills.[66] Untreated OSA is found to be linked to poorer simulated driving performance[67] and increased risk of road traffic accidents.[68] The implications of OSA and impaired driving performance among occupational drivers cannot be over-emphasized, and they are also exposed to the additional risks of sleepiness caused by shift work, hypnotic and other drug use and alcohol influence.[69-73] Appropriate treatment with nasal Continuous Positive Airway Pressure (CPAP) could reduce the risks of traffic accidents imposed by OSA.[74,75]

These neurocognitive dysfunctions are attributed to the obstructive breathing events causing cerebral arousals and hypoxia during sleep, though the exact contribution of each mechanism is not clearly defined. In recent decade, scientists have uncovered a number of biochemical and molecular changes accounting for the neural injury in the brain as a result of long term intermittent hypoxia using murine models.[76-78]

Systemic Hypertension

Longitudinal and cross-sectional studies have shown a strong association between OSA and systemic hypertension.[79] Hypertension occurs in 30 to 50% of OSA subjects in clinical studies, while 30 to 80% of hypertensive subjects have OSA.[80,81]

The pathophysiology of systemic hypertension in OSA patients is complicated.[81] Compelling evidence has suggested that the activation of sympathetic nervous system and renin-angiotensin axis as a result of arousals and hypoxia led to peripheral vasoconstriction and sustained hypertension. Repetitive cycles of hypoxia also triggered oxidative stress and vascular inflammation, both could lead to increased blood pressure independent of sympathetic activation. A large scale prospective study over 4 years in Wisconsin showed that the odds ratios for developing incident hypertension were 1.4, 2.0 and 2.9 for subjects with AHI 0-4.9, 5-14.9 and ≥15, respectively, compared to those with AHI of zero.[82]

Obstructive sleep apnea is also listed as one of the important predisposing conditions to consider during the workup for resistant hypertension.[83] Systemic review and meta-analyses have included a number of open-label and controlled studies and found a reduction of mean systolic blood pressure of about 2 mm Hg with CPAP therapy and this lowering of mean systolic blood pressure is significant in the terms of alleviation of both cardiovascular, cerebrovascular risk and mortality.[79,84]

Heart Failure

Persistent breathing effort to overcome obstructed upper airway results in significant swing of intra-thoracic pressure, which could lead to increase in left ventricular wall tension. In concert with the repetitive surges of sympathetic activity resulting in increased heart rate and blood pressure, there is an increase in myocardial oxygen demand. Recurrent hypoxia further compromised the oxygen delivery to the myocardium. An epidemiological study in Canada has revealed high prevalence of OSA (26%) and central sleep apnea (21%) in 218 subjects with systolic heart failure.[85] The presence of OSA was reported to be associated with more left ventricular hypertrophy in subjects with nonischemic dilated cardiomyopathy.[86] In a prospective cohort study, following up subjects with systolic heart failure for 2.9±2.2 years, significantly higher mortality occurred in the group with untreated OSA (24%), as compared to the group with mild or no OSA (12%).[85] Randomized trials have convincingly demonstrated the improvement of left ventricular systolic function and lowering of sympathetic activity subsequent to treatment with CPAP in subjects with both heart failure and OSA.[87,88]

Arrhythmia

Obstructive sleep apnea is believed to create an autonomic profile with both profound vagal activity associated with bradyarrhytmias, and sympathetic over-activity leading to tachyarrhythmias and ectopics.[89] In the Sleep Heart Health Study, severe sleep disordered breathing posed two to fourfold higher odds of complex arrhythmias, including Atrial Fibrillation (AF), nonsustained ventricular tachy-cardia and complex ventricular ectopy than those without sleep disordered breathing after adjustment for potential confounders.[90] Patients with untreated OSA had twice the risk of recurrent atrial fibrillation within 1 year of electrical cardioversion to sinus rhythm than those who were treated with CPAP.[91] Treatment of OSA with CPAP for 1 month resulted in 59% reduction in frequency of ventricular premature beats during sleep in heart failure subjects.[92]

Pulmonary Hypertension

Pulmonary hypertension is reported to be present in 20 to 40% of patients with OSA in the absence of other cardio-respiratory disorders.[93] It is often of mild degree (mean pulmonary arterial pressure 30 to 40 mm Hg), while more severe pulmonary hypertension due to severe OSA per se is not common, and has been linked to severe nocturnal desaturations and mortality.[94] In the case of marked pulmonary hypertension, or clinically manifest right heart failure, further considerations should be given to the presence of concomitant diseases, such as obesity hypoventilation syndrome, chronic obstructive pulmonary disease or left heart failure.

Atherosclerotic Diseases

The intermittent hypoxia and sleep fragmentation in OSA are believed to initiate a cascade of pathological events contributing to early atherosclerosis. Oxidative stress, endothelial dysfunction, vascular inflammation and heightened sympathetic activity have been demonstrated in OSA subjects, all of which directly lead to vascular injury. In addition to the prevalent vascular comorbidities (hypertension, diabetes mellitus, obesity), the risk of atherosclerotic vascular disease are much aggravated in OSA subjects.[95] Carotid intima-media thickness, an early sign of atherosclerosis, was shown to be significantly increased in subjects with severe OSA.[96] This is partially reversible with CPAP treatment.[97]

Cross-sectional data from the Sleep Heart Health Study showed greater odds for stroke in the highest AHI quartiles than those with no OSA (OR 1.58). Cohort studies with mean follow up period of 4 to 4.5 years have shown an 2 to 4.5 times increased risk of incident stroke in those with moderate to severe OSA after adjustment for confounders.[98,99] However, whether effective treatment of OSA in stroke survivors improved neurological outcomes remains unanswered, and the application of CPAP in this group of subjects is notoriously limited by poor tolerance and compliance.[99]

Disorders of Glucose Metabolism

The metabolic syndrome, characterized by central obesity, insulin resistance, dyslipidemia and high cardiovascular risks, causes tremendous impacts on the health care system in many developing countries.[3] A number of clinical and epidemiological studies have found an association between OSA and worse insulin resistance, insulin insensitivity and diabetes mellitus.[100]

Recent literature also suggests the occurrence of poorer glycemic control in diabetic subjects with concomitant OSA, as compared to those without OSA.[101] Beneficial effects of CPAP therapy on disorders of glucose metabolism have been demonstrated in some open-label or uncontrolled studies, but the results were inconsistent in a few randomized controlled trials.[100] Well-designed adequately powered randomized trials would resolve such controversy and reveal the benefits of CPAP treatment in terms of clinically interested outcomes. Such pieces of evidence could provide solid ground in better use of public resources in health care planning, particularly in face of resource constraint.

TREATMENT

General Measures

Weight reduction is always advocated for obese or overweight subjects, as improvements in OSA severity and obesity-related complications have been consistently reported.[17] OSA patients should also avoid alcohol, especially in the late evening, and hypnotics (particularly benzodiazepines) as both could reduce muscle tone and aggravate sleep apnea. Maintaining good sleep hygiene could also improve sleep quality. Positional therapy could improve OSA in certain patients whose sleep apnea occurs mainly in the supine position, , but practical ways to achieve consistent lateral posture during sleep are lacking. Treatment of allergic rhinitis potentially alleviates sleep apnea, and would also facilitate the use and acceptance of nasal continuous positive airway pressure.

Continuous Positive Airway Pressure Treatment

Positive airway pressure therapy during sleep applied via the nasal route constitutes the mainstay of treatment for OSA in adults. It acts as a pneumatic splint by delivering a positive intraluminal pressure that maintains the upper airway patency during sleep. It is indicated in patients with severe OSA (AHI ≥30) with or without symptoms, or those with mild-to moderate OSA (AHI 5-30) with symptoms or comorbid conditions (hypertension, heart or cerebrovascular diseases).[102,103] Randomized controlled trials have shown that CPAP not only reduce the AHI, but also improve both subjective and objective sleepiness.[104] Evidence is also available, which reveals its beneficial role in improving quality of life of both patients and bedpartners, reducing risk of motor vehicle accidents, improving blood pressure control and a number of cardiovascular parameters and outcomes.[102,105]

To be effective, the level of CPAP must exceed the critical closing pressure of the upper airway. The treatment pressure is typically determined during an attended in-laboratory CPAP titration with PSG documentation. Alternatively, a split night titration can be undertaken to obtain the diagnosis of OSA in the first half of the night and determine the effective PAP in the later half of the night. Though this can make a better use of the resources, inadequate REM sleep in the early night could potentially lead to underestimation of apnea severity. However, manual titration in the sleep laboratory is resource-demanding and costly. The Autotitrating PAP (APAP) device is increasingly used, in attended or unattended setting, to determine the appropriate treatment pressure, provided that careful patient selection and interpretation of the tracings are pursued. APAP titration, particularly used in home setting, is recently found to be more cost-effective than manual laboratory titration, with similar clinical outcomes.[106] A pressure prediction formula, based on simple anthropometric and sleep variables, has been developed for estimation of therapeutic pressure levels.[107,108] A large multicenter study has shown no difference in CPAP compliance and other outcomes by using prediction formula compared to conventional CPAP titration.[107,109] In-laboratory titrations offers the chance of giving CPAP education to the patients, and this must be adequately provided as outpatient if home titration is being used.

Suboptimal compliance is one of the major limitations in the use of CPAP treatment. Continuous technical advances in the interface and machine algorithm aim to enhance further its user-friendliness. In addition to being a somewhat cumbersome device causing inconvenience, there are a number of side effects that could reduce patient acceptance (Table 129B.4). A comprehensive approach to commencement of PAP treatment, including education, objective adherence monitoring, early intervention for side effects, early clinic follow up, telephone and clinic support is pivotal to optimize compliance. Patients tend to overestimate their own compliance.[110] Most current devices provide objective compliance information on either nightly turn-on time or mask-on time of the PAP. Numerous models of interfaces have also been designed to maximize patient's comfort while avoiding mask-related side effects. In addition to the conventional continuous PAP (CPAP), there are various newer modes of pressure delivery (Bilevel PAP-BPAP, autoadjusting PAP-APAP, flexible PAP) to make patients more comfortable, though evidence showing improved compliance with their use is lacking. Bilevel PAP and autoadjusting PAP are similarly efficacious in reducing daytime sleepiness and controlling apnea as compared to CPAP.[111,112] Heated humidification has been shown to improve compliance, especially in patients with nasal congestion and mucosal dryness.[113,114] These interventions should be implemented as early as possible, as the pattern of use of PAP in the long run is often established in the early course of treatment.[115]

Oral Appliance

Oral appliances (OA) are worn during sleep to increase the dimension of upper airway and reduce its collapsibility. The updated practice parameters recommend their use for mild-to-moderate OSA, or for patients with severe OSA who are unable to tolerate CPAP or refuse CPAP.[116] There are mainly two types of OA: mandibular advancement splints and tongue-retaining devices. Mandibular advancement devices work by anchoring to the dental arches and mechanically protrude the mandible to widen the upper airway. Tongue retaining devices apply suction force to maintain the tongue in a protruded position during sleep, which can be used in edentulous patients. OA is in general less efficacious than

TABLE 129B.4: Common PAP-related side effects and interventions

Side effects	*Interventions*
Mouth dryness	Chin strap, heated humidity, oronasal mask
Airleak with red eyes or noise	Proper mask size and fitting to facial contour, proper mask application
Skin breakdown	Proper mask fitting, avoid over tightening, nasal pillow
Claustrophobia	Nasal pillow, desensitization
Nasal congestion	Nasal steroid, antihistamine, nasal decongestant, heated humidification, oronasal mask
Exhalation difficulty	Lower pressure, Flexible PAP, Bilevel PAP
Pressure intolerance	Ramp, Flexible PAP, Bilevel PAP, APAP
Aerophagia/bloating	Reduce pressure, Bilevel PAP, Flexible PAP

CPAP in controlling OSA (complete response with AHI<5 in 40%, partial response with reduced AHI to less than half in 25%, treatment failure in 35 to 40%), it carries the advantages of being more portable, convenient and thus higher patient acceptance.[117] The reported compliance with OA (77% at 1 year) is higher than that reported with CPAP (about 50% using CPAP for at least 4 hours per night for >70% of nights). Literature is emerging to support the beneficial effect of OA on daytime sleepiness, quality of life, neuropsychological function and blood pressure.[117] Adverse effects of OA include gum and tooth pain, temporomandibular joint discomfort, excessive salivation, while in the long term, dental changes with overbite or overjet. Reassessment PSG with oral appliance is indicated to document the efficacy of OA, as unlike CPAP, its efficacy is not accurately predictable in the individual.

Surgical Options Targeting Upper Airway Obstruction

The aim of OSA surgery is to eliminate anatomical elements contributing to upper airway collapse, or to facilitate functional compensation to reduce airway resistance during sleep, without causing permanent impairment in upper airway function. It is often a second line approach or as an adjunct to other treatment options in the setting of adult OSA.

Tracheostomy has now become obsolete and mainly considered as the last resort for treatment of OSA. Upper airway abnormalities amenable to surgery include those involving the nasal cavity (deviated septum, polyps, hypertrophic turbinates), oropharynx (palatine tonsils, elongated uvula, redundant mucosal folds, low hanging palate) and hypopharynx (lingual tonsils, large tongue base). The role of surgery is more prominent in pediatric OSA than adult OSA, since anatomical obstruction, including enlarged tonsils is a major etiological factor leading to OSA in children and early correction of such anatomical abnormalities is also paramount to prevent abnormal craniofacial development and irreversible damage to pharyngeal dilator reflexes.[118]

Preoperative upper airway assessment is necessary to determine the exact level of obstruction and plan the optimal surgical approach. Preoperative nasopharyngoscopy and cephalometric analysis are performed to identify the site and degree of obstruction. Different surgical procedures address specific airway abnormalities and staged multimodality surgical approach may be required especially in the case of multilevel obstructions. Patients with severe OSA and severe nocturnal desaturation would need to be started on preoperative CPAP and continued postoperatively for weeks until the reassessment PSG.

Uvulopalatopharyngoplasty (UPPP) enlarges the oropharyngeal lumen by removing redundant tissues from the soft palate, tonsillar pillars and uvula. It is currently the most widely performed OSA surgery in adults, and is generally more effective in patients with primarily oropharyngeal obstruction. UPPP is highly effective for reducing snoring, with success rates between 70 to 90%, but the effect of eliminating OSA is much less impressive (significant response with >50% reduction of AHI in 50%, cure rate with AHI<5 in 16% only).[119-121] Furthermore, the therapeutic effect of UPPP is usually not sustained as recurrence occurs in most patients with initial improvement after 5 years. Other surgical options include the reduction of soft tissue by radiofrequency ablation, tonsillectomy, midline glossectomy, maxillomandibular advancement, hyoid myotomy and suspension, genioglossus advancement.[123,124] but both their short or long-term efficacy have not been well documented in adults. Hence, nonselected advocation of surgical treatment for treatment of OSA is not recommended.

Other Treatment Options

Weight loss may be achieved by more aggressive means, such as bariatric surgery and it has been shown to be a highly effective means of treating OSA, in short-term follow up studies. It can be considered in patients with BMI ≥40 kg/m^2 or those with BMI ≥35 kg/m^2 with comorbidities. At one year, a 31% decrease in BMI was accompanied by a 75% reduction in AHI.[125] The problem of recurrent weight gain in the long term poses a concern.

A number of pharmacological agents have been studied previously, but so far no medications are shown to be consistently effective for treatment of OSA. Pharmacologic weight reduction, if effective, will alleviate OSA. Modafinil, a stimulant of central nervous system, was shown in several randomized controlled studies to improve residual sleepiness, vigilance and quality of life in patients with OSA treated with CPAP.[126] However, being a CNS stimulant, its nondiscriminant use is not encouraged, and it is certainly not to be used in itself for the treatment of OSA, as it has no effect on the upper airway obstruction or AHI.[126]

Issues Pertaining to Treatment of OSA in Developing Countries

Despite the fact that CPAP remains the most efficacious treatment of OSA, the high costs in rental, purchase and maintenance could limit its use in resource-limited settings. Notwithstanding, OSA is a chronic disease, with far-reaching adverse effects on health outcomes, personal performance, productivity, quality of life, social consequences. Several economic analyses of CPAP, mainly involving the developed countries, have convincingly demonstrated the cost-effectiveness of CPAP treatment in moderate-severe OSA. It is also highly efficient in reducing motor vehicle crashes and the associated socioeconomic loss.[127-130]

Oral appliances are in general inferior to CPAP in the terms of efficacy, but the higher patient acceptance and probably compliance as well, could potentially magnify its actual benefits in comparison to CPAP. In a recent cost-effectiveness study, CPAP remained the most economically attractive approach compared to OA and lifestyle modification.[131,132] However, such benefits may not be readily extrapolated to the settings in developing countries, since many other diseases and conditions could interfere with health outcomes and productivity to a remarkable degree, so, that the impact from CPAP might become negligible. Cost-effectiveness studies to be carried out in the developing countries would help quantify the exact benefits and assist in health care planning.

To obtain the benefits of CPAP, a set of functional equipment, the accessories and most importantly, the support measures, are required. Adequate education could ensure proper application of the CPAP, improve compliance, and maximize treatment efficacy. Trained personnel in this highly specialized field would be required in order to provide appropriate support to the patients. An efficient and well-trained sleep team and a systematic follow up approach would facilitate the best use of resource in the developing countries.

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Section

17

RESPIRATORY CRITICAL CARE

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Respiratory Failure

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DEFINITION

Respiratory failure can be defined as a syndrome in which the respiratory system fails to meet one or both of its gas exchange functions, oxygenation and carbon dioxide elimination.[1] In practice, respiratory failure is said to be present if the PaO_2 values are less than 60 mm Hg while breathing room air. It is further classified as type I (or hypoxemic respiratory failure) if the $PaCO_2$ levels are less than 45 mm Hg or type II (or hypercapnic respiratory failure) if the $PaCO_2$ levels are more than or equal to 45 mm Hg.[2] Some authors also classify it further into type III or perioperative respiratory failure and type IV or shock-related respiratory failure. However, there is no specific advantage of these further characterizations.

At sea level, the normal value of PaO_2 in healthy adults is 80–100 mm Hg.[3] This falls progressively with increasing age (approximately 5 mm Hg/decade after 10 years). At 60 years, it is around 75 mm Hg and falls by 1 mm Hg/year, thereafter till the age of 90 years.[4] It is also dependent upon both the concentration of inspired oxygen (FiO_2) and the partial pressure of gas in the atmosphere (P_{atm}). As a rough guide, if PaO_2 is less than five times the fraction of inspired oxygen concentration (FiO_2), patient is probably hypoxemic on room air. Hypoxemia is decrease in the arterial oxygen tension, and is defined as $PaO_2 > 80$ mm Hg while breathing room air. On the other hand, hypoxia defines oxygen depletion at the tissue level. It is important to differentiate between hypoxemia and hypoxia.[5] The classic example is anemia where patients may be hypoxic, but not hypoxemic. Hypoxemia is further classified as mild if PaO_2 <80 mm Hg, moderate if PaO_2 <60 mm Hg and severe if PaO_2 <40 mm Hg.

CLASSIFICATION

The primary functions of the respiratory system are removal of Carbon Dioxide (CO_2) from blood entering the pulmonary circulation, provision of adequate Oxygen (O_2) to blood leaving the pulmonary circulation. If these functions are to be carried out appropriately, there must be adequate fresh air in the alveoli for delivery of O_2 and removal of CO_2 (ventilation), adequate circulation of blood through the pulmonary vessels (perfusion), reasonable movement of gas between alveoli and pulmonary capillaries (diffusion) and appropriate contact between alveolar gas and pulmonary capillary blood (ventilation-perfusion matching).

Respiratory failure may be acute or chronic (Table 130.1). Acute Respiratory Failure (ARF) refers to disorders of recent onset (hours to days). It implies that respiratory failure has developed before physiologic compensation can occur. On the other hand, chronic respiratory failure develops over months to years, allowing compensatory mechanisms to improve oxygen transport and to buffer respiratory acidosis.[6-8] Acute respiratory failure can also be superimposed on chronic respiratory failure, as in acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD). Acute respiratory Failure is characterized by life-threatening derangements in arterial blood gases and acid-base status while the manifestations of chronic respiratory failure are less dramatic and may not be as readily apparent.[9] Acute type-1 respiratory failure is usually seen in diseases of lung parenchyma, cardiovascular system and lower airways. The causes are due to various physiological processes primarily due to ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch but also include other

TABLE 130.1: Causes of respiratory failure

Acute	Chronic
Type 1 Acute pulmonary edema Pneumonia Acute lung injury/acute respiratory distress syndrome Pneumothorax Severe acute asthma	*Type 1* Interstitial lung diseases—idiopathic pulmonary fibrosis, sarcoidosis and others Lymphangitis carcinomatosis Chronic pulmonary embolism Chronic heart failure
Type 2 Acute exacerbations of chronic obstructive pulmonary disease Tension pneumothorax Guillain-Barrè syndrome Myasthenia gravis Laryngeal edema Inhaled foreign body	*Type 2* Chronic obstructive pulmonary disease Obesity hypoventilation syndrome Motor neuron disease and other neuromuscular disorders

mechanisms such as low inspired concentration of oxygen, impairment of diffusion, intrapulmonary shunting, and low mixed venous oxygen content (Table 130.1).

Mechanisms of Respiratory Failure

Hypoxemic (Type 1) Respiratory Failure

Hypoxemic respiratory failure (also called type 1, nonventilatory or normocapneic respiratory failure) is characterized by a low PaO_2 and a normal or low $PaCO_2$.[10,11] Although there are four pathophysiological mechanisms that can cause hypoxemia, namely low partial pressure of O_2 (FiO_2), diffusion impairment, right-to-left shunt and ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch, the underlying physiological aberration causing hypoxemia is predominantly $\dot{V}/\dot{Q}$ mismatch. The classic example of acute hypoxemic respiratory failure is the Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS).

Both O_2 and CO_2 diffuse readily down their concentration gradients through the alveolar wall and pulmonary capillary endothelium.[12] Under normal circumstances, equilibration of both the gases is complete within one-third of the transit time of erythrocytes through the pulmonary capillary bed. Thus, even in disease states in which diffusion of gases is impaired, the impairment is unlikely to be severe enough to prevent equilibration of CO_2 and O_2. In patients with interstitial lung diseases, where diffusion is perceived by many as the mechanism of hypoxemia, a diffusion abnormality rarely results in arterial hypoxemia at rest.[13] However, if the transit time in the pulmonary circulation is shortened, as occurs with exercise, and diffusion is impaired, then diffusion limitation may contribute to hypoxemia. Exercise testing can often demonstrate such physiologically significant abnormalities due to impaired diffusion. The ratio of pulmonary ventilation to pulmonary blood flow for the whole lung at rest is about 0.8 to 1 (4–6 liters of minute ventilation divided by 5–6 liters of blood flow every minute). It is this matching of distribution of ventilation and perfusion that is the most important determinant of gas exchange.[14]

The ventilation-perfusion mismatch is the final common pathway to cause hypoxemia in most pulmonary diseases (Fig. 130.1). An area of lung that is well perfused but not ventilated acts as a right to left shunt (physiological shunt) whereas an area that is well ventilated but not perfused acts like a dead space

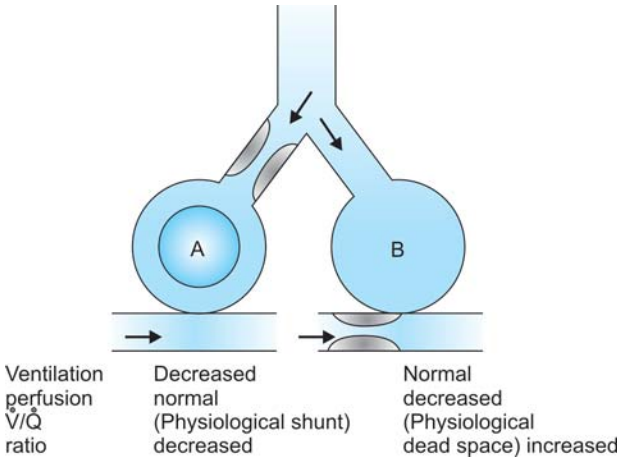

Fig. 130.1: Primary mechanism of hypoxemic respiratory failure—shunt physiology

(physiological dead space). The spectrum of $\dot{V}/\dot{Q}$ ratios in a healthy lung would vary between zero (perfused but not ventilated) to infinity (ventilated but not perfused). The ideal $\dot{V}/\dot{Q}$ ratio of one indicates perfectly matched ventilation and perfusion. Although $\dot{V}/\dot{Q}$ mismatch includes both physiological shunt and physiological dead space but in clinical parlance, the term generally denotes physiological shunt mechanism as physiological dead space, is rarely, if ever the cause of hypoxemia. In an alveolar-capillary unit with a $\dot{V}/\dot{Q}$ ratio of 0 (physiological shunt), the blood leaving the unit has the composition of mixed venous blood entering the pulmonary capillaries, i.e. PO_2 of 40 mm Hg and PCO_2 of 46 mm Hg, whereas in an alveolar-capillary unit with a high $\dot{V}/\dot{Q}$ ratio (physiological dead space) the small amount of blood leaving the unit has partial pressures of O_2 and CO_2 as 150 mm Hg and 0 mm Hg approaching the composition of inspired gas.[13,14]

The efficiency of gas exchange can be evaluated clinically by measuring the PaO_2, $PaCO_2$ and the alveolar-arterial (A-a) DO_2 gradient.[15] Thus, patients with hypoxemia may be divided into those with a normal gradient and those with an increased gradient (Fig. 130.2). The alveolar PO_2 can be calculated from the alveolar air equation:

$$PAO_2 = (P_B - P_{H_2O})\ FiO_2 - (PaCO_2/R)$$

where PAO_2 is the alveolar PO_2, FiO_2 is the fraction of inspired O_2, P_B is barometric pressure (760 mm Hg at sea level), P_{H_2O} is the water vapour pressure (47 mm Hg at sea level) and R is the respiratory exchange ratio (assumed to be 0.8). The alveolar arterial gradient is derived by subtracting PaO_2 from PAO_2. In a healthy individual, the (A-a) DO_2 is normally less than 15 mm Hg at room air; this value increases by 3 mm Hg every decade and can be as high as 30 mm Hg in elderly patients. Hypoxemic respiratory failure most often occurs due to conditions that increase the (A-a) DO_2.[16]

Hypercapnic (Type 2) Respiratory Failure

The normal respiratory rate is about 12–16 times per minute with the tidal volume of each breath being around 500 ml. About 30% of the air inspired with each breath remains in the conducting airways of the lung and does not reach the alveoli. This component of the inspired gas that is not available for gas exchange is called the "anatomic dead space" component. The remaining 70% reaches the alveolar zone and can participate in gas exchange. If the total ventilation each minute is 7 L, then 2 L/min is the dead space ventilation and 5 L/min is the alveolar ventilation. In diseases where some alveoli are ventilated but not perfused, then the component of the anatomical dead space gets increased.[13,14] If total dead space ventilation is increased but total minute ventilation is unchanged, then alveolar ventilation falls. Gas exchange is critically dependent on alveolar ventilation rather than total minute ventilation. The $PaCO_2$ is directly proportional to the amount of CO_2 produced per minute and inversely proportional to alveolar ventilation (V_A), according to the relationship:

$$PaCO_2 = 0.863 \times VCO_2/V_A$$

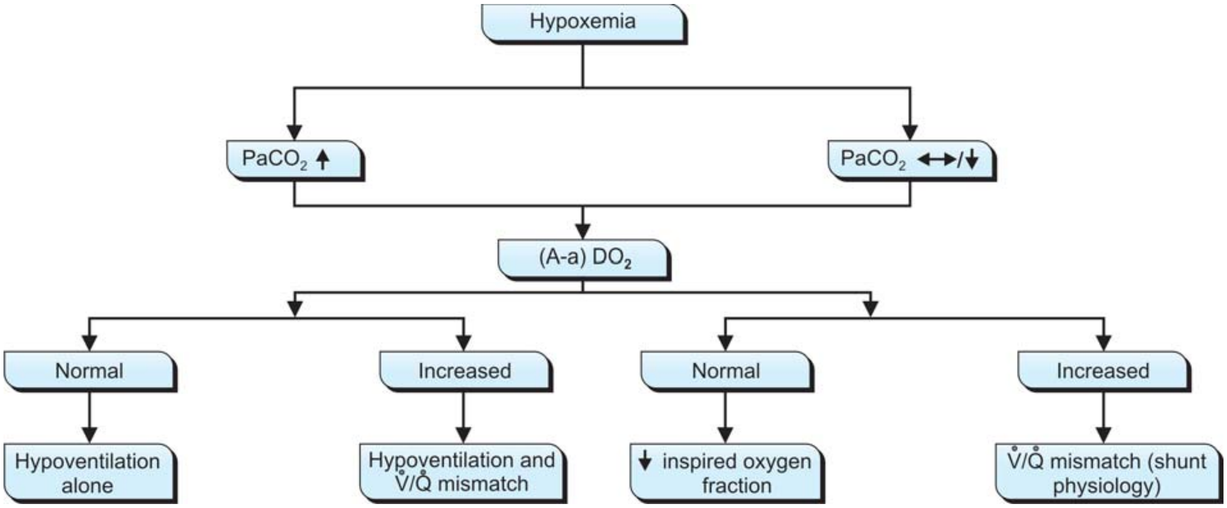
Hypoxemia
PaCO2 ↑
PaCO2 ↔/↓
(A-a) DO2
Normal
Increased
Normal
Increased
Hypoventilation alone
Hypoventilation and V̇/Q̇ mismatch
↓ inspired oxygen fraction
V̇/Q̇ mismatch (shunt physiology)

Fig. 130.2: Importance of calculating alveolar-arterial gradient in patients with acute respiratory failure

where CO_2 is expressed in ml/min, V_A in L/min, and $PaCO_2$ in mm Hg

At fixed CO_2, when alveolar ventilation increases, $PaCO_2$ falls, and when alveolar ventilation decreases, $PaCO_2$ rises. Maintaining a normal level of O_2 in the alveoli (and consequently in arterial blood) also depends on provision of adequate alveolar ventilation to replenish alveolar O_2. Thus, hypercapnic respiratory failure results from any cause that leads to decrease in alveolar ventilation.[6-8,12,15] Multiple mechanisms operate to cause hypercapnia in COPD, the most common cause of type 2 respiratory failure. The mechanisms can be easily remembered by the mnemonic COPD.

- C- central hypoventilation
- O- obstructive physiology with air trapping
- P- peripheral inspiratory muscle weakness due to inflammatory cytokines
- D- diaphragmatic dysfunction.

Clinical Manifestations of Respiratory Failure

A combination of arterial hypoxemia and tissue hypoxia leads to the typical manifestations of hypoxemic failure. Hypoxemia causes hyperventilation due to stimulation of carotid body chemoreceptors with resultant tachypnea. There may be cyanosis, the degree of which depends on the concentration of the hemoglobin and the patient's perfusion. Hypoxia stimulates anaerobic metabolism with the generation of lactic acid that further stimulates ventilation. Mild hypoxia may also lead to impaired mental performance. With progression of hypoxia alteration in the sensorium, somnolence, coma and seizures can occur, leading to permanent brain damage. Hypoxemia causes stimulation of the sympathetic nervous system, and resultant tachycardia, diaphoresis and systemic vasoconstriction. Severe hypoxia can lead to bradycardia, vasodilation, hypotension, myocardial ischemia, infarction, arrhythmias and cardiac failure. Symptoms and signs also reflect not just acute hypoxemia, but also the underlying cause of respiratory failure. Patients with acute hypercapnic respiratory failure largely present with central nervous system disturbances. Hypercapnia causes central nervous system depression leading to lethargy, somnolence, coma, asterixis, restlessness, tremors, slurred speech, headache and papilledema. Symptoms of hypercapnia may overlap those of hypoxemia.

Diagnosis

Arterial Blood Gas Analysis

Respiratory failure may be associated with a variety of clinical manifestations. As these are nonspecific and respiratory failure may be present without dramatic signs or symptoms, this emphasizes the importance of measuring arterial blood gases in all patients in whom respiratory failure is suspected. The arterial blood gas analysis measures pH, PaO_2, $PaCO_2$ and HCO_3. The partial pressure is the driving pressure for the gas in blood and not a measure of the quantity of gas in the blood. Thus, the actual O_2 content in the blood depends on the solubility of O_2 in plasma and the quantity of hemoglobin. The PaO_2 determines what percentage of hemoglobin is saturated with O_2, based on the position on the oxyhemoglobin dissociation curve. Oxygen content in blood can be determined by adding the amount of O_2 dissolved in plasma to the amount bound to hemoglobin, according to the equation:

$$O_2 \text{ content} = 1.34 \times [\text{hemoglobin}] \times O_2 \text{ saturation} + 0.0031 \times PaO_2$$

In arterial blood, the amount of O_2 transported dissolved in plasma (approximately 0.3 ml O_2 per deciliter of blood) is trivial compared to the amount bound to hemoglobin (approximately 20 ml O_2 per deciliter of blood). In arterial blood gas analysis, PaO_2 is the measurement used to assess the effect of respiratory disease on the oxygenation status. The PaO_2 gives an assessment of the hypoxemia whereas the oxygen content denotes the level of hypoxia.[16]

Pulse Oximetry

Pulse oximetry is a noninvasive assessment of the oxygenation status, as measurement of PaO_2 requires arterial puncture. The pulse oximeter calculates oxygen saturation (rather than PaO_2) based on measurements of absorption of two wavelengths of light by hemoglobin in pulsatile, cutaneous arterial blood. Due to differential absorption of the two wavelengths of light by oxygenated and nonoxygenated hemoglobin, the percentage of hemoglobin that is saturated with oxygen, i.e. the SaO_2 can be calculated and displayed instantaneously. As oxyhemoglobin dissociation curve becomes relatively flat above PaO_2 of 60 mm Hg (corresponding to SaO_2 of 90%), the oximeter is relatively insensitive to changes in PaO_2 above this level. In conditions where cutaneous perfusion is decreased such as hypotension, the signal from the oximeter may be less reliable or even unobtainable. Other forms of hemoglobin, such as carboxyhemoglobin and methemoglobin, are not distinguishable from oxyhemoglobin when only two wavelengths of light are used. The SaO_2 values are not reliable in the presence of significant amounts of either of these forms of hemoglobin. Finally, the pulse oximeter does not indicate anything about CO_2 elimination.[16]

Chest Radiograph

Chest radiography is essential because it frequently reveals the cause of respiratory failure. However, distinguishing between cardiogenic and noncardiogenic pulmonary edema often is difficult, and may require clinical judgement and echocardiography.

Pulmonary Function Tests (PFTs)

Generally PFTs should not be performed in patients with ARF. However, PFTs are valuable in the evaluation of chronic respiratory failure.

A decrease in Forced Expiratory Volume in one second/Force Vital Capacity ratio indicates airflow obstruction, whereas a reduction in both the FEV_1 and FVC and maintenance of the FEV_1/FVC ratio suggest restrictive lung disease. Respiratory failure is uncommon in obstructive diseases when the FEV_1 is greater than 1 L and in restrictive diseases when the FVC is more than 1 L.

Treatment

The principles of managing respiratory failure are outlined below:

- As most patients are critically ill, management should take place in a high dependency unit/intensive care unit (ICU) setting.
- Alleviation of hypoxia is the immediate aim of treatment.
- Treatment of basic underlying condition such as pneumonia, pulmonary edema, etc.
- Support with mechanical ventilation either noninvasive or invasive. This is to "buy" time for specific therapies such as antibiotics to act.

Oxygen Therapy

Hypoxemia is the major immediate threat to organ function. Therefore, the first objective is to reverse and/or prevent tissue hypoxia.[13] Oxygen therapy is started immediately on admission after an arterial blood sample is obtained for assessment of blood gas tensions. The goal of supplemental oxygen is to maintain a PaO_2 of 55–60 mm Hg corresponding to SpO_2 of 89–92%. A common mistake committed by physicians, nursing staff and occasionally the patient's attendants is to increase the flow of oxygen to improve oxygen saturation. However, one should not forget that oxygen is a "drug" and should be carefully administered since excess oxygen has got its own problems. In a patient with COPD who has chronic type II respiratory failure and hypercapnia, the ventilatory stimulus for hypercapnia is lost and patients' ventilatory drive is maintained by hypoxemia. Administration of excess amounts of oxygen can blunt this ventilatory drive with resultant hypercapnia and acute respiratory acidosis superimposed on type II respiratory failure that could be potentially life-threatening. Excess oxygen therapy has been shown to prolong hospital stay probably because it can lead to generation of harmful reactive oxygen species, which can exacerbate tissue injury. Excess oxygen can also lead to hypercapnia by ventilation perfusion disturbances, Haldane effect and by causing numerous areas of microatelectasis. Another reason why PaO_2 is not increased more than 60 mm Hg is because it corresponds to oxygen saturation (SaO_2) of around 90%; from the oxygen content equation we can conclude that there is no benefit of increasing PaO_2 above 60 mm Hg except in situations of hyperbaric oxygen delivery. In arterial blood, the amount of O_2 transported dissolved in plasma (approximately 0.3 ml O_2 per deciliter of blood) is trivial compared to the amount bound to hemoglobin (approximately 20 ml O_2 per deciliter of blood). Due to the sigmoid shape of the oxyhemoglobin dissociation curve, it is important to differentiate between the partial pressure and the content of oxygen in the blood. The partial pressure is only the driving pressure for the gas in blood and not a measure of the quantity of gas in the blood. Thus, the actual O_2 content in the blood depends on the solubility of O_2 in plasma and the quantity of hemoglobin. The PaO_2 determines what percentage of hemoglobin is saturated with O_2, based on the position on the oxyhemoglobin dissociation curve. Hemoglobin is almost fully (>90%) saturated at a PO_2 of 60 mm Hg and little additional O_2 is carried by hemoglobin even with a substantial elevation of PO_2 above 60 mm Hg. On the other hand, significant O_2 desaturation of hemoglobin occurs once PO_2 falls below 60 mm Hg and onto the steep descending limb of the curve.

Another important consideration in acutely ill patients is the type of oxygen delivery device which is used. Low-flow oxygen delivery systems provide oxygen at flow rates that are lower than patient's inspiratory demands; thus when the total ventilation exceeds the capacity of the oxygen reservoir, room air is entrained.[17-19] The final concentration of oxygen delivered depends on the ventilatory demands of the patient, the size of the oxygen reservoir and the rate at which the reservoir is filled. At a constant flow, the larger the tidal volume, the lower the FiO_{2-} and vice versa.[13] In contrast, the high-flow systems provide a constant FiO_2 by delivering the gas at flow rates that exceed the patient's peak inspiratory flow and by using devices that entrain fixed proportion of room air. In acute situations, it is always better to use high-flow devices as one can, to a reasonable extent, guarantee the oxygen delivered. On the other hand, with the use of a low flow device, oxygen delivery would not be dependent on the patient's minute ventilation. Once the patient has been stabilized, one can shift to nasal prongs, as it proves more comfortable for the patient.

The appropriate FiO_2 is selected with the help of alveolar gas equation.[13] We also know that the ratio of PaO_2 to P_AO_2 is independent of FiO_2. For example, a patient of COPD has PaO_2 of 35 mm Hg and $PaCO_2$ of 58 mm Hg on room air; the FiO_2 requirement to bring PaO_2 of 60 mm Hg is calculated as follows:

$P_AO_2 = [FiO_2 (P_{atm} \text{ minus } P_{H_2O})] - (PaCO_2/R)$

$= [0.21 (760\text{-}47)] - (58/0.8) = 77.3$

$PaO_2/P_AO_2 = 35/77 = 0.45$

To get the desired PaO_2 of 60 mm Hg, the P_AO_2 must increase for the same PaO_2/P_AO_2 ratio, i.e.

$35/77 = 60/\ P_AO_2\ (x) = 0.45$

$P_AO_2\ (x) = 77 \times 60/35$

$P_AO_2 = 133.3$

The desired FiO_2 (for PaO_2 of 60 mm Hg) can be determined again from the alveolar gas equation as above, i.e.

$133 = FiO_2 \times 713\text{-}\ (58/0.8)$

$FiO_2 = 28.8$

Noninvasive Ventilation (NIV)

Noninvasive ventilation refers to the provision of inspiratory pressure support plus Continuous Positive Airway Pressure (CPAP) via a nasal or facemask, i.e. without an endotracheal airway.[20-25] It has been used for diverse forms of respiratory failure and has revolutionized the management of respiratory failure.[26-32] Although CPAP does not actively assist inspiration and is not traditionally a ventilatory mode, it is considered a form of NIV when used as a therapy for respiratory failure. The key to the successful application of NIV is identification of the appropriate patient for its use. Once patients who require immediate intubation are eliminated, a careful assessment of the patient's condition determines whether the patient requires NIV.[21] This requires clinical evaluation and may also involve a NIV trial. NIV is an effective tool in improving the clinical outcome of patients with different etiologies of ARF especially acute exacerbations of COPD,[33] cardiogenic pulmonary edema,[20,21] weaning patients with chronic respiratory failure especially COPD[34] and management of ARF in immunocompromised patients.[35,36] It not only avoids the need for endotracheal intubation but also reduces other complications such as occurrence of nosocomial infections, duration of ICU stay and the overall cost of hospitalization.[37]

Important determinants of NIV success are properly fit and comfortable interface and ventilator settings.[21,32] Masks are firmly secured with elastic straps to the face in order to avoid air leaks and consequent malfunction. The nasal mask is usually well tolerated because it causes less claustrophobia and discomfort.[38] It allows eating, drinking and expectorating. Conversely, a facial mask is preferable in severe respiratory failure, because dyspneic patients breathe through the mouth in order to bypass resistance of the nasal passages, and mouth opening during nasal mask ventilation results in air leakage and decreased effectiveness.[39] Hence, full facemasks are utilized for ARF whereas nasal masks are preferred for use in the chronic setting. The optimal ventilator settings are determined by the ability to reduce the work of breathing (assessed clinically by reduction in respiratory rate to <30–35 breaths per minute) by providing an adequate level of pressure support (usually >8–10 cm H_2O) against the discomfort imposed by high pressures (Table 130.2).

The application of NIV should be performed in an area where there is constant availability of adequate staff that is trained in use of NIV.[40] To assure the success of NIV, close monitoring is necessary, especially during the initial period. The patients need to be monitored with regular clinical observation, continuous pulse oximetry and on-demand arterial blood gas measurements. Favorable subjective responses such as tolerance of the mask and NIV pressures and reduction of respiratory distress further help achieve good results. Although the optimal duration of the initial NIV trial remains uncertain, a response within 1–4 hours of initiation is a reasonable expectation.[41] Finally, patients who are failing

TABLE 130.2: Protocol for application of noninvasive ventilation in acute respiratory failure

- Full facemask better tolerated in the acute setting
- Start with an inspiratory pressure support of 6–8 cm H_2O and CPAP of 3–4 cm H_2O
- Adjustments
  - Increase inspiratory pressure and CPAP by 2 and 1 cm H_2O, respectively
  - Titrate to tidal volume (>5 ml/kg), respiratory rate (<35 breaths/minute) and blood gases
  - Maximum inspiratory pressure and CPAP generally used is 15–16 cm H_2O and 7–8 cm H_2O, respectively
- Air leaks should be minimized
- CPAP is rarely used in acute respiratory failure.

NIV trial should be promptly intubated and mechanically ventilated as delays in endotracheal intubation in patients being managed with NIV have been shown to be associated with decreased survival.[42]

We have significant experience with the use of NIV. In a study involving 63 patients, NIV failures were higher in ARF associated with other causes (15/39, 38.4%) compared to ARF associated with COPD (3/24, 12.5%). Only the etiology of ARF (ARF due to other causes) was associated with NIV failure on a multivariate analysis.[23] In another study involving 40 patients with hypoxemic ARF, NIV failures were higher in ARDS group (12/21, 57.1%) than hypoxemic ARF due to other causes (7/12, 36.8%). The only factor associated with NIV failure was the baseline PaO_2-FiO_2 ratio on a univariate analysis.[24] In a recently conducted randomized controlled trial, we randomized patients with acute asthma to the standard medical therapy (SMT) arm (n=28) or NIV plus SMT (n=25). The improvement in respiratory rate, FEV_1 and PaO_2-FiO_2 were seen equally in both groups. However, increment in FEV_1 by 50% at 4 hours was greater in the NIV arm. Not only the mean dose of broncho-dilators required was lesser in the NIV group, but the ICU and hospital length of stay was significantly shorter in NIV group. There were four instances of SMT failure and all these patients improved with the application of NIV. Two patients failed NIV and required endotracheal intubation.[43]

Endotracheal Intubation and Invasive Ventilation

Patients who are in severe respiratory distress and those who fail treatment with oxygen and NIV generally require endotracheal intubation and invasive ventilation. Another indication for intubation is airway protection in patients with altered mental status. The aim of invasive ventilation is to correct hypoxemia and maintain alveolar ventilation appropriate to patient's metabolic requirements. It has been recognized since 1970 that mechanical ventilation, if not applied properly, could cause harm.[44] However, only recently this concept has been applied in day-to-day practice. A new era of ventilatory management began in 1990 when it was showed that minimizing pulmonary overdistension and allowing permissive hypercapnia decreased mortality in patients with ARDS.[45] The clinical importance of ventilator associated lung injury was aptly highlighted by the ARDS Network study.[46] Although patients without ALI are still ventilated with large tidal volumes, recent studies have shown that use of higher tidal volumes can cause ventilator associated lung injury even in patients with normal lungs.[47-55] Recognition of this fact has led to paradigm shift in the ventilatory management with use of lower tidal volumes even in patients with normal lungs. The current ventilatory strategy aims at minimizing complications of mechanical ventilation. The principles are to prevent initiation of additional alveolar injury and facilitate healing of the underlying condition. The ventilation is thus pressure targeted employing lower tidal volumes. The aim is to have adequate blood gases and normalization of physiological parameters is not considered important (Table 130.3).

An important consideration is the choice of ventilator that should be used for mechanically ventilating these patients. No ventilator is clearly better than any other. The machine is selected based on the spectrum of patients, the financial resources of the ICU and the available expertise in handling the equipment. Clearly, the people operating the ventilator are more important

TABLE 130.3: Parameters and goals for invasive mechanical ventilation in different categories of respiratory failure

	Restricted lung	Obstructed lung	Normal lung
Prototype	ARDS	Acute asthma	Neuromuscular respiratory failure
Mode	V-ACMV	V-ACMV	V-ACMV
Initial tidal volumes	4–6 ml/kg	4–6 ml/kg	6–8 ml/kg
Respiratory rate	18–35/minute	8–12/minute	14–18/minute
PEEP	Based on FiO_2; 0.XX (FiO_2) x 20	5–8 cm H_2O	Up to 5 cm H_2O
I:E	1:1–1:2	1:3–1:6	1:2–1:3
Flow waveform	Descending ramp	Square waveform	-
	Goals		
Plateau pressure	≤ 30 cm H_2O	≤ 30 cm H_2O	-
PaO_2	~ 55–60 mm Hg	~ 55–60 mm Hg	~ 60–80 mm Hg
pH	7.2–7.4	7.2–7.4	-

than the machine. Other important issue is the mode to be used for mechanical ventilation. Again no mode is clearly superior. The choice of a particular mode is often guided by institutional policy or personal preference. Another controversial area is the choice of a volume controlled or pressure controlled strategy. There is no strong evidence base for the pressure controlled ventilation although logically it is likely to be equivalent to the volume controlled mode because it is the settings rather than the mode that is the important issue. It is best to initiate ventilation with a volume assist controlled mode ventilation and once the patient improves, shift the patient to pressure support ventilation. As a protocol, we rarely if ever use synchronized intermittent mandatory ventilation for either initial ventilation or later for weaning. Newer modes of ventilation are increasingly being promoted to decrease the hazards of conventional ventilation and improve patient-ventilator interactions. However, none of the newer modes of ventilation has been shown superior to conventional modes. Also, the indications, efficacy and safety are still clinically uncertain and are not being widely utilized.

CONCLUSION

In conclusion, the management of respiratory failure hinges on two basic principles, i.e. oxygen therapy for alleviation of hypoxemia and aggressive treatment of basic disease. Oxygen should be administered through high-flow (Venturi mask) system. NIV should be judiciously used in ARF as inappropriate use of NIV may lead to delayed intubation in some patients. Eventually, mechanical ventilation is required in patients who fail NIV or develop respiratory arrest.

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131

Acute Respiratory Distress Syndrome

Jean I Keddissi, D Robert McCaffree

The Acute Respiratory Distress Syndrome (ARDS) is a serious and frequently encountered entity in modern intensive care units. Since its initial description in 1967 by Ashbaugh et al,[1] our understanding of its epidemiology, pathophysiology and clinical course have greatly improved. This has recently resulted in management changes, which are affecting outcome, and are likely to result in newer therapeutic modalities.

In this chapter, we will review the current knowledge of ARDS. We will also review in details all the available therapies, with focus on the large trials that have enhanced our understanding of this syndrome.

Definition

For decades, attempts to define ARDS lacked specific criteria,[2,3] causing uncertainty in terms of its true incidence, natural history and appropriate management. Initially called the adult respiratory distress syndrome, the term acute respiratory distress syndrome is now used since it does occur in children.

In 1994, an American/European Consensus Conference[4] proposed the following clinical criteria to define the syndrome: Presence of acute widespread, bilateral radiographic infiltrates on the chest X-ray, hypoxemia ($PaO_2/FiO_2 < 200$), without any evidence of left atrial hypertension. Acute Lung Injury (ALI), a less severe and often earlier form of ARDS, is considered present if PaO_2/FiO_2 is <300. The definition is simple and takes into consideration the severity of the lung injury, expressed as the degree of hypoxemia (ARDS versus ALI). However, it does not take into consideration the underlying cause, nor does it consider any accompanying extrapulmonary manifestation. In addition, it does not incorporate any physiological measurement of lung mechanics. Nevertheless, the 1994 definition has gained widespread acceptance and is now being used in daily practice as well as in clinical trials.

Epidemiology

Estimates of the true incidence of ARDS and ALI varied widely, in part due to the lack of a uniform definition. Estimates ranged from 1.5 to 75 cases per 1,00,000 people.[5] The first estimates based on the 1994 definition used an 8-week prospective cohort study in Scandinavia and reported an incidence of 17.9 cases of ALI and 13.5 cases of ARDS per 1,00,000.[6] More recently, a prospective, population-based, cohort study in 21 hospitals in and around King County, Washington, from April 1999 through July 2000, ARDS was estimated to occur in 64 cases/1,00,000 person-years, while ALI occurred in 86 cases/1,00,000 person-years.[7]

Etiology

Sepsis remains the most common cause of ARDS and carries the worst prognosis,[8] with 40% of sepsis cases developing ALI or ARDS.[9,10] Other frequently encountered etiologies include pneumonia (bacteria, virus, fungal), aspiration, shock and trauma (Table 131.1). The presence of multiple predisposing factors increases the risk significantly.[10] Additionally, observational data suggest that inappropriate ventilatory settings in mechanically ventilated patients may contribute to the development of ARDS (i.e. iatrogenic ARDS).[11]

TABLE 131.1: Clinical entities associated with ARDS/ALI

- Acute pancreatitis
- Acute upper airway obstruction
- Aspiration (gastric acid, near drowning)
- Drugs (amiodarone, tocolytics, salicylates, opiates, etc.)
- Iatrogenic ARDS
- Inhalation injury
- Neurogenic pulmonary edema
- Nonthrombotic embolic events (amniotic, tumor, etc.)
- Pneumonia
- Pulmonary embolism
- Reperfusion injury (postlung transplant, lung re-expansion)
- Sepsis (most common)
- Shock
- Transfusion-related acute lung injury (TRALI)
- Trauma.

Clinical Picture

Clinically, the picture is characterized by the rapid onset of hypoxemic respiratory failure, in a patient with a predisposing underlying condition. The hypoxemia is typically refractory to oxygen replacement, frequently requiring the institution of invasive mechanical ventilation. Radiographically, bilateral patchy or asymmetric infiltrates are present, frequently indistinguishable from those seen in cardiogenic pulmonary edema.[12] Computed Tomography (CT) typically reveals areas of consolidation, alveolar filling with atelectasis, predominantly in the dependent zones (Fig. 131.1).[13] In later stages, the CT may reveal diffuse interstitial opacities, with bullae formation. Pulmonary compliance is decreased[14] and evidence of pulmonary hypertension and right ventricular failure may be seen.[5] Pneumothorax may develop in 10 to 13% of the cases, but is not clearly related to the airway pressures, nor is it associated with a significantly increased mortality rate.[15]

Pathophysiology

ARDS is a progressive syndrome, characterized by distinct histopathological stages (Fig. 131.2). Initially, an acute, exudative stage is characterized by the presence of alveolar edema in the absence of an elevated hydrostatic pressure. This edema is secondary to capillary injury, with increased alveolar-capillary membrane permeability, a feature considered to be the hallmark of ARDS. The normal alveolar epithelium is also affected, with the flat type I cell (typically making up 90% of the surface area) easily injured. Cuboidal type II

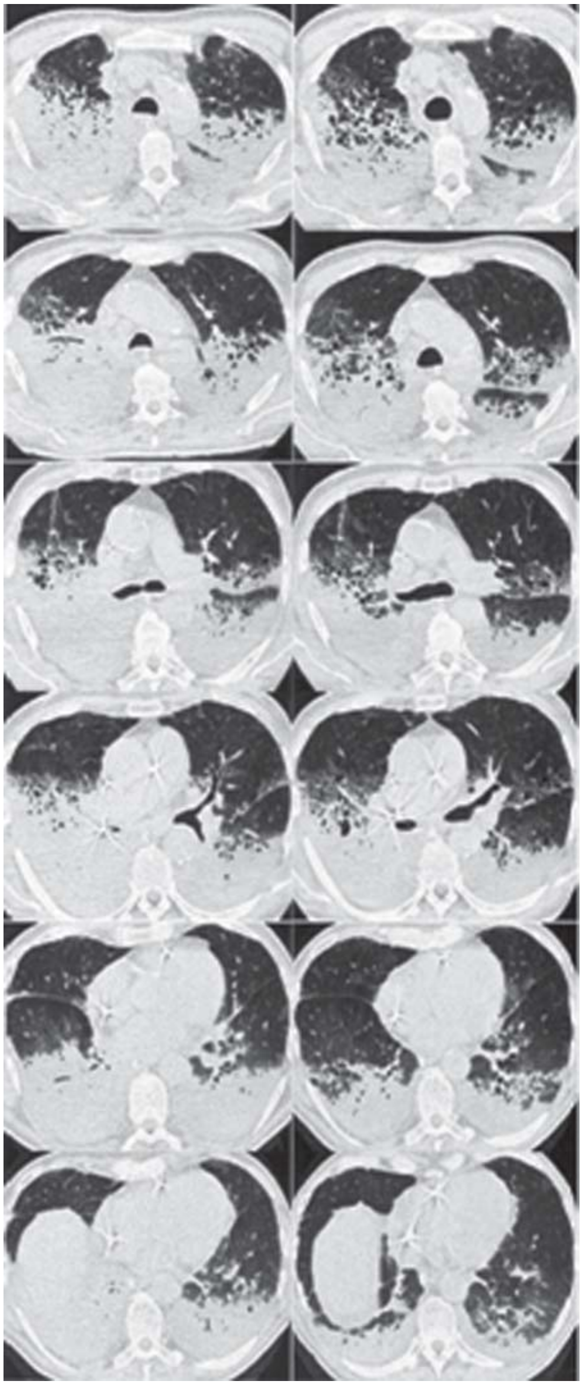

Fig. 131.1: Computed tomographic scans obtained in a 61-year-old patient with "patchy" acute respiratory distress syndrome caused by aspiration pneumonia in the postoperative period of a hip replacement. A selection of contiguous 1 cm thick computed tomographic sections obtained with zero end-expiratory pressure (left images) and positive end-expiratory pressure (PEEP) of 15 cm H_2O (right images) is presented (Adapted with permission from Rouby et al)[13]

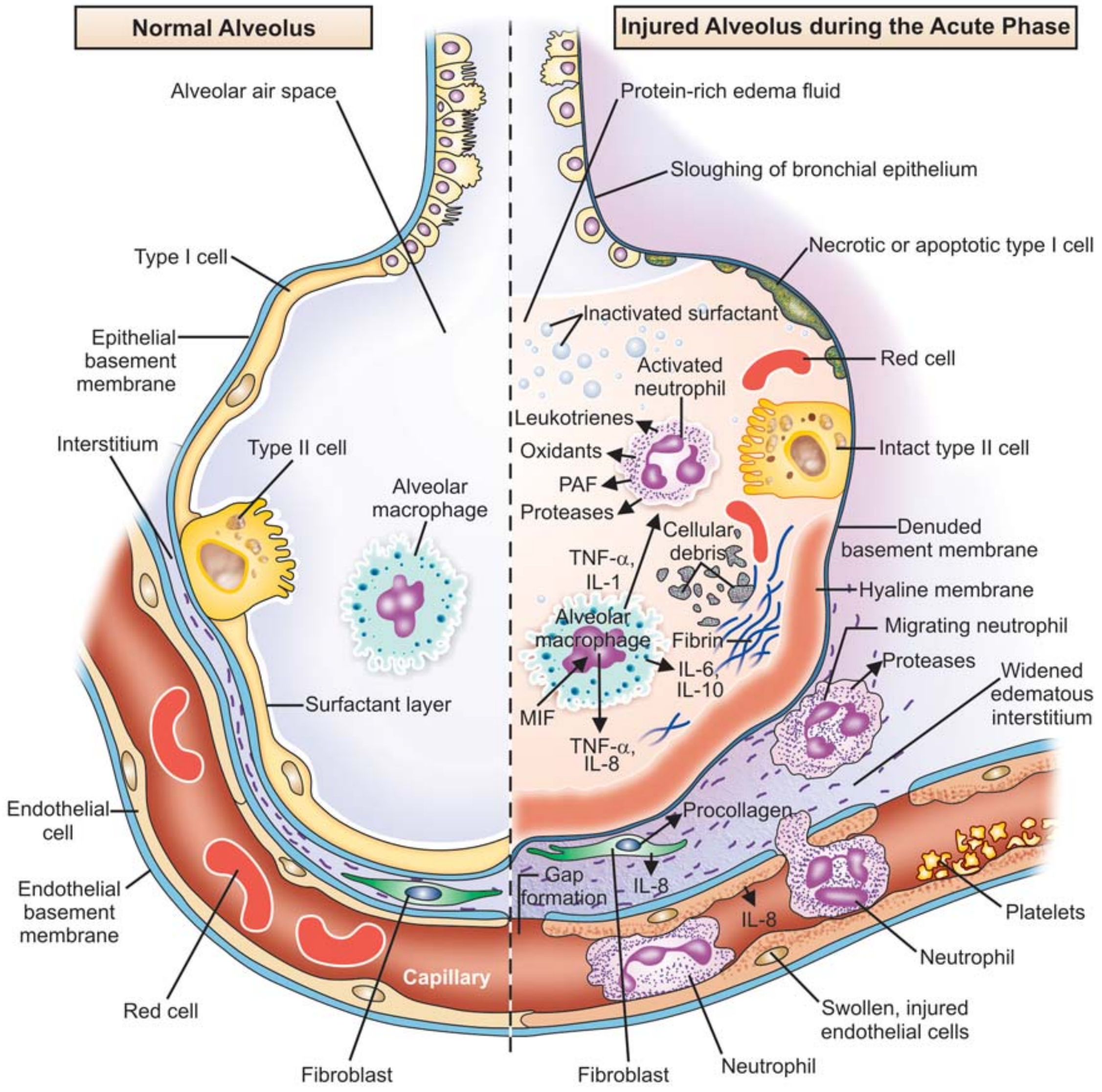
Normal Alveolus
Injured Alveolus during the Acute Phase
Alveolar air space
Type I cell
Epithelial basement membrane
Interstitium
Type II cell
Alveolar macrophage
Surfactant layer
Endothelial cell
Endothelial basement membrane
Red cell
Capillary
Fibroblast
Protein-rich edema fluid
Sloughing of bronchial epithelium
Necrotic or apoptotic type I cell
Inactivated surfactant
Activated neutrophil
Red cell
Leukotrienes
Oxidants
PAF
Proteases
Intact type II cell
TNF-α, IL-1
Cellular debris
Denuded basement membrane
Hyaline membrane
Alveolar macrophage
Fibrin
Migrating neutrophil
IL-6, IL-10
Proteases
Widened edematous interstitium
MIF
TNF-α, IL-8
Procollagen
Gap formation
IL-8
IL-8
Platelets
Neutrophil
Swollen, injured endothelial cells
Fibroblast
Neutrophil

Fig. 131.2: The normal alveolus (left-hand side) and the injured alveolus in the acute phase of ALI/ARDS syndrome (right-hand side). In the acute phase of the syndrome (right-hand side), there is sloughing of both the bronchial and alveolar epithelial cells, with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and marginating through the interstitium into the air space, which is filled with protein-rich edema fluid. In the air space, an alveolar macrophage is secreting cytokines (IL-1, 6, 8, and 10, and TNF-α), which act locally to stimulate chemotaxis and activate neutrophils. Macrophages also secrete other cytokines, including IL-1, IL-6 and IL-10. IL-1 can also stimulate the production of extracellular matrix by fibroblasts. Neutrophils can release oxidants, proteases, leukotrienes and other proinflammatory molecules such as platelet-activating factor (PAF). A number of anti-inflammatory mediators are also present in the alveolar milieu including IL-1 receptor antagonist, soluble TNF receptor, autoantibodies against IL-8 and cytokines such as IL-10 and IL-11 (not shown). The influx of protein rich edema fluid into the alveolus has led to the inactivation of surfactant. MIF denotes macrophage inhibitory factor (Adapted with permission from Wade et al)[5]

cells are typically more resistant and would eventually differentiate into type I after injury, restoring the normal alveolar architecture.[5]

As a result, massive amount of edema fluid and plasma proteins leak into the alveolar space, with subsequent formation of hyaline membranes. These membranes appear in the first 24–48 hours, reach a maximum around day 4 and start to decrease after 6–7 days.[16,17] In addition, fluid removal from the alveolar space is significantly impaired in the majority of patients and maximal alveolar fluid clearance, when present, may be associated with better clinical outcomes.[18]

Activated inflammatory cells, primarily macrophages and neutrophils, accumulate in the interstitium. Whether these cells are the cause or the results of the lung injury is not entirely known. Proinflammatory cytokines are released into the lungs including Interleukin (IL)-1β, IL-8 and tumor necrosis factor (TNF)-α.[19,20] These cytokines play a major role in the lung response to infection or injury, but have a potential role in the cellular response, microvascular injury and the extrapulmonary organ failures seen in ARDS.[20] In addition, neutrophil matrix metalloproteinase (MMP)-9 level is significantly increased.[19] Studies have also shown the presence of anti-inflammatory cytokines such as IL-10 and IL-11, and inhibitors of proinflammatory cytokines including IL-1 receptor antagonist and soluble TNF receptor.[21,22]

Surfactant activity and composition is altered, resulting in elevated surface tension, leading to alveolar collapse.[23] This contributes to the development of decreased lung compliance seen in ARDS/ALI.[24] Furthermore, the presence of excess protein in the alveolar space leads to the disintegration of the large phospholipids macroaggregates into smaller aggregates, which are less active and dysfunctional[25,26] (Fig. 131.3). In addition to the decreased lung compliance, this results in impaired gas exchange and increased pulmonary arterial pressures.[27,28]

Although the above injury may resolve completely after the acute phase, some patients progress and develop evidence of pulmonary fibrosis, with persistent hypoxemia. The alveolar space becomes filled with mesenchymal cells, their products, in addition to new blood vessels.[29] When present, the fibrosis starts around day 3 and becomes dominant at day 7, leading experts to consider day 7 as the cutoff between the early stage (exudative phase) and late stage (proliferative phase) of ARDS. Finally, it appears that the presence of pulmonary fibrosis, diagnosed on the basis of fiberscopic transbronchial lung biopsy, closely correlates with mortality in established ARDS.[30]

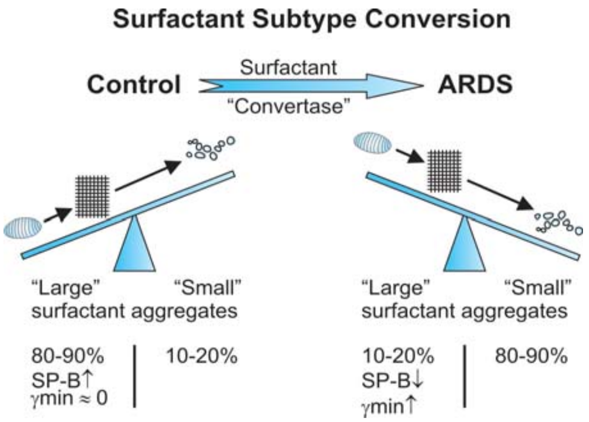

Fig. 131.3: Surfactant containing protein B (SP-B) or C (SP-C) is generally more resistant to plasma protein inhibition (surfactant convertase). These hydrophobic proteins help to maintain the integrity of the large aggregate forms of surfactant that would otherwise be converted rapidly into less active small aggregates in the presence of excess protein (Adapted with permission from Dernaika et al)[20]

Management

General Measures

Careful search of the underlying etiology is crucial in the management of patients with ARDS. Treatable infections should be addressed and the need for surgical drainage evaluated. The patients should be monitored for the development of nosocomial infections. Adequate nutrition should be provided, with the enteral route always preferred when feasible. In addition, patients should be placed on prophylaxis against gastrointestinal bleeding and thromboembolic events.

Invasive Mechanical Ventilation

Endotracheal intubation and mechanical ventilation are almost always needed in patients with ARDS. Mechanical ventilation aims to correct the severe hypoxemia encountered in this setting. Historically, normalizing the partial pressure of carbon dioxide was also considered a primary goal. Although life saving, it became gradually evident that mechanical ventilation can have major negative consequences in terms of exacerbating lung injury through a process termed as Ventilator-induced Lung Injury (VILI). Until recently, few prospective randomized trials have addressed the optimal way of ventilation patients with this syndrome.

Tidal Volume

Achieving normal blood gas parameters was historically done at the expense of high tidal volume. Tidal volumes in excess of 10 ml per kilogram of ideal body weight were used.[31] High tidal volume and high airway pressures were thought to be beneficial in opening collapsed alveoli (i.e. recruitment). However, if one considers the fact that collapsed alveoli have low compliance and do not adequately participate in tidal ventilation, the potential for injury with the use of high pressure/volume becomes evident. In fact, the volume of aerated lung in patients with ARDS is significantly reduced. Therefore, these aerated units are at an increased risk of hyperinflation, not only in the presence of high tidal volume and high transpulmonary pressure, but even at modest pressures.[32] Hyperinflation and overdistention leads to the development of VILI. Consequences include disruption of the alveolar epithelium and capillary endothelium.[33] In addition, evidence clearly show that overdistention will result in an inflammatory process involving cytokines and mediators release,[32,34] a process that appear to be systematic in nature, possibly contributing to the development of multisystem organ failure.[35]

Based on theoretical and animal data, the American College of Chest Physicians recommended in 1993 that patients with ARDS be ventilated with a plateau pressure that is less than 35 cm of H_2O.[36] This was followed by the first clinical trial to support the benefit of a low tidal volume strategy. Amato et al randomly assigned 53 patients with early ARDS to conventional ventilation (tidal volume of 12 ml/kg of body weight, $PaCO_2$ levels of 35–38 mm Hg and lowest PEEP for acceptable oxygenation) versus protective mechanical ventilation (tidal volume <6 ml/kg, permissive hypercapnia, PEEP above the lower inflection point on the static pressure-volume curve, driving pressures <20 cm H_2O above PEEP and preferential use of pressure limited ventilatory modes).[37] As compared to conventional ventilation, the protective strategy was associated with decreased 28-day mortality (38% versus 71%, p<0.001), a higher rate of weaning from mechanical ventilation and a lower rate of barotraumas. However, the difference in the rate of survival to hospital discharge did not reach statistical significance (45% versus 71%, p=0.37).

Based on this preliminary data, the Acute Respiratory Distress Syndrome Network (ARDSNet) conducted a larger study (861 patients),[38] comparing traditional ventilation treatment, which involved an initial tidal volume of 12 ml/kg of predicted body weight with a plateau pressure of 50 cm of H_2O or less, with ventilation with a lower tidal volume, involving an initial tidal volume of 6 ml/kg of predicted body weight and a plateau pressure of 30 cm of water or less. The study used a predetermined combination of FiO_2 and PEEP (Table 131.2), with a PaO_2 goal of 55–80 mm Hg, or an oxyhemoglobin saturation of 88 to 95%. Mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0% versus 39.8%, P=0.007). In addition, the number of days without ventilator use during the first 28 days after randomization was greater in the low tidal volume group (12±11 versus 10±11; P=0.007). Finally, the study showed a lower plasma interleukin-6 concentration in the low tidal volume group, indicating that the low tidal volume strategy has beneficial systemic anti-inflammatory consequences.

TABLE 131.2: Combination of FiO_2/PEEP in the ARDSnet trial.[38] The lowest combination that maintained a PaO_2 of 55–80 mm Hg or an oxyhemoglobin saturation of 88 to 95%, was used

FiO_2	Positive end-expiratory pressure
0.3	5
0.4	5–8
0.5	8–10
0.6	10
0.7	10–14
0.8	14
0.9	14–18
1.0	18–24

At this point, one can ascertain that a tidal volume of 6 ml/kg is better than 12 ml/kg in ARDS. However, it is important to use the ideal body weight, and not the actual weight, to calculate the tidal volume. The ideal body weight (IBW) can be calculated as follows: For men, IBW = 50.0 + 0.91 (height in cm=152.4); and for women, IBW = 45.5 + 0.91 (height in cm=152.4).[33] One also has to remember that the use of low tidal volume can result in CO_2 retention, i.e. permissive hypercapnia with respiratory acidosis. This could be treated with a higher respiratory rate and with the administration of sodium bicarbonate. The latter remains controversial, and likely unnecessary except in the presence of severe acidosis. However, the exact pH at which the use of bicarbonate is necessary (if at all) remains controversial,[33] with some experimental data suggesting that permissive hypercapnia is not only safe, but potentially beneficial.[39] Nevertheless, it should be used carefully in patients with heart disease and is relatively contraindicated in patients with elevated intracranial pressure.

In addition, several questions remain unanswered. Is an intermediate tidal volume an acceptable alternative? And would an even lower tidal volume (less than 6 ml/kg) provide any additional benefit, especially in the presence of high plateau pressure? And can a higher tidal volume in the presence of low plateau pressure (i.e. high respiratory system compliance) be used safely? Finally, whether low tidal volume would be beneficial in nonARDS respiratory failure is unknown. These questions remain open to debate and will require large prospective randomized trails to answer.

Positive End-expiratory Pressure (PEEP)

An arterial oxyhemoglobin saturation of about 90% is typically targeted in patients with ARDS. This may be difficult to achieve, even in the presence of high FiO_2. This constitutes the- main indication for PEEP in ARDS. It is used primarily as a means of supporting oxygenation, PEEP increases the functional residual capacity and prevents small airways and alveoli from collapsing, leading to improvement in the ventilation-perfusion ($\dot{V}/\dot{Q}$) matching.[40-42] It also prevents the repetitive opening and closing of alveoli, referred to as atelectrauma. However, the prophylactic use of PEEP at 8 cm H_2O in patients at risk for ARDS was not successful.[43]

Clinicians have to be aware of the potential for side effect associated with PEEP, primarily circulatory depression and barotrauma. Consequently, the concept of best PEEP in ARDS remains elusive, with some advocating the use of the pressure-volume curve as a means to determine the best PEEP, as one component of an overall safe ventilatory strategy[20] (Fig. 131.4).

As noted previously, when comparing conventional versus protective ventilation,[37] Amato attempted to control for the effect of PEEP. He used the lowest PEEP for acceptable oxygenation in the conventional group (9.3 ± 0.5 cm H_2O), while PEEP above the lower inflection point on the static pressure-volume curve was used in the protective ventilation group (13.2 ± 0.4 cm H_2O). Even though the difference in the 28-day mortality in favor of the intervention group (38% versus 71%, $p<0.001$) could have been related to the difference in PEEP, the results were criticized for the high mortality in the conventional group, and the lower tidal volume in the protective ventilation one.

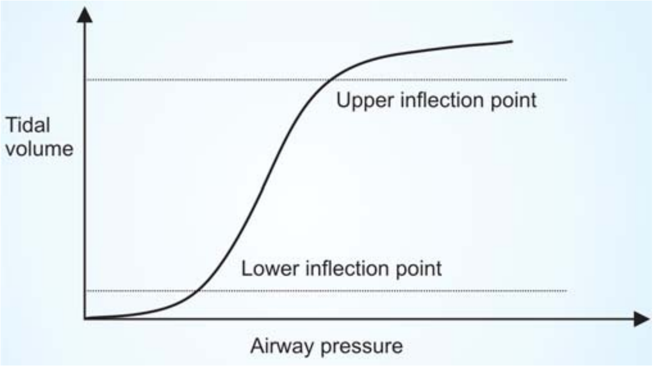

Fig. 131.4: Pressure-volume relationship of the lung. Positive end-expiratory pressure above the lower inflection point prevents the cyclic opening and collapse of alveolar units, while ventilation above the upper inflection point leads to alveolar overdistention and lung injury. Ventilation within these two points can potentially reduce the risk of iatrogenic alveolar injury

Following the Amato study, the low tidal volume ARDSnet trial used a combination of FiO_2 and PEEP designed to maintain a PaO_2 goal of 55–80 mm Hg[38] and no attempt was used to adjust the PEEP based on the pressure-volume curve. The study was therefore not designed to address the PEEP effect on mortality.

In an attempt to answer this question, the ARDS network randomized 549 patients with acute lung injury and ARDS to mechanical ventilation with low (8.3 ± 3.2 cm H_2O) or high PEEP levels (13.2 ± 3.5 cm H_2O).[44] PEEP was set according to different tables of predetermined combinations of PEEP and fraction of inspired oxygen. As with previous trials, the lower inflection point of the pressure-volume curve was not used to set the PEEP levels. Low tidal volume of 6 ml/kg was used in both groups. Survival, ventilator and intensive care unit (ICU)-free days, inflammatory cytokines and rate of hospital discharge were all similar in both groups.

More recently, a French study tried to answer the same question using a different strategy.[45] Patients with ALI, ventilated with a tidal volume of 6 ml/kg of predicted body weight, were randomized to "minimal distension strategy" versus "increased recruitment strategy". In the former, PEEP and plateau pressure were set as low as possible without falling below oxygenation targets (PaO_2 goal of 55–80 mm Hg, or an oxyhemoglobin saturation of 88 to 95%). External PEEP was set to maintain a total PEEP (external + intrinsic PEEP) between 5 and 9 cm H_2O. In the increased recruitment strategy, PEEP was adjusted based on airway pressure and was kept as high as possible without increasing the plateau pressure above 28–30 cm H_2O, regardless of its effect on oxygenation. Even though total PEEP levels were different between groups (8.4 ± 1.9 versus 15.8 ± 2.9 on day 1, $p <.001$), the mortality rates were similar (31.2% versus 27.8%, p=NS). However, the increased recruitment strategy improved lung function and reduced the duration of mechanical ventilation and that of organ failure.

Finally, an international trial assessing the use of high PEEP as part of an "open-lung" strategy in patients with ALI/ARDS,[46] resulted in no significant difference in all-cause hospital mortality or barotrauma compared with an established low tidal volume strategy.

Based on these trials, it appears that high levels of PEEP do not improve survival in patients with ARDS. Since side effects may occur with these high levels, the lowest PEEP that keeps acceptable levels of oxygenation and airway pressure may be used.

Mode of Ventilation

Traditional volume-assist control mode remains widely used in patients with ARDS, whether in daily clinical practice or in most recent large clinical trials.[38,44,45] It has the advantage of being relatively simple and easy to monitor as compared to the newer modalities. No studies have shown an outcome benefit when using newer modes of ventilation.

Airway Pressure Release Ventilation (APRV) is a relatively new modality that has been advocated to be used in ARDS. It is a pressure-targeted, time-cycled mode that shares some similarities with pressure-controlled ventilation, allowing the ability for spontaneous breathing. Studies have shown possible oxygenation benefit over controlled mechanical ventilation in patients with ARDS.[20] Others found a lower incidence of ARDS in trauma patients when ventilated with APRV.[47] However, since it can potentially increase the end-inspiratory stress[48] and therefore can cause volutrauma, more studies are needed to assess its effect on mortality before it could be recommended as a routine modality in ARDS.

Other ventilatory modalities include the use of partial liquid ventilation. Perfluorocarbon is a liquid with characteristics that makes it appealing to use in ARDS. It combines rapidly with gas ventilation and stabilizes alveoli by covering the alveolar lining.[49] It may possess anti-inflammatory properties,[50] and can shift the blood away from dependent regions of the lung.[51] Large doses can cause lung injury with pulmonary edema. Several phase I/II trials have assessed its use, but it should be considered experimental until more definitive studies are done.[20]

Recruitment Maneuvers in ARDS

Recruitment maneuvers involve the application of a high and sustained airway pressure, enough to open collapsed alveoli. This is done in the presence of sufficient PEEP application that will maintain these units open. The goal is to reverse the atelectasis and improve oxygenation. However, the effect on oxygenation has been variable, and the potential for adverse hemodynamic effects is concerning.[20] In addition, no data on outcome in patients with ARDS is available. Therefore, this maneuver cannot be routinely recommended in patients with ARDS.

Noninvasive Ventilation

The use of Noninvasive Ventilation (NIV) in hypercapnic respiratory failure has been shown to decrease the need for intubation, the length of hospital stay as well as the mortality rate.[52,53] Its effect on patients with hypoxemic respiratory failure, including ALI/ARDS, is less clear. When comparing NIV to invasive mechanical ventilation in immunocompetent patients with acute respiratory failure not due to chronic obstructive pulmonary disease, Antonelli found fewer complications and a trend toward better survival in the NIV group.[54] A similar trend toward lower mortality was also seen with bi-level positive airway pressure when compared to usual medical care in patients with hypercapnic and hypoxemic respiratory failure.[55]

When compared to the immunocompetent patients, immunosuppressed patients with ARDS/ALI are at higher mortality risk from ventilator associated pneumonia, approaching 90 to 100%.[56] Therefore, a strategy, such as NIV, that avoids invasive mechanical ventilation could theoretically reduce mortality in this population. In fact, in a randomized trial of intermittent NIV compared with standard treatment with supplemental oxygen and no ventilatory support, Hilbert et al. found that the early initiation of NIV in 52 immunosuppressed patients with pneumonitis and acute respiratory failure was associated with significant reductions in the rates of endotracheal intubation and serious complications.[57] An improved likelihood of survival to hospital discharge was also seen. Significant reduction in the rate of ventilator-associated pneumonia and sinusitis was noted, which is the likely explanation for the observed improvement in mortality.

Based on these studies, it appears that careful patients' selection is a key to success when using NIV in ARDS/ALI. One must use and consider the patients' comorbidities as well as the severity of the respiratory failure when deciding whether to institute NIV or proceed directly to endotracheal intubation with invasive mechanical ventilation.

Fluid Management/Pulmonary Artery Catheter

Fluid management in ARDS is a delicate issue. On one hand, many patients with ARDS have underlying sepsis, may have intravascular fluid deficit and/or may be they are hypotensive. On the other hand, the fact that ARDS is a normal pressure pulmonary edema means that any fluid administration has the potential to worsen the pulmonary edema, increase the alveolar flooding, and decrease the PaO_2/FiO_2. Theoretically, this is a situation where measuring the pulmonary capillary wedge pressure would guide therapy and may result in outcome improvement. Trials have suggested that those ARDS patients who achieve negative fluid balance have improved outcome.[58-60] In addition, excessive fluid administration in trauma-related ARDS patients was associated with increased mortality.[61]

In order to answer the question, the ARDS network conducted a large prospective trial comparing conservative and liberal fluid management strategies, using protocols applied for seven days in 1000 patients with ALI.[62] During the first seven days, the mean cumulative fluid balance was 136 ± 491 ml in the conservative strategy group and 6992 ± 502 ml in the liberal strategy group ($p < 0.001$). As compared with the liberal strategy, the conservative strategy improved the oxygenation index, lung injury score and the number of ventilator-free days. There was no difference in shock, use of dialysis, or in the primary outcome of 60-day mortality (Fig. 131.5). Overall, it was felt that these results support the use of a conservative strategy of fluid management in patients with ALI.

Using the same population in a 2x2 design, Wheeler et al. compared the benefits and the risks of pulmonary-artery catheters (PAC) to those of a central venous catheters (CVC) in ALI.[63] PAC-guided therapy did not improve survival or organ function but was associated with more complications than CVC-guided therapy (predominantly arrhythmias), suggesting that PAC should not be routinely used for the management of ALI (Fig. 131.6).

Other Supportive Therapies

Prone Position

The use of prone position in ARDS consistently results in oxygenation improvement.[64,65] The reason for this improvement is unclear.[20,66,67] Several possibilities have been suggested, including atelectasis reversal, alveolar recruitment, with increased lung volume, decreased shunt fraction and improved ventilation-perfusion mismatch. Other possible mechanisms include the release of the effect of the heart weight on the left lung, and better drainage and clearing of respiratory secretions.

Two recent randomized large trials evaluated the effect of prone on survival. In the first one,[68] Gattinoni randomized 304 ARDS patients to supine versus prone position for a minimum of 6 hours/day. Even though he found a significant improvement in oxygenation in the prone group, there was no difference in survival. In a larger trial enrolling 791 patients meeting criteria for ALI[69] Guerin et al. assessed the effect of prone position, used for atleast 8 hours/day. The 28-day mortality was similar to the control group. Even though the PaO_2/FiO_2 ratio was significantly higher in the prone group, this group has a higher incidence of pressure sores, selective intubation and endotracheal tube obstruction, raising safety concerns regarding this therapy.

At this point, prone position can be used as salvage therapy in ARDS patients with refractory hypoxemia.

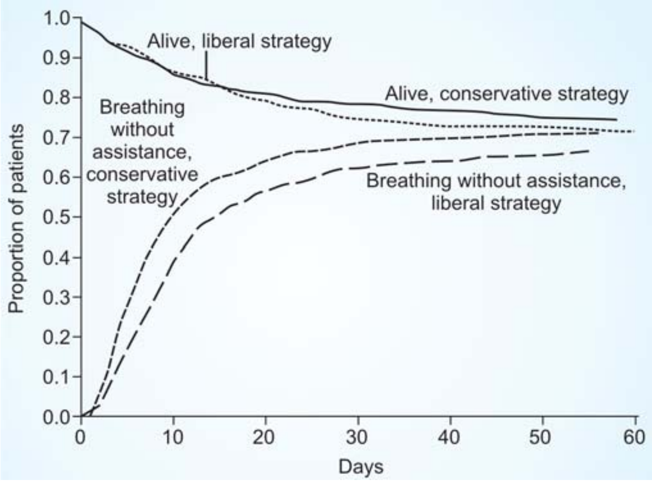

Fig. 131.5: Comparison of two fluid management strategies in ALI: Probability of survival to hospital discharge and of breathing without assistance during the first 60 days after randomization (Adapted with permission from Wiedemann et al)[62]

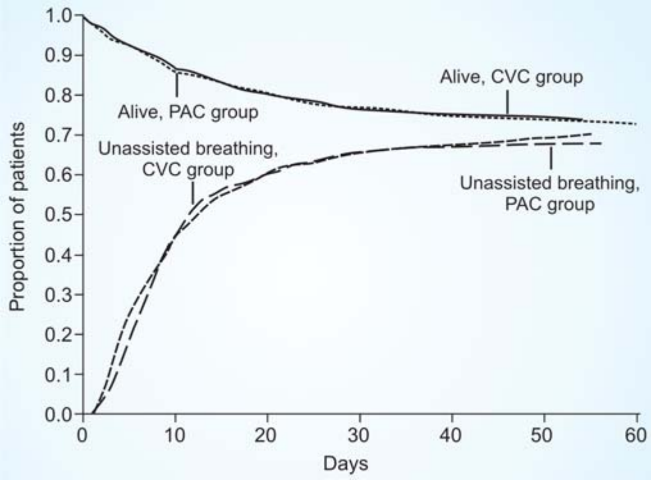

Fig. 131.6: Pulmonary artery versus central venous catheter to guide treatment of ALI: Kaplan-Meier estimates of the probability of survival and of survival without the need for assisted ventilation during the first 60 days after randomization (Adapted with permission from Wheeler et al)[63]

Current evidence do as not support its routine use in all patients with ARDS/ALI, especially that a survival benefit has not been demonstrated and the potential for side effect is concerning. Whether different approaches involving longer proning duration or better patients' selection could lead to a reduction in mortality remains an open question. Further studies are inevitably needed to try to answer it.

Inhaled Nitric Oxide (iNO)

Inhaled nitric oxide is a powerful vasodilator. When used in patients with ARDS, it has the potential to improve the ventilation-perfusion mismatching, with reduction in the pulmonary vasoconstriction and hypertension seen in those patients.[70] It is rapidly deactivated by the hemoglobin and therefore, has practically no systemic effects.[71] The effect of iNO on oxygenation is dose dependent, with maximal improvement seen between 1 and 10 parts per million (ppm).[72]

The use of iNO was evaluated in multiple clinical trials,[73,74] with some combining it with the use of prone position.[75,76] Using a low dose (5 ppm) in patients with ALI (defined as $PaO_2/FiO_2 < 250$) not due to sepsis and without evidence of nonpulmonary organ dysfunction, Taylor found an improvement in the oxygenation within the first 24 hours of therapy, an effect that was lost after two days of treatment.[73] There was no effect on mortality rate or duration of ventilatory support. Similar results were found by other investigators.[74] When combined with prone position, an additive effect on oxygenation was seen, but no firm data on survival is available.[75,76]

In clinical practice, as with any salvage therapy in ARDS, iNO may be utilized in patients with refractory hypoxemia, keeping in mind that the beneficial effect is likely to be time limited.

Surfactant Therapy

As mentioned previously, the surfactant composition and function is affected in patients with ARDS.[23,77,78] Therefore, replacement therapy is an appealing modality, with animal models showing improvement in gas exchange.[79] In addition, survival of neonates with ARDS was improved with the use of surfactant.[80]

Several studies evaluated surfactant therapy in adults with ARDS. Evaluating a nebulized synthetic surfactant in a placebo-controlled trial involving 725 patients with sepsis-related ARDS, Anzueto et al. found no effect on oxygenation, length of stay in the intensive care unit, duration of mechanical ventilation or survival. Results of this study may have been affected by the low dose used (5 mg/kg/d).[81] On the other hand, another trial showed significant and rapid improvement in the PaO_2/FiO_2 when natural bovine surfactant extract was administered bronchoscopically, also in sepsis-induced ARDS.[82] Finally, two randomized, double-blind trials involving 448 patients with ARDS from various etiologies, evaluated up to four intratracheal doses of a recombinant protein C-based surfactant given within 24 hours of enrollment.[23] Oxygenation improved significantly in the first 24 hours, but the benefit was lost after 48 hours of treatment. There was no benefit in terms of the 28-day survival or in the number of ventilator- free days.

Therefore, it appears that surfactant replacement may have the potential to improve oxygenation in ARDS, but no effect on mortality is yet demonstrated. However, more studies are needed to control for several variables, including the type of surfactant used, the route of administration (Nebulized versus bronchoscopic) and the duration of therapy.

Steroids

The use of steroids in ARDS has been one of the most controversial issues over the last several decades. As powerful anti-inflammatory agents, it is reasonable to expect some beneficial effect in such an intense inflammatory milieu.

In studies performed in the 1980s, high dose steroids in the early stage of ARDS proved to be ineffective.[83, 84] Revisiting this issue, a recent randomized, double-blind, placebo-controlled trial evaluated the use of methylprednisolone infusion (1 mg/kg/d up to 28 days) in severe early ARDS ($\leq$72 hours).[85] Treatment with steroids was associated with a reduction in the duration of mechanical ventilation, ICU stay and ICU mortality (20.6% versus 42.9%; $p=0.03$). Interestingly, treated patients had a lower rate of infections ($p = 0.0002$).

In terms of steroid use in the late proliferative phase of ARDS, several case series were reported.[86-88] In 1998, Meduri published the results of a randomized controlled trial assessing the effect of prolonged methylprednisolone (initial dose at 2 mg/kg/day, and duration of treatment of 32 days), in 24 patients with nonresolving ARDS.[89] The hospital-associated mortality was significantly lower in the methylprednisolone group (12% versus 62%, $p=0.03$). Meduri's study was criticized due to the relatively low survival rate in the placebo group.

In order to answer the question of steroids in late ARDS, the ARDS network conducted a multicenter trial comparing high-dose methylprednisolone to placebo in 180 patients. There was no survival benefit in the steroid group (29.2% versus 28.6%, p=1.0), despite a significant improvement in lung mechanics, gas exchange and ventilator-free and shock-free days. Methylprednisolone did not increase the rate of infectious complications but was associated with a higher rate of neuromuscular weakness.

Finally, a recently meta-analysis of selected trials showed that prolonged administration of systemic steroids is associated with favorable outcomes and survival benefit when given before day 14 of ARDS.[90]

In conclusion, the use of steroid in ARDS remains controversial at best. Any possible benefit should be weighted against the potential for adverse effects including infections and neuromuscular weakness.

Protein C

Activated Protein C (APC) has anti-inflammatory, antithrombotic and fibrinolytic activities.[91] Replacement in ALI was advocated after its levels were found to be decreased in patients with ALI/ARDS.[92] It was also associated with higher mortality rate and less ventilator-free days. However, a recent randomized placebo-controlled trial failed to show a beneficial effect, with no difference in the 60-day mortality or the number of ventilator-free days in ALI patients receiving placebo or APC.[93]

Prognosis and Outcome

The outcome of patients with ARDS depends primarily on the underlying cause of lung injury. Survival to home discharge appear to be lowest in patients with sepsis and highest in patients with trauma and ARDS.[8] Until recently, the mortality ranged from 40 to 60%, with the majority of deaths being related to sepsis and nonrespiratory organ dysfunction.[5] More recent reports suggest that the mortality may be decreasing.[38,44,45,94] Reasons for this improvement are not entirely clear, but are likely related to the use of low tidal volume, better supportive care and better management of sepsis.

Predictors of death include chronic liver disease, nonpulmonary organ dysfunction, age and sepsis. Initial oxygenation and ventilation indices do not predict outcome.[5]

Even though the 28-day mortality has been a traditional primary end-point in studies of ARDS, following patients for up to 1 year shows that a significant percentage of deaths actually occurs beyond the 28-day cutoff,[95] raising the potential need for longer monitoring when evaluating new interventions or therapies. Anxiety, depression and posttraumatic stress disorder were frequent in this study, while predictors of mortality included age, sepsis, extrapulmonary organ failure and the premorbid functional status. In addition, patients with ARDS lose a significant amount of weight during their hospitalization, averaging around 18%.[96] Most recover their weight gradually, but remain below their admission weight at 12 months. Proximal muscle weakness and a decrease in 6-minute walk test are common. Radiographic abnormalities remain present in 80% of cases at 12 months. Mild restrictive pattern is seen at three months, gradually improving with most values back within normal limits at 12 months. Oxygen requirement is uncommon after 12 months.

Longer follow-up showed that ARDS can result in significant neurocognitive and emotional morbidity and decreased quality of life that persists at least two years after hospital discharge.[97]

CONCLUSION

ARDS continues to be one of the major challenges facing modern critical care medicine in the 21st century. Major advances have been achieved in the last few years in terms of understanding the syndrome, but translating this knowledge into improved outcome has proved more challenging than initially thought. Except for the low tidal volume strategy, no intervention was shown to be unequivocally effective in reducing mortality. Nevertheless, several salvage therapies are available (e.g. iNO, prone position, etc.), with relatively good impact on oxygenation. One should use them only in patients with refractory hypoxemia and even though the quality of clinical trials has improved over the last decade, further studies are still needed to advance our understanding of this syndrome and to translate that understanding into reduced morbidity and mortality.

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Sepsis

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INTRODUCTION

Sepsis has been acknowledged as an entity since the time of Hippocrates. Without knowing of the cause of sepsis, or even the significance of the accompanying fevers, early treatments had little chance. Progress made by scientists in the 19th and early 20th centuries provided a new therapeutic target when they discovered the link between microorganisms to sepsis, though the impact remained unacceptably high despite the use of antibiotics. Throughout the 20th century, our knowledge of sepsis proliferated with the understanding that its deadly nature was not necessarily due to the illness-causing pathogens, but the disproportionate inflammatory response of our own immune systems to those pathogens. We then understood that the mechanisms that protected us from overwhelming infection on a daily basis could be turned against us to cause organ failure and death. Unfortunately, attempts to alleviate the devastating effects of sepsis with the use of powerful immunosuppressants did not have the impact we had hoped for.

Today, despite rapidly advancing research about the mechanisms of sepsis and septic shock, it remains a leading cause of death. We now have a vast armamentarium of weapons against sepsis, from simple hydration and antibiotics to medications directed at molecular targets. Yet the burden of sepsis remains unacceptably high and it is highest in parts of the world where resources may be limited, without access to the newest treatments. The good news is that many of the therapies directed at reducing mortality due to sepsis are readily available and effective when used in the appropriate manner. Most recent research suggests that an organized, systematic approach to the diagnosis and treatment of sepsis is the key to success. In that light, many suggested guidelines exist, which can be altered to suit the needs and resources of developing countries.

Definition

The term *sepsis* is derived from the Greek word for "putrefaction".[1] Our first recorded uses of the word come from Hippocrates, Aristotle and the poet Homer.[2] As our understanding of the process behind the word changed, so did the definition of the word. In 1914, we were introduced to the concept that had guided our ideas about sepsis over the past century: the systemic symptoms of sepsis were due to pathogens in the bloodstream.

The most commonly used definition of sepsis came from a consensus conference sponsored by the American College of Chest Physicians (ACCPs) and the Society of Critical Care Medicine (SCCM) in 1992.[3] Four important definitions were presented from this conference: the Systemic Inflammatory Response Syndrome (SIRS), sepsis, severe sepsis and septic shock (Table 132.1); additionally the concept of the Multiple Organ Dysfunction Syndrome (MODS) was introduced. As the name suggests, SIRS constitutes the systemic inflammatory response, due to infection, trauma, burns or other causes. The term sepsis is used to describe SIRS that is due to an infection. Noninfectious SIRS can progress similarly to sepsis, but is treated differently, so will not be discussed here. When sepsis progresses to cause organ dysfunction, hypo-perfusion or hypotension, it is severe sepsis. The final stage in the progression of sepsis is septic shock, which is sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities. The natural progression of severe sepsis and septic shock lead to irreversible organ failure and death. These definitions remain widely used in both clinical medicine and research settings, though the sponsoring organizations have abandoned them as obsolete.

In 2001, the ACCP and SCCM joined with the European Society of Intensive Care Medicine, the American Thoracic Society, and the Surgical Infection Society to update the definitions.[4] This scheme maintains a similar structure, referring to SIRS, sepsis, severe sepsis and septic shock (Table 132.1). The major update is a much broader definition of SIRS to more closely reflect the experience of the bedside clinician caring for a patient that "looks septic". The new list of signs and symptoms includes many more physical examination and laboratory findings than in the previous definition. This updated version is less useful for research purposes, since the definitions are more imprecise, but designed to assist the practicing clinician. The new definition of sepsis also does not require an infection to be confirmed if it is strongly suspected clinically. The definitions of severe sepsis and septic shock remain essentially unchanged. A staging system, intended to be used to stratify patients based on their baseline risk for adverse outcomes and their potential to respond to therapy. It is known as the PIRO system, which stands for Predisposition, Insult or Infection, Response, and Organ dysfunction. While useful in certain circumstances, the staging system has not gained the same popularity as the classification structure listed in Table 132.1.

Epidemiology, Outcomes and Costs

The impact of sepsis throughout the world is costly in the terms of lives lost and the financial burden on the society. Many of the recent studies examining the epidemiology of severe sepsis and septic shock have been based in the United States,[5,6] Europe,[7-11] or Australia/New Zealand.[12] Based on these studies, the estimated incidence of sepsis is 50–100/100,000 of these populations, though the most recent of these studies[11] reported an incidence of 25/100,000 in a limited Spanish population. The absolute incidence of sepsis in the US is estimated to be 750,000 cases per year. Severe sepsis and septic shock accounted for 12 to 27% of intensive care unit (ICU) admissions in these studies, and mortality rates ranged from 35 to 56% at one month. The mean ages reported were 59–65, and infection was confirmed with positive cultures in less than 75% of the cases. The incidence of sepsis is expected to rise in the years to come, due to the practice of performing more invasive procedures and increased immunosuppression.

The epidemiology of sepsis in developing countries is less defined. Two recent studies have investigated the incidence, outcomes and costs of sepsis in Brazil.[13,14] The incidence density of all categories of sepsis in five ICUs was calculated as approximately 57 per 1,000 patient days, which was generally higher than that reported in industrialized nations. The mean age of patients with sepsis was similar to the other studies. The respiratory tract was the most common site of infection. The mortality rates for patients with sepsis, severe sepsis and septic shock were 34, 47 and 52%, respectively. The median daily ICU cost of a septic patient in Brazil was found to be $934 US. Interestingly, despite similar total costs, length of hospital stay, and admission illness severity, patients at private hospitals had significantly better mortality rates than those at public institutions.

The World Health Organization[15] does not specifically track sepsis statistics. However, there is data regarding the epidemiology and outcomes of infectious diseases overall. While it is impossible to separate the specific causes of morbidity or death due to infectious diseases (as severe diarrhea may lead to dehydration or meningoencephalitis may cause a CNS insult without systemic inflammation), these numbers can give us a general idea of the relative impact sepsis may have in developing areas of the world. Figures 132.1A and B show the incidence of infectious diseases (excluding HIV seropositivity), and the morbidity and mortality due to those infectious diseases. While the overall numbers do not appear remarkably different relative to one another, simple calculations reveal that the death rate per infection is higher in low and lower-middle income countries (1 in 436) than the worldwide rate (1 in 453), and the rate in the Southeast Asia Region (SEAR) (1 in 379) is even higher than that. The significance of this statistic is unclear, though if sepsis is considered to be a major contributor to these deaths, limited resources presumably play a role in the higher mortality rate.

Pathogenesis

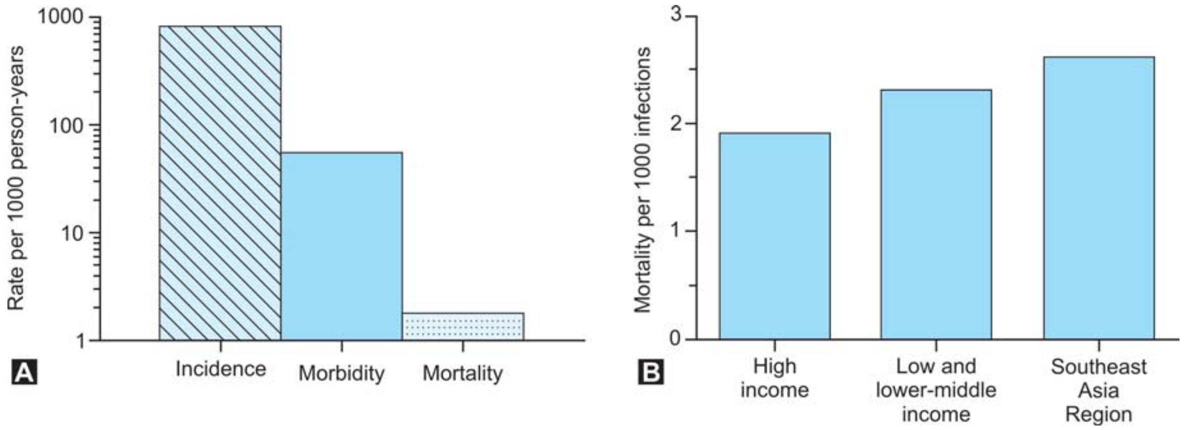
By definition, sepsis is the result of one or more pathogens invading the body and causing infection. The most common causes of sepsis worldwide are bacterial agents (93%). Sepsis can also result from viruses, fungi and protozoa (Table 132.2); in fact, almost any pathogen that causes infection can result in sepsis. When considering the likely etiology of sepsis in an individual patient, it is important to consider the prevalent

TABLE 132.1: Definitions of sepsis

*1992 Consensus Committee**	*2001 International Sepsis Definitions Conference*[†]
SIRS Two or more of the following in response to an insult: 1. Temperature >38°C or <36°C 2. HR >90 beats per minute 3. RR >20 breaths per minute or PaCO$_2$ <32 mm Hg 4. WBC count >12,000 per mm^3 or <4,000 per mm^3 or >10% immature band forms	SIRS "Some" of the following: 1. General variables a. Core temperature >38.3°C b. Core temperature <36°C c. Heart rate >90 per minute d. Tachypnea e. Altered mental status f. Significant edema or positive fluid balance (>20 mL/kg over 24 hr) g. Plasma glucose >120 mg/dL in the absence of diabetes 2. Inflammatory variables a. WBC count >12,000 per μL b. WBC count <4000 per μL c. Normal WBC count with >10% immature forms d. Plasma C-reactive protein >2 SD above the normal value e. Plasma procalcitonin >2 SD above the normal value 3. Hemodynamic variables a. Arterial hypotension (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg) b. SvO$_2$ >70% c. Cardiac index >3.5 L/min/m^2 4. Organ dysfunction variables a. PaO$_2$/FIO$_2$ <300 b. Urine output <0.5 mL/kg per hr for at least 2 hr c. Creatinine increase >0.5 mg/dL d. INR >1.5 or aPTT >60 sec e. Absent bowel sounds f. Platelet count <100,000 per μL g. Plasma total bilirubin >4 mg/dL 5. Tissue perfusion variables a. Lactate >1 mmol/L b. Decreased capillary refill or mottling
Sepsis The systemic response to infection: 1. SIRS and 2. Documented infection	Sepsis 1. SIRS and 2. Documented or suspected infection
Severe sepsis Sepsis associated with organ dysfunction: 1. Sepsis and 2. One of the following: a. Sepsis-induced hypotension (SBP <90 mm Hg or reduction by ≥ 40 mm Hg from baseline in the absence of other causes of hypotension) or b. Lactic acidosis or c. Oliguria or d. Acute alteration in mental status	Severe sepsis Sepsis complicated by organ failure: 1. Sepsis and 2. Organ dysfunction (see SIRS 4)
Septic shock Severe sepsis and one of the following despite adequate fluid resuscitation: 1. Sepsis-induced hypotension (see Severe sepsis 2a) 2. Requirement of vasopressor or inotropic therapy	Septic shock Acute circulatory failure due to sepsis: 1. Sepsis and 2. Persistent arterial hypotension (see SIRS 3a) despite adequate volume resuscitation and 3. No other cause of hypotension

* From ref. 3. Reprinted with permission from the American College of Chest Physicians

[†] From ref. 4. Reprinted with permission from Wolters Kluwer Health



Figs 132.1A and B: **Impact of infectious diseases worldwide in 2004, as reported by the World Health Organization.** (A) The worldwide incidence, morbidity in disease-adjusted life years, and mortality rates due to infection (excluding HIV) are depicted. All values are reported in rate per 1,000 person-years. (B) The mortality rate relative to infection rate is shown in high income, low and lower-middle income countries, and the Southeast Asia region

TABLE 132.2: Representative causative agents of sepsis

Bacteria

Gram-positive
- *Staphylococcus aureus*
- Coagulase-negative *Staphylococcus*
- *Streptococcus*
- *Enterococcus*
- *Listeria*
- *Nocardia*
- *Peptostreptococcus*
- *Peptococcus*
- *Clostridium*
- *Corynebacterium*

Gram-negative
- *Pseudomonas*
- *E. coli*
- *Proteus*
- *Enterobacter*
- *Klebsiella*
- *Haemophilus*
- *Neisseria*
- *Moraxella*
- *Salmonella*
- *Shigella*
- *Vibrio*
- *Yersinia*
- *Bacteroides*
- *Fusobacterium*
- *Bordetella*

Mycobacteria
- Tuberculosis
- Non-Tb mycobacteria

Contd...

Contd...

Viruses
- Influenza
- Herpes simplex virus
- Respiratory syncytial virus
- Cytomegalovirus
- Varicella-zoster virus
- Parainfluenza
- Enterovirus
- Adenovirus
- Measles
- Dengue
- Parvovirus B-19

Fungi
- Candida *albicans*
- Non-albicans *Candida*
- Aspergillus
- *Cryptococcus*
- *Histoplasma*
- Coccidioides
- Mucor

Protozoa
- Plasmodium
- Babesia
- Leishmania
- Toxoplasma
- Filaria
- Paragonimus
- Schistosoma
- Entamoeba

pathogens in the region, the setting in which the infection was acquired (outpatient, hospital or ICU), and host factors, including immunosuppression, comorbidities, medications, lifestyle and travel. All of these factors will narrow or broaden the list of potential causative agents. It is clear from Figure 132.1 that the vast majority of infections do not lead to significant morbidity or death. There are clearly host abnormalities, which lead to sepsis that do not depend entirely on the invading organism. The expression of toxins from invading pathogens, such as lipopolysaccharide (LPS) or staphylococcal toxic shock syndrome toxin 1 (TSST-1), or release of molecules from damaged host tissues are thought to act as triggers for sepsis. These molecules are known as damage-associated molecular patterns (DAMPs) and are recognized by toll-like receptors (TLRs) on neutrophils, macrophages and other innate immune cells.[16] Early sepsis is characterized by the activation of $CD4^+$ Th1 cells and the release of proinflammatory mediators, leading to systemic inflammation and SIRS.

The propagation of sepsis is complicated, involving multiple systems and pathways (Fig. 132.2), with resulting end-organ damage.[16-18] Innate immune cells also activate complement C5a, with the resulting activation of the complement cascade. The complement cascade not only augments the inflammatory response, but is also involved in a complex feedback loop with both the intrinsic and extrinsic coagulation pathways. The

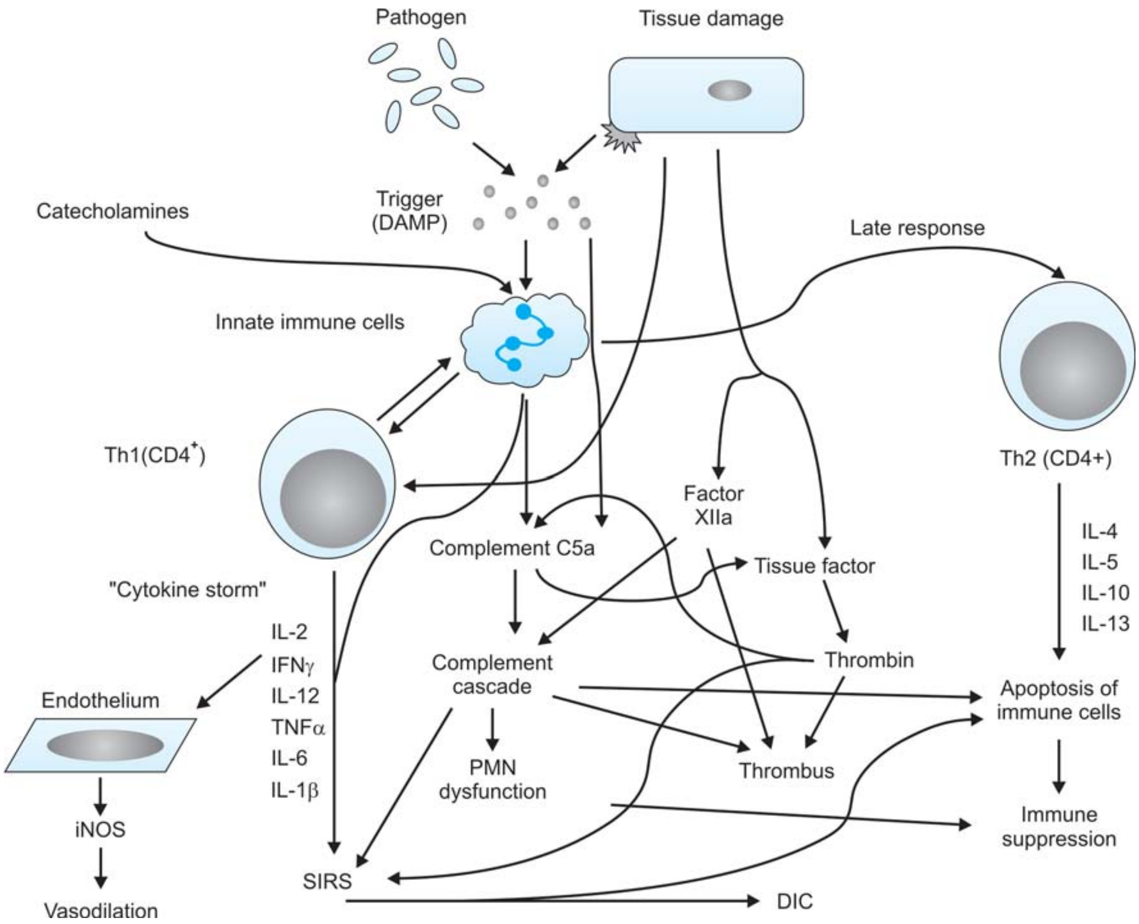

Pathogen
Tissue damage
Trigger (DAMP)
Catecholamines
Late response
Innate immune cells
Th1(CD4+)
Th2 (CD4+)
Factor XIIa
Complement C5a
Tissue factor
"Cytokine storm"
IL-2
IFNγ
IL-12
TNFα
IL-6
IL-1β
IL-4
IL-5
IL-10
IL-13
Endothelium
Complement cascade
Thrombin
Apoptosis of immune cells
PMN dysfunction
Thrombus
iNOS
Immune suppression
SIRS
Vasodilation
DIC

Fig. 132.2: **The pathologic immune response in sepsis.** Sepsis is initiated by molecules expressed by pathogens and released by damaged host tissue, which stimulate the innate immune cells (neutrophils, macrophages, monocytes and dendritic cells). The early response of sepsis is characterized complex interactions between the proinflammatory adaptive immune system, complement cascade, and the intrinsic and extrinsic coagulation cascades. The late response is characterized by an anti-inflammatory response by the adaptive immune system, and immune cell dysfunction and apoptosis, resulting in an immunosuppressed state.

DAMP: damage-associated molecular patterns; Th1 and Th2: T helper lymphocytes, subtypes 1 and 2; $CD4^+$: expression of CD4 glycoprotein surface marker; PMN: polymorphonuclear lymphocytes or neutrophils; SIRS: systemic inflammatory response syndrome; DIC: disseminated intravascular coagulation; iNOS: induced nitric oxide synthetase.

coagulation cascades themselves are activated by the damaged tissues that triggered the sepsis in the first place, and uncontrolled activation results in microvascular thrombosis, inhibited fibrinolysis, and disseminated intravascular coagulation (DIC). Activated thrombin can promote the inflammatory pathway, providing another feedback loop. Unchecked systemic inflammation increases intrinsic nitric oxide synthetase activity in endothelial cells, resulting in arterial vasodilation and hypotension. This hypotension is initially counteracted by the release of catecholamines by adrenergic cells. Catecholamines also function to further activate leukocytes. Conversely, the stimulation of the vagus nerve will suppress inflammation through the activation of nicotinic acetylcholine receptors on macrophages. The result of the combination of systemic inflammation, cytokine storm, arterial hypotension, and DIC is often multiple organ dysfunction and failure.

The late phase of sepsis is characterized by immunosuppression. Previously activated Th1 cells evolve into $CD4^+$ Th2 cells, with the production of anti-inflammatory cytokines. Persistent inflammation and activation of the complement cascade result in apoptosis of immune cells, neutrophil dysfunction, hypothermia and anergy. In the immunosuppressed state, the host is no longer able to fight off infection and is susceptible to nosocomial infections. Apoptosis also occurs in other systems, including the adrenal medulla. As adrenal medullary cells are lost, catecholamine function decreases and arterial hypotension becomes more pronounced. A similar process may also lead to adrenal insufficiency. As the sepsis resolves, the immunosuppressed state will eventually recover. In patients with severe baseline comorbidities however, the immunosuppression may progress, with resulting death.

Clinical Features and Evaluation

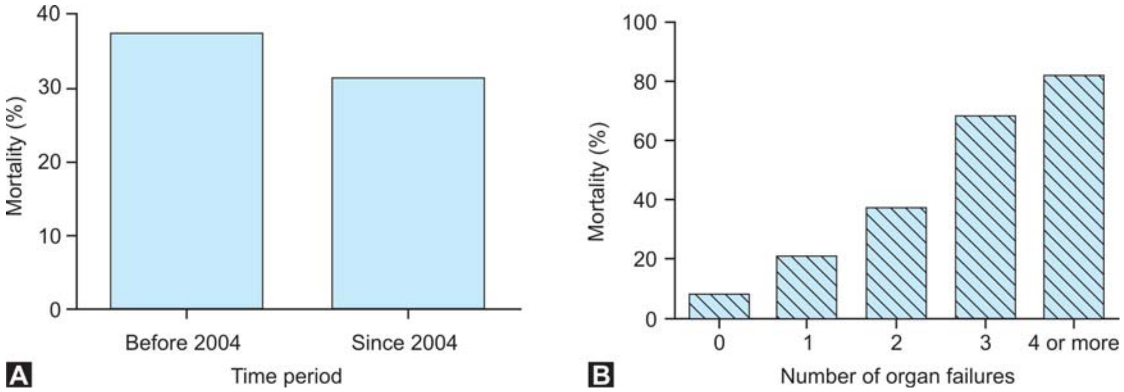
The patient with sepsis will often present with the symptoms of SIRS. The signs of SIRS are summarized in the report from the 2001 International Sepsis Definitions Conference (see Table 132.1). In general, these patients may complain of fever or chills, fatigue, malaise, anorexia, and sometimes complaints specific to the source of infection. Whether or not there are complaints reflecting organ dysfunction, such as confusion or poor urine output, the clinician must always be aware of these signs, which can reflect progressing sepsis. Physical examination findings should always begin with vital signs and a general impression of the patient. Septic patients will show vital signs reflective of SIRS, including fever or hypothermia, tachycardia, tachypnea, and possibly hypotension. In the general impression, there will be useful information that can provide a snapshot of the patient's overall condition, as well as the premorbid status. This impression will be important in assessing the level of care a patient will require; be aware that some patients' general appearance may not reflect the true extent of their illness. The remainder of the physical examination will vary, depending on the source of infection. The physical examination may be unrevealing in this regard, especially in the elderly or immunocompromised patient population, so laboratory and imaging must be relied on.

Basic laboratory data can help in the diagnosis of sepsis and organ dysfunction. These basic investigations should include a complete and differential blood counts, chemistry panel, including glucose, liver function tests and coagulation tests. Other diagnostic tests may be clinically indicated for initial diagnosis, including serum C-reactive protein, procalcitonin and serum lactate. Work-up to determine the source of sepsis will be directed by the patient history and physical examination, and may include urinalysis, chest and/or abdominal imaging, and lumbar puncture, depending upon the clinical situation.

Physical examination and laboratory evidence of organ dysfunction and failure will be seen in a significant proportion of septic patients. Any organ system can show the effects of sepsis, and mortality increases with the number of organ systems affected. Table 132.3 provides a summary of some of the findings that can be seen in organ system dysfunction. In cases where specific treatments are available, the appropriate clinical evaluation should be undertaken.

Cultures will ideally be drawn prior to the initiation of antibiotics, but only if it will not delay the dosing of antibiotics. Cultures should be taken from the blood and from the presumed site of infection. If the site of infection is unknown, cultures from multiple sites may be taken, which may eventually reveal the source. A minimum of the two sets of blood cultures can be obtained, at least one from each vascular access catheter in place. If the source is an abscess, deep tissue infection, or a mechanical device, cultures can be sent from the surgical or drainage specimens, once obtained. The rate of microbiological confirmation of infection has been reported to be in the range of 58 to 76%,[11,12,19-21] so the diagnosis of sepsis should not be discounted if infection is still strongly suspected.

More invasive monitoring may be indicated in the cases of severe sepsis or septic shock to guide therapies. Arterial blood gas assessment is required in patients with



Figs 132.3A and B: Predicted mortality rates due to sepsis. (A) The overall mortality rate due to sepsis has decreased since the launch of the Surviving Sepsis Campaign in 2004, in those adhering to the established protocols for the treatment of sepsis. (B) Predicted mortality due to sepsis and septic shock, based on the number of failed organs or organ systems

acid-base disorders and more frequently in mechanically ventilated patients. Patients with hypotension will most likely need invasive blood pressure monitoring, which may require arterial catheterization. Central venous and pulmonary artery catheterization may also be required to monitor the mixed venous (SvO_2) or central venous ($ScvO_2$) oxygen saturation, or Central Venous Pressure (CVP).

Prognosis

The prognosis of sepsis, uncomplicated by organ dysfunction or septic shock can be cause for optimism. With progression of sepsis to severe sepsis and septic shock portends escalating mortality. The severity of a septic episode is often graded by the number and type of organ dysfunction or failure.[4,22-25] There is a mortality risk associated with most individual organ failures (Table 132.3), which may or may not improve with specific treatment.[20,26-42] Additionally, studies have consistently shown an escalating mortality rate associated with a higher number of concurrent organ system failures (Figs 132.3A and B), suggesting that Multiple Systems Organ Failure (MSOF) may represent a final common pathway leading to death.

Likewise, the baseline health characteristics of an individual patient play an important role in that patient's ability to recover from a serious insult. One theory suggests that a healthy, young patient with sepsis will mount a strong immune response, followed by a transient hypoimmune state, and then recovery. Meanwhile, a septic elderly patient with multiple pre-existing dysfunctional organs will only mount a minimal inflammatory response, with a prolonged immunodepressed state, possibly followed by death.[17]

Multiple ICU scoring systems have been developed to assist the clinician in medical evaluation and treatment decisions in critically ill patients[22-24,43,44] (Table 132.4). The APACHE II remains perhaps the most widely used scoring system, mostly due to the vast literature based on this system and the availability in the public domain free of cost. The scoring system assigns points for 12 acute physical examination or laboratory findings, as well as age and chronic health; the higher the sum of the points, the higher the predicted mortality.[43] The APACHE II score is currently recommended to determine the suitability of potentially harmful treatments in septic patients.[45] Other scoring systems, such as the MODS and SOFA systems each assign points (0–4) based on the degree of acute dysfunction in six systems. Again, higher sums predict higher mortality. Other scoring systems also exist for use in septic patients, each with advantages and disadvantages.

Management

As demonstrated in Figure 132.1, the multiple cascades responsible for the propagation of sepsis are intertwined to the point that the interruption of the process, once started, is nearly impossible with a single therapy. The ideal treatment would target a common pathway or several pathways at once. More practical is the use of several agents at the same time, in a strategic manner, to stop or slow the progression at several key points. The past decade has produced significant advancement in the development of the systematic protocols necessary for the effective management of sepsis.

TABLE 132.3: Organ systems affected in severe sepsis and septic shock

Organ system	*Clinical manifestations*	*Associated mortality*	*Management (in addition to supportive care)*
Nervous system	Encephalopathy	24%	Sedation, stimulus control
	Critical illness neuromyopathy	21-55%	Avoid aggravating medications (neuromuscular blockade, corticosteroids)
Respiratory	ALI, ARDS, hypoxemic respiratory failure	21-47%	Oxygen, mechanical ventilator support
Cardiovascular	Hypotension, tachycardia	28-43%	Vasopressors, inotropes, mechanical CV support
	Myocardial injury and dysfunction	29-48%	
Kidneys	Olig- or anuric AKI	15-46%	Electrolyte management, renal replacement therapy
Hematologic	Cytopenias	23-53%	Blood product transfusions
	Coagulopathy	17-51%	
	Microvascular thrombosis/DIC	43-50%	Activated protein C
Gastrointestinal	Shock liver, acute hepatic failure, hyperbilirubinemia	14-54%	Avoidance of hepatotoxic agents
	Ileus	Not defined	Bowel rest, parenteral nutrition
Endocrine	Hyperglycemia	22-53%	Insulin
	Adrenal insufficiency	25-80%	Glucocorticoids
	Thyroid hormone abnormalities	44-62%	Generally none (in sick euthyroid), other abnormalities may require specific treatment
Skin	Rash, wounds	Varies by cause	Wound care, prevent superinfection

TABLE 132.4: Scoring systems applicable to sepsis

Scoring system	*Description*	*Advantages*	*Disadvantages*
GCS (Glasgow Coma Score)	Neurologic scale (3-15) to assess level of consciousness	Simple; applicable to all trauma and medical patients; used in other scoring systems	Single organ system
APACHE II (Acute Physiology and Chronic Health Evaluation)	Calculated (0-71) within 24 hrs of admission using common physiologic and demographic data, and prior health status	Widely used; online scoring systems; can assist in treatment decisions	Imprecise in predicting the mortality of a single patient; revised (APACHE III) in 1991
SOFA (Sepsis-related / Sequential Organ Failure Assessment)	Calculated (0-24) based on degree of organ failure in 6 systems	Can be calculated sequentially in the same patient	Multiple possible comparisons (admission, maximum, change in maximum), not one standard
MOD (Multiple Organ Dysfunction) score	Calculated (0-24) based on degree of organ failure in 6 systems	Can be calculated sequentially in the same patient	Complicated CV measures; similar to but less prevalent than SOFA
SAPS II (Simplified Acute Physiology Score)	Calculated on 17 variables after 24 hours, using common physiologic and demographic data and prior health status	Can be used in a variety of diseases; compare the morbidity of a patient/group to others	Imprecise in predicting the mortality of a single patient; revised (SAPS III) in 2005

Antibiotics and Infection Source Control

The effective use of proper antibiotics is the only therapy that can truly stop sepsis before it gets going. Antibiotics, if given early, will either destroy or halt the replication of the pathogen, and in some cases will also absorb the toxins released. The antibiotic selection must be appropriate for the clinical situation, however. Several studies have examined the effect of the initial antibiotic regimen in septic patients.[46,47] In all cases, mortality was increased in patients that had delays in getting appropriate antibiotics for the pathogen that was eventually isolated. In the septic population, the appropriate initial antibiotic is any antibiotic that will target the causative pathogen. There are few cases where the microbiologic answer is available immediately. A suggested strategy is to administer a regimen of antibiotics that will broadly cover most, if not all, of the microbes to which the individual patient is at risk, based on medical history, personal habits, and the endemic pathogens. Once the organism has been isolated, the antibiotics can be titrated as appropriate. Rapid identification of the organism may be accomplished by examining a stain, such as a Gram stain, of the body fluid, later confirming the isolate with culture.

In some cases, antibiotics alone will not be enough to clear the infection without additional intervention. Some examples of this scenario include abscess formation, deep-seated skin/soft tissue infections, and infected mechanical devices. Abscesses may be present in a septic patient with no identifiable source of infection. Drainage of the abscess may be needed to clear the infection completely. Likewise, deep-seated infections often require debridement. In these cases, the appropriate intervention should be considered, provided the clinical situation allows for such a procedure. Mechanical devices sometimes present a therapeutic dilemma. Every attempt should be made to remove the infected foreign body from the patient, allowing the antibiotics to clear the infection, though that approach is not always practical. In such circumstances, improvisation is necessary, often requiring long-term treatment and close monitoring. Intravascular access devices should also be removed, especially in the case of documented bloodstream infections.

Hemodynamic Support and Monitoring

Sepsis-induced hypotension is caused by a number of factors, which result in intravascular hypovolemia and arterial vasodilation. The goal of correcting hypotension is to maintain adequate tissue perfusion. Tissue perfusion can be assessed by serum lactate, end-organ function, and SvO_2 (SvO_2 can be approximated by $ScvO_2$ minus 5%). Lactate clearance and $ScvO_2$ are similar in demonstrating tissue hypoperfusion and guiding treatment decisions.[48] If there is evidence of hypotension or tissue hypoperfusion, aggressive rehydration should be initiated immediately. In septic patients, intravenous fluid administration is the method of choice to achieve rehydration. Isotonic crystalloid solutions, such as normal saline or lactate Ringer's solution, have been shown to be as safe and effective as colloid solutions, such as albumin, dextran or hydroxyethyl starch, in critically ill patients.[49,50] Additionally, there has not been any difference demonstrated between various crystalloids or between any of the colloid solutions.[51] As soon as tissue hypoperfusion is documented, intravenous (IV) crystalloids should be administered in bolus fashion, 20 mL/kg or 500–1000 mL (or the colloid equivalent) over 20–30 min each, to achieve a CVP of 8–12 cm H_2O (12–15 cm H_2O if mechanically ventilated).

If the blood pressure remains low (MAP <65 mm Hg) after adequate fluid resuscitation, vasopressor therapy is indicated. The agents of choice in septic shock are dopamine and norepinephrine. Both agents activate catecholamine receptors, can be titrated to achieve a goal MAP ≥65 mm Hg, and are equally effective in septic shock.[52,53] These vasopressors can be used concurrently if the primary medication is at its maximum dose. Second line agents include phenylephrine, vasopressin and epinephrine. Phenylephrine and epinephrine also work at the catecholamine receptors. Vasopressin works through a unique mechanism and functions well as an adjunct to catecholamine pressors, especially in catecholamine-resistant septic shock.[54]

In patients that still have evidence of tissue hypoperfusion despite achieving adequate arterial blood pressure through fluid resuscitation and vasopressor therapy, there remain a few strategies to improve tissue perfusion. Anemia is often concurrent with sepsis. Transfusion of red blood cells to achieve a goal hematocrit ≥30% will augment the oxygen carrying capacity of the blood that is able to perfuse the tissues. Dobutamine also has a role in this circumstance, as either dobutamine or epinephrine will provide inotropic support, improving cardiac output.[55]

Ventilatory Support

Respiratory failure is common in sepsis. This may be due to the inability to maintain supraphysiologic ventilation, which is a result of high metabolic requirement or as a compensation mechanism for metabolic acidosis. Alternatively, hypoxic respiratory failure may develop due to acute lung injury, as a direct result of infection or indirectly from the sepsis syndrome. These patients often require invasive ventilation, adhering to low tidal volume and high positive end-expiratory pressure lung-protective strategies developed for Acute Respiratory Distress Syndrome (ARDS).[56] Because sepsis tends to progress initially, patients with respiratory failure rarely resolve with Noninvasive Positive Pressure Ventilation (NIPPV) alone. In fact, the use of NIPPV is generally contraindicated in respiratory failure due to septic shock, except in special circumstances. Because sepsis increases the ventilatory requirements in these patients, standard weaning parameters may be insufficient. Discontinuation of positive pressure ventilation may not be successful until other organ failures have begun to resolve, acid-base disturbances have corrected, and vasopressors have been weaned.

Glucose Control

Hyperglycemia alone portrays increased mortality in critically ill patients,[38, 39] and intensive insulin therapy has been shown to improve mortality in a surgical ICU population.[57] Proposed benefits of glucose control include prevention of immune dysfunction, reduction of systemic inflammation, endothelial protection, and preservation of mitochondrial structure and function, all of which are important in sepsis. When medical ICU patients only have been studied, the results are less clear. At best, intensive insulin therapy did not improve mortality in medical ICU populations,[40] in particular in septic patients receiving concurrent corticosteroids.[58] At worst, intensive insulin therapy increased episodes of severe hypoglycemia and mortality in a mixed population of medical and surgical ICU patients.[41] In these studies, intensive insulin therapy involved continuous infusion of insulin, with the goal blood sugar of 80–100 mg/dL. Conventional insulin therapy was defined differently in some cases, but often involved continuous infusion, with blood sugar goals set to either 180–200 mg/dL or <180 mg/dL. While it is generally accepted that blood sugar control is important in critically ill patients, tight blood sugar control may be harmful in septic patients. Based on current literature, the goal of treatment should be to keep the blood sugar <180 mg/dL.

Corticosteroids

The use of corticosteroids in the treatment of sepsis has had a long and complex history, yet its use remains controversial. Corticosteroids were used in very high doses in the 1970's for the treatment of severe infection, with some reported benefit in hemodynamics and oxygen delivery.[59] Two large randomized, controlled studies reported in 1987 demonstrated no benefit of high-dose methylprednisolone (30 mg/kg initial dose) to patients with sepsis.[60, 61] The concept of relative adrenal insufficiency in septic shock was introduced, and several studies have since evaluated the efficacy of lower dose corticosteroids (hydrocortisone 200–300 mg/day). Relative adrenal insufficiency predicts higher mortality in septic shock.[20,26,27] A multicenter trial in 2002 demonstrated a mortality benefit among a subgroup of septic shock patients that demonstrated an inadequate response to an Adrenocorticotropic Hormone (ACTH) stimulation test (post-ACTH serum cortisol increase >9 μg/dL over baseline), though there appeared to be a trend toward decreased mortality in all subjects with vasopressor-unresponsive septic shock.[62] The use of fludrocortisone as an adjunct to hydrocortisone is not recommended, since hydrocortisone also has minera-locorticoid activity, and a recent study did not show a benefit with the use of fludrocortisone used in this manner.[58] Another recent trial did not show a mortality benefit among subjects with septic shock or the subgroup of ACTH nonresponders.[63] Given these conflicting results, hydrocortisone (200–300 mg/day, divided into 3–4 doses daily) may be used in septic shock complicated by hypotension refractory to vasopressors. ACTH unresponsiveness is not necessary to justify the use of hydrocortisone.

Activated Protein C

Functional endogenous protein C is deficient in some septic patients, which has a profound effect on the progression of sepsis and the development of organ failure.[18,64] The use of recombinant human-activated protein C (rhAPC, drotrecogin alfa) has been advocated in the most severe cases of sepsis. Among the numerous mechanisms by which activated protein C reduces the complications of sepsis are by blocking thrombin production, decreasing phagocyte chemotaxis and adhesion, inhibiting tissue factor and proinflammatory cytokines, minimizing apoptosis of lymphocytes and endothelial cells, and inhibiting the suppression of fibrinolysis.[21,64] Several studies have been done over the past decade, demonstrating a mortality benefit in severe sepsis and septic shock with single or multiple organ failure.[21,65,66] As expected by its mechanism of action, patients administered drotrecogin alfa have an increased risk of serious bleeding events, including intracranial hemorrhage and gastrointestinal (GI) bleeding, so it should not be used in patients at risk for hemorrhage, recent surgery, or anticipated need for surgery. A follow-up study specifically evaluated the use of rhAPC in patients with the low risk of death (APACHE II score <25 or single organ failure), finding no benefit.[45] Given the risk of serious bleeding complications and lack of efficacy in the low-risk population, this medication should only be used as an adjunct to the proven therapies described previously, in the patients at highest risk of death, without bleeding risk. The formal indications for use of drotrecogin alfa in the US and Europe reflect similar views.

Standardized Protocols

Perhaps the most important development over the past decade is the refinement of protocols, or quantitative resuscitation strategies, regarding the evaluation and management of sepsis. The creation of standard definitions of sepsis, severe sepsis and septic shock[3, 4] allowed for the introduction of these protocols, similar to those now prevalent in many other areas of medicine. An "early goal-directed therapy" protocol was created for a single center for severe sepsis and septic shock.[19] In this protocol, patients meeting set criteria for severe sepsis and septic shock were monitored closely in the emergency room for six hours, undergoing a sequence of measures (volume resuscitation, vasopressors, red blood cell transfusion, and dobutamine) aimed at improving tissue perfusion, as defined by a goal $ScvO_2 \geq 70\%$. The protocol resulted in an absolute reduction in 28-day mortality of 16%; similar results and reduction in ICU usage were noted when the protocol was translated into clinical practice.[67] Since, that time numerous studies have reported mortality improvement and cost reduction when similar protocols were implemented.[68-73] A recent meta-analysis found reduced mortality with the early application of quantitative resuscitation strategies to septic patients.[74]

The Surviving Sepsis Campaign was launched in 2004 with a reported goal of reducing global mortality from severe sepsis by 25% by 2009. The campaign was a collaboration of the ESICM, the International Sepsis Foundation (ISF) and the SCCM. Guidelines were released in 2004 and updated in 2008,[75,76] providing evidence-based guidelines for the diagnosis and management of sepsis. More practical bundles for sepsis resuscitation (first 6 hours) and sepsis management (first 24 hours) were also developed and distributed, and a database was created to track outcomes (Table 132.5).[77] Analysis of the database indicates that compliance with the sepsis bundles is associated with improved mortality.[78] Many hospitals have created their own sepsis protocols, based on the evidence in the literature and their own unique circumstances. Otherwise the Surviving Sepsis Campaign bundles can be adapted for the purposes of an individual institution.

TABLE 132.5: Sepsis bundles from the surviving sepsis campaign‡

Sepsis resuscitation bundle

To be completed within six hours of the identification of severe sepsis

- Measure serum lactate
- Obtain blood cultures prior to antibiotic administration
- Administer broad-spectrum antibiotic within three hours of ED admission and within one hour of non-ED admission
- Treat hypotension and/or elevated lactate with fluids
  - Deliver an initial minimum of 20 mL/kg of crystalloid or an equivalent
- Apply vasopressors for ongoing hypotension
  - Maintain MAP >65 mm Hg
- Maintain adequate CVP and $ScvO_2$ if persistent hypotension (septic shock)
  - Achieve CVP >8 mm Hg
  - Achieve $ScvO_2$ >70% or SvO_2 >65%

Sepsis management bundle

To be completed within 24 hours of presentation

- Administer low-dose steroids for septic shock in accordance with a standardized ICU policy
- Administer rhAPC in accordance with a standardized ICU policy
- Maintain glucose control lower limit of normal, but <180 mg/dL
- Maintain a median inspiratory plateau pressure <30 cm H_2O for mechanically ventilated patients

‡ From ref. 77. Reprinted with permission from the Society of Critical Care Medicine

Goals of Care

As described earlier, severe sepsis often affects debilitated individuals, with numerous comorbidities that increase expected mortality from the sepsis episode. It is vital to have open discussions with the patient (if possible) and caregivers regarding the severity of illness, likely outcomes and treatment recommendations. Though it remains the responsibility of the physician to determine a reasonable plan, patient autonomy must be respected and the patient may accept or decline any treatment.[79] Depending on the clinical situation, it may be appropriate to offer palliation to the patient for the sole purpose of relieving suffering, especially if the expected mortality is unacceptably high. Frank discussions, early and often, with the patient and caregiver may minimize suffering for the patient, as well as anxiety and depression in the caregiver.[80]

Considerations for Developing Countries

As shown earlier (Fig. 132.1), the mortality rate due to infection is higher in developing regions of the world than in high-income countries. One study done in India, evaluating mortality in patients with acute respiratory failure,[25] demonstrated a higher mortality per organ failure (excluding respiratory) than shown in Figure 132.3, with the exception of four organ failures (only one case in the study). Another study done in Kathmandu on a young patient population (mean age 34 years) with SIRS showed an overall mortality of 40% in the ICU.[81] Another study in Brazil found a sepsis-related mortality rate of 43.8%.[14] On the other hand, the Brazilian population study that described the incidence of sepsis there[13] found a 34.7% mortality rate in septic patients, marginally better than that quoted prior to the initiation of the Saving Sepsis Campaign. Perhaps the most wide-reaching study is the PROGRESS International Sepsis Registry,[82] which tracked 12,881 patients with severe sepsis in 276 ICUs in 37 countries. Notably, mortality was 45% in the developing countries versus 30% in the developed countries, possibly due to the variety in management strategies employed in different countries. For example, while systemic antibiotics were given in 99% of all patients, fluid resuscitation and vasopressors were used in 94% of patients in Germany versus 62% of patients in India. Heterogeneity in patient population and severity of disease among the various countries make comparative conclusions difficult to draw from these studies. It seems apparent, though, that the mortality benefits seen in tightly controlled research protocols are not yet being seen worldwide, especially in developing countries.

The management strategy outlined earlier represents the preferred approach to the septic patient, based on evidence-based protocols and recommendations, though limited resources and lack of access to diagnostic tools may force reconsideration of the plan.[83,84] Diagnosis of sepsis may not be straightforward when access to invasive monitoring and laboratory facilities is limited. Medications may be in short supply or altogether unavailable. The ICU environment may also be unsuitable for caring for the septic patient, if one is even accessible. The key will be to identify the available measures that will have the most benefit to these particular patients (Table 132.6). In cases where vital interventions and diagnostic tools are not available, resources should be dedicated to bringing them to the area. Working in an organized and coordinated manner will help assure that each patient is getting the appropriate care.

Diagnostic tools are important in the evaluation of sepsis. Basic, necessary laboratory tests would include a complete blood count, basic biochemical tests, urinalysis and microbiologic culture capabilities. Additionally, depending on the regional importance of these tests, rapid HIV and malaria diagnostic tests may be necessary. Arterial blood gas measurement is useful in many cases, though each individual measure may be estimated from other tests, if needed. The measurement of serum lactate, an indicator of tissue perfusion is strongly suggested to guide management.

Systemic antibiotics are absolutely necessary in the treatment of the all stages of sepsis. The particular antibiotic regimen chosen will depend on the unique set of pathogens to which the patient is at risk. In many developing countries, this will include mycobacteria, viruses and protozoa, in addition to common bacteria. In the areas of the world with the high endemic rates of HIV infection, an expanded list must be considered. Parenteral antibiotics are generally preferred, especially in the more severe cases of sepsis, due to the high prevalence of bowel dysfunction and inconsistent GI absorption of medications. If parenteral antibiotics are not available, the enteral route may be used, provided the patient can swallow or enteral access is achieved. Regardless of the route, the antibiotics chosen must be appropriate and timely. Once the causative organism is identified, antibiotics may be narrowed.

Invasive hemodynamic monitoring may not be practical in some areas of the world. Arterial catheterization may not be realistic in many cases, nor is it always necessary. Similarly, central venous access may not always be required, especially if peripheral IV access can be obtained. The exception is in the case of vasopressor requirement, since most vasopressors are caustic if extravasated and require central venous access for administration. One reason to consider central venous access is for monitoring of $ScvO_2$, since blood pressure monitoring alone is insufficient for assessing tissue perfusion. Alternatively, serum lactate levels can be substituted, as a part of the chemistry testing discussed earlier.

Hemodynamic support is necessary in the many cases of sepsis, especially in progression to severe sepsis and septic shock. Isotonic IV fluids are the initial treatment

TABLE 132.6: Strategies for treatment of sepsis in developing countries

Intervention	*Goal treatments*	*Modifications (author recommendations only)*
Diagnosis	Clinical evaluation, laboratory data, assessment of organ systems, imaging, microbiologic confirmation	Clinical evaluation, basic laboratory data, other modalities where available
Antibiotics	Early administration of broad-spectrum parenteral antibiotics, taper based on microbiological results	Early administration of oral vs. parenteral antibiotics, possibly antimalarials or antimycobacterial meds, taper if micro is available
Hemodynamic monitoring	Invasive BP and CVP monitoring, $ScvO_2$ or lactate as goals	Clinical exam, other data as available if invasive monitoring not available
Fluid resuscitation	IV crystalloids or colloids, fluid challenge for low BP, additional fluids based on CVP and tissue perfusion parameters	IV (crystalloid vs. colloid) vs. oral rehydration, fluid challenge for low BP, additional fluids based on available clinical data
Hemodynamic support	Norepinephrine vs. dopamine (central venous catheter) for BP, dobutamine or RBC transfusion if needed for tissue perfusion	Dopamine (central venous catheter) for BP, RBC transfusions if Hct <30% and shock, dobutamine if available
Mechanical ventilation	ARDS ventilation (low tidal volumes) if indicated, directed by ABGs, weaning protocol	Oxygen, SpO2 monitoring, mechanical ventilation, ABGs if available and needed
Glucose control	Continuous IV insulin, goal blood sugar <180 mg/dL	Intermittent SQ insulin if able, blood sugar 180-200 or >200 depending on capabilities
Corticosteroids	Consider low dose IV hydrocortisone in vasopressor-unresponsive septic shock	Consider low dose IV hydrocortisone in vaso-vasopressor-unresponsive septic shock
Activated protein C	Consider rhAPC in septic shock with APACHE II >25 and no bleeding risk	Direct resources elsewhere if the hospital system or the patient cannot afford
Treatment protocols	Hospital-based protocols integrated with SSC Sepsis Resuscitation and Sepsis Management bundles	Hospital-based protocols integrated with SSC Sepsis Resuscitation and Sepsis Management bundles

of choice for sepsis-induced hypotension. Albumin is more widely used in Australia and Asia, possibly owing to better availability and/or lower cost.[82] Albumin is also more portable than saline, making it more attractive for use in remote regions. Limited resources may restrict the availability of IV fluids of any kind. In that case, those with mild disease and tolerating oral fluids may undergo a trial of oral fluid resuscitation. Vasopressors are often required to maintain adequate blood pressure and tissue perfusion. Dopamine and norepinephrine are considered equivalent in septic shock, though norepinephrine must be protected from light and requires refrigeration, while dopamine does not. Dopamine is thought to be stable for a minimum of 48 hours at room temperature,[85] making it more suitable for emergency rooms or remote locations, though hot and humid environments may reduce its shelf-life. Dobutamine and red blood cell transfusions are both recommended in cases where initial fluid resuscitation and blood pressure support fail to provide adequate tissue perfusion. Dobutamine must also be stored unmixed or refrigerated, though is also useful in the episodes of non-septic cardiogenic shock. In areas where blood donation is safe and economical, transfusion of red blood cells (RBCs) should be considered in anemic patients (hematocrit <30%) in shock, even if parameters of tissue perfusion cannot be measured. These two interventions are a part of successful early sepsis resuscitation protocols, though the role of these individual treatments in the success of those protocols is unclear. The expected benefit must be weighed against the necessary investment required to institute these therapies.

Mechanical ventilation becomes necessary when sepsis or SIRS manifest as ALI or ARDS. A more thorough discussion of mechanical ventilation is presented elsewhere in this book. The principles remain the same when applied to sepsis in developing countries. The use of portable ventilators may allow fewer ventilators to be used over a wider area, maximizing the use of scarce resources.

Glucose control remains an important part of sepsis management, with a goal blood sugar of <180 mg/dL. Optimal control is often achieved by using IV insulin in a continuous infusion. This method is labor-intensive and not always necessary. In many cases, subcutaneous insulin or intermittent IV insulin doses can achieve the same goals. Glucose testing kits and insulin should be available and used anywhere septic patients are cared for. If these resources are unavailable, periodic blood sugar monitoring is recommended during laboratory evaluation, though tight glucose control is generally not practical using this method and higher goals (>200 mg/dL) are suggested to prevent hypoglycemia. Oral hypoglycemics are not appropriate in the acute management of a septic patient.

Low-dose systemic corticosteroids should be considered in patients with septic shock that is not responsive to vasopressor therapy. Activated protein C provides a mortality benefit to patients with septic shock at the highest risk of death only. Both therapies are only recommended for use as adjuncts to the standard treatments previously described, and limited resources should be dedicated to those standard treatments.

The development of standardized protocols may be the area of most benefit to developing countries. The cost to develop a protocol specific to a hospital is minimal, especially given the fact that the Surviving Sepsis Campaign guidelines and protocols were developed with the aim of improving survival worldwide. The protocols are basic enough that they can be adapted to any unique situation. For example, in South America, the Latin American Sepsis Institute was created to "share sepsis information with scientific and lay communities in Latin America",[86] highlighting the difficulty in disseminating any information, even well-validated protocols, worldwide. Effective communication and well-defined roles are crucial in implementing the SSC guidelines as intended. The initial sepsis resuscitation bundle is meant to be completed within six hours, requiring rapid diagnosis and effective triage and management decisions in the emergency room or outpatient settings. Rapid access to diagnostic laboratory and imaging services is necessary to complete this goal. After the initial six hour resuscitation bundle, the sepsis management bundle is dominated by hospital-specific protocols. These protocols can easily be generated based on current literature and available resources.

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Nonpulmonary Critical Care

Adebayo Esan, Lavanya Irugulapati, Liziamma George

INTRODUCTION

Patients are admitted to critical care units with several disease processes other than respiratory failure. In addition, patients admitted with respiratory failure often develop further organ dysfunctions that require aggressive management. In this chapter, we will discuss some of the common nonpulmonary critical care diagnoses and their corresponding management.

GASTROINTESTINAL DISEASE IN CRITICAL CARE

Gastrointestinal Bleeding

Gastrointestinal (GI) bleeding is a medical emergency necessitating admission to the critical care unit. It is common in males and elderly patients.[1] Upper GI bleed is defined as bleeding above the level of the ligament of Treitz while lower GI bleed is bleeding below the level of the ligament of Treitz.[2] Upper GI bleed tends to occur more commonly than its lower GI counterpart and has a mortality that ranges from 6 to 12% as opposed to 5% in lower GI bleed.[3,4] Recurrent acute or chronic bleed from the digestive tract without an obvious etiology after a normal esophagogastroduodenoscopy (EGD) and colonoscopy is known as obscure GI bleed.[5] The most common causes of upper and lower GI bleeding are listed in Tables 133.1 and 133.2 respectively.

TABLE 133.1: The common causes of upper gastro-intestinal bleeding.

- Peptic ulcer disease - MCC worldwide (duodenal ulcers, gastric ulcers, stomal ulcers)
- Erosive gastritis, esophagitis and duodenitis (alcohol, aspirin, NSAIDs)
- Esophageal and gastric varices (caused by portal hypertension)
- Mallory-Weiss syndrome
- Stress ulcers
- AVM
- Malignancy
- Aortoenteric fistula

Abbreviations: GI: Gastrointestinal, MCC: Most common cause, NSAIDs: Non-steroidal anti-inflammatory drugs, AVM: Arteriovenous malformation.

TABLE 133.2: The common causes of lower gastro-intestinal bleeding

- Diverticulosis
- Hemorrhoids
- AVM/Angiodysplasia/Aortoenteric fistula
- Neoplasia
- Polyps
- Benign anorectal disease (fissures, ulcers)
- Upper GI source
- Small bowel source

Abbreviations: GI: Gastrointestinal, AVM: Arteriovenous malformation.

Upper Gastrointestinal Bleeding

Clinical features: Clinical manifestations depend on the rate and amount of bleeding. These patients should be promptly assessed for hemodynamic status, which involves measuring the pulse rate, blood pressure, urine output and postural hemodynamic changes. Pulse rate of ≥100 beats per minute, systolic blood pressure <100 mm Hg, postural changes, i.e. an increase in the pulse of ≥20 beats per minute or a drop in systolic blood pressure of ≥20 mm Hg on standing are significant. Airway protection is needed for patients with altered mental status or massive hematemesis. History of alcohol abuse, Non-steroidal Anti-inflammatory Drug (NSAID) usage, liver disease and family history of gastrointestinal or other malignancies, recent retching, prior surgery and other medication usage may point to the etiology of GI bleeding. Elderly patients, who potentially have an age-related compromised cardiac reserve, may present with symptoms of chest pain and shortness of breath rather than GI bleed, suggestive of myocardial ischemia. Other symptoms such as fatigue and dyspnea tend to occur with chronic blood loss. Signs specific for upper GI bleeding include hematemesis, bloody gastric lavage, melena and hematochezia. Bleeding through the rectum is usually indicative of lower GI bleeding; however, massive upper GI bleeding can cause fresh blood to pass through the rectum.[6] Because of the possible contributing factors and associated complications, patients should also be examined for signs of liver and cardiac disease.

Diagnosis: The initial step performed in patients with suspected upper GI bleed is to place a nasogastric tube, so as to aspirate gastric contents. While a coffee-ground aspirate or fresh blood is diagnostic of upper GI bleed, its absence will not rule out upper GI bleed in up to 20% of patients.[7] The presence of blood in the stomach is an indication for an urgent EGD for either diagnostic and/or therapeutic purposes. The use of cold or iced saline lavages in these patients has not been shown to improve outcome.[8] However, diagnostic evaluation should only be undertaken after initial stabilization of the patient has taken place.

In order to assess the severity of GI bleeding as well as to evaluate for any contributing etiological factors, the following laboratory tests should be performed: a complete blood count, electrolytes, urea and creatinine, liver function tests and coagulation profile. Blood samples should also be sent for typing and cross-matching. It is important to note that the hematocrit may be normal in recent massive GI bleed and can, therefore result in an underestimation of the severity.

Management: Irrespective of the bleeding site, the management of acute GI bleeding should include hemodynamic stabilization, localization of the bleeding site and specific therapeutic interventions.[9,10] Supplemental oxygen should be provided to ensure adequate tissue oxygenation and all patients should also be placed on cardiac monitors.

Intravascular volume repletion with crystalloid infusion through two large bore (16 or 18 gauge) intravenous lines should begin immediately. Patients with unstable vital signs even after initial stabilization should be transfused with packed red cells. A guide for hemodynamic assessment and transfusion requirement is shown in Table 133.3.[11]

In cases with exsanguinating blood loss, attempts at localization and control of bleeding through endoscopic or surgical procedures should be done simultaneously. The threshold for transfusion must be individualized as the majority of patients do not require transfusion unless the hemoglobin (Hb) level is less than 7 g/dl.[12]

The Blatchford and Rockall scoring systems are used for risk stratification of upper GI bleeding (Tables 133.4

TABLE 133.3: The signs, symptoms and fluid replacement strategies in patients with hypovolemic (hemorrhagic) shock

Clinical evaluation and initial management of hypovolemic shock				
Blood loss (mL)	<750	750 to 1500	1500 to 2000	>2000
Blood loss (%bv)	<15%	15 to 30%	30 to 40%	>40%
Pulse rate	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mmHg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14 to 20	20 to 30	30 to 40	>35
Urine output (mL/hr)	>30	20 to 30	5 to 15	Insignificant
Mental status	Slightly anxious	Mildly anxious	Anxious and confused	Confused and lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Abbreviation: BV: Blood volume
Adapted from Grenvick A et al.[11]

TABLE 133.4: The Blatchford bleeding score which predicts the need for treatment in patients with upper gastrointestinal bleeding. A higher score (≥ 6) is associated with an increased risk of re-bleeding while a lower score (< 6) is associated with a decreased re-bleeding risk

At presentation	*Points*
• Systolic blood pressure (mm Hg)	
100 to 109	1
90 to 99	2
< 90	3
• Blood urea nitrogen	
6.5 to 7.9 mmol/L	2
8.0 to 9.9 mmol/L	3
10 to 24.9 mmol/L	4
≥25 mmol/L	6
• Hemoglobin for men	
12.0 to 12.9 g/dL	1
10.0 to 11.9 g/dL	3
<10.0 g/dL	6
• Hemoglobin for women	
10.0 to 11.9 g/dL	1
<10.0 g/dL	6
• Other variables at presentation	
Pulse ≥ 100	1
Melena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2

Adapted from Blatchford O et al.[13]

and 133.5).[13,14] Higher scores are indicative of rebleeding and death while lower scores identify patients who do not need urgent intervention.[15] Localization of bleeding site is the cornerstone of the management of upper GI bleeding. Endoscopy should be performed within 24 hours of patient presentation. The administration of promotility agents are not routinely recommended before endoscopy. Furthermore, the risk of rebleeding based on endoscopic findings can be assessed using Forrest classification (Table 133.6).[16,17] Patients with grades 2C and 3 are considered low risk for rebleeding, while patients with high-risk lesions should undergo endoscopic hemostasis to prevent recurrent bleeding.[16] A second-look endoscopy is not routinely recommended. In addition, in patients with coagulation abnormalities, endoscopy should not be delayed and the risk/benefit ratio should be assessed carefully.

Medical therapy should be used as an adjunct to endoscopic therapy. Pre-endoscopic administration of proton pump inhibitors (PPIs) decreases the need for endoscopic intervention.[18] Administration of a PPI has also been shown to decrease rebleeding, surgical intervention and mortality.[19,20] In addition, it is reported that in patients with recurrent bleeding, repeated endoscopy is preferred to surgical intervention.[21]

Angiography and embolization is recommended for patients in whom acute bleeding is not controlled

TABLE 133.5: The Rockall scoring system which is used to identify patients at risk for developing unfavorable outcomes following acute upper gastrointestinal bleeding. A complete Rockall score of ≤ 2, i.e. following endoscopy is associated with a good prognosis, i.e. low risk for re-bleeding and death[14]

Variable	*Points*		
• **Age**			
< 60 yrs	0	Clinical Rockall score (0 to 7)	Complete Rockall score (0 to 11)
60 to 79 yrs	1		
> 80 yrs	2		
• **Hemodynamic status**			
Shock absent: SBP > 100 mm Hg and HR < 100 beats/min	0		
Shock absent: SBP > 100 mm Hg and HR > 100 beats/min	1		
Shock present: SBP < 100 mm Hg and HR > 100 beats/min	2		
• **Co-existing illness**			
Ischemic heart disease, congestive heart failure and other major illness.	2		
Renal failure, hepatic failure, metastatic cancer	3		
• **Endoscopic diagnosis**			
No lesion observed, Mallory-Weiss tear	0		
Peptic ulcer, erosive disease, esophagitis	1		
Cancer of upper GI tract	2		
• **Endoscopic stigmata of recent hemorrhage**			
• Clean based ulcer, flat pigmented spot	0		
• Blood in upper GI tract, active bleeding, visible vessel, clot	2		

Abbreviations: SBP: Systolic blood pressure, HR: Heart rate.

TABLE 133.6: The endoscopic appearance and associated re-bleeding risk in patients with upper gastrointestinal bleeding

Class	*Appearance*	*Risk of Re-bleeding*
1A	Spurting blood	Very high → early surgical intervention
1B	Oozing blood	Very high
2A	Non-bleeding visible vessel	High
2B	Adhering clot	High
2C	Flat lesions and pigmented spot	Low
3	Clean base ulcer	Low

by endoscopic treatment. Successful angiographic identification of the bleeding site requires a bleeding rate of 0.5 to 1 ml per minute.[22] The complications of this procedure include bowel ischemia, infarction and contrast-induced renal failure.

The surgical team should be involved early in the management of these patients so as to augment prompt response when all else has failed in ensuring hemostasis.

Recapitulation: Patients with upper GI bleeding require a multidisciplinary approach; initial stabilization improves outcome for these patients; patients should be risk stratified for management in the critical care unit; early endoscopy (within 24 hours) is the cornerstone for management; medical therapy using PPIs is an adjunct to endoscopic therapy. An algorithm for the management of upper GI bleeding is shown in Figure 133.1.[23]

Lower Gastrointestinal Bleeding

Clinical features: Lower GI bleeding is defined as bleeding distal to the ligament of Treitz. These patients tend to present with hematochezia or maroon colored stools. The common etiologies contributing to the development of lower GI bleeding are shown in Table 133.2.

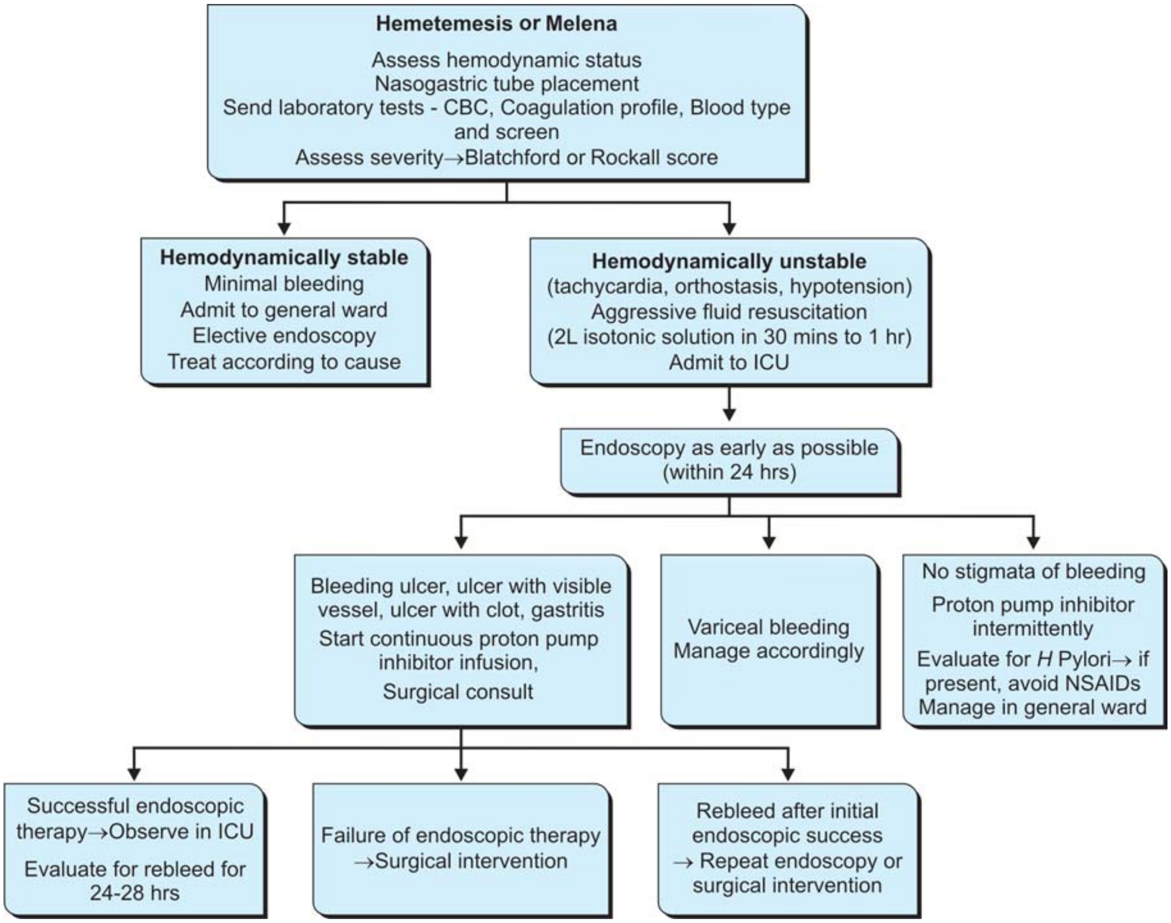
Hemetemesis or Melena
Assess hemodynamic status
Nasogastric tube placement
Send laboratory tests - CBC, Coagulation profile, Blood type and screen
Assess severity→Blatchford or Rockall score
Hemodynamically stable
Minimal bleeding
Admit to general ward
Elective endoscopy
Treat according to cause
Hemodynamically unstable
(tachycardia, orthostasis, hypotension)
Aggressive fluid resuscitation
(2L isotonic solution in 30 mins to 1 hr)
Admit to ICU
Endoscopy as early as possible (within 24 hrs)
Bleeding ulcer, ulcer with visible vessel, ulcer with clot, gastritis
Start continuous proton pump inhibitor infusion,
Surgical consult
Variceal bleeding
Manage accordingly
No stigmata of bleeding
Proton pump inhibitor intermittently
Evaluate for H Pylori→ if present, avoid NSAIDs
Manage in general ward
Successful endoscopic therapy→Observe in ICU
Evaluate for rebleed for 24-28 hrs
Failure of endoscopic therapy →Surgical intervention
Rebleed after initial endoscopic success → Repeat endoscopy or surgical intervention

Fig. 133.1: The management of upper gastrointestinal bleeding, which is focused around hemodynamic stabilization and localization of the bleeding site.
Abbreviations: CBC: Complete Blood Count, ICU: Intensive Care Unit, *H pylori: Helicobacter pylori,* NSAID: Non-Steroidal Anti-inflammatory Drug.

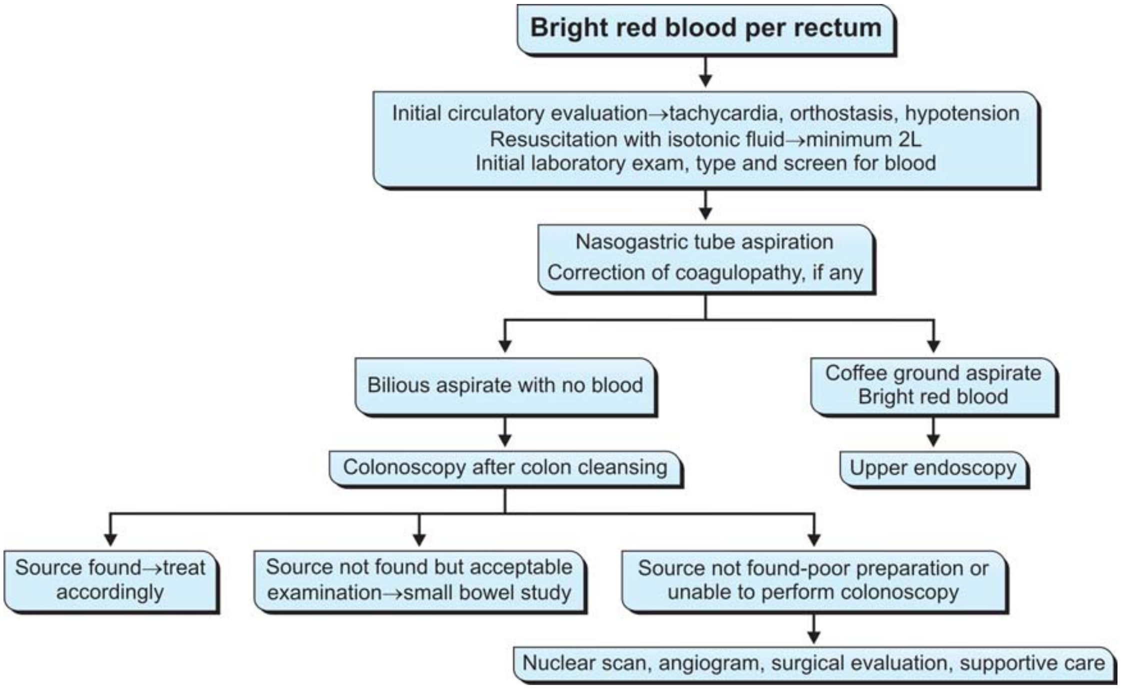
Bright red blood per rectum
Initial circulatory evaluation→tachycardia, orthostasis, hypotension
Resuscitation with isotonic fluid→minimum 2L
Initial laboratory exam, type and screen for blood
Nasogastric tube aspiration
Correction of coagulopathy, if any
Bilious aspirate with no blood
Coffee ground aspirate
Bright red blood
Colonoscopy after colon cleansing
Upper endoscopy
Source found→treat accordingly
Source not found but acceptable examination→small bowel study
Source not found-poor preparation or unable to perform colonoscopy
Nuclear scan, angiogram, surgical evaluation, supportive care

Fig. 133.2: An algorithmic approach to the management of lower gastrointestinal bleeding

Diagnosis: The initial stabilization of lower GI bleeding is not different from that of upper GI bleeding. The localization of bleeding is done by colonoscopy which identifies the bleeding in 60 to 80% of cases. The other options are nuclear scanning using technetium-99m-labeled red blood cell (Tc-99 m RBC) scan and arteriography. Radionuclide scanning is a more sensitive but less specific modality (may not localize the lesion and no therapeutic intervention can be done) and requires at least 0.1 to 0.5 ml of bleeding per minute. Barium studies have no role in the evaluation of lower GI bleed. A multi-detector Computed Tomography (CT) scan has been used to localize massive GI bleeding in some reports.[24] Arteriography of both superior and inferior mesenteric arteries can be used to identify the source of bleeding. Some studies recommend radionuclide scanning before angiography, so as to decrease the incidence of negative tests.

Management: An algorithm for the management of lower GI bleeding is demonstrated in Figure 133.2.[25]

Acute Variceal Hemorrhage

Acute variceal hemorrhage is one of the complications of portal hypertension requiring critical care unit admission. Patients with Child Pugh classification of B or C (Table 133.7) have a higher incidence of variceal bleeding and are associated with a mortality of 15 to 20%.[26] Patients often present with massive upper GI bleeding associated with hemodynamic instability.

The specific treatment strategies include the use of medications, endoscopy, surgical interventions, transjugular intrahepatic shunt, balloon tamponade and the prevention of recurrent bleeding. After initial stabilization of the patient, medications directed towards splanchnic vasoconstriction should be utilized to decrease portal pressure. The commonly used agents are vasopressin, telipressin, somatostatin and its analogues. Vasopressin causes direct vasoconstriction of splanchnic arterioles leading to decreased portal pressure. The major side effects include systemic vasoconstriction, particularly coronary vessels. The use of nitrates in addition to vasopressin is recommended to decrease these side effects with added therapeutic benefit.[27] Notably, vasopressin has minimal effects on rebleeding. Telipressin, a vasopressin analogue can be used as an alternative to vasopressin, which has less side effects than vasopressin. Somatostatin, an indirect vasoconstrictor of splanchnic circulation, rapidly decreases the portal pressure with minimal side effects. It is superior to vasopressin in patients with variceal hemorrhage.[28] The infusion is continued for 2 to 5 days and has no significant effect on mortality.

TABLE 133.7: The modified Child-Pugh classification of the severity of liver disease with the associated risk of mortality[26]

Parameters	*Points Assigned*		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/liter)	<2.8 g/dL (<28 g/liter)
Prothrombin time (Seconds over normal)	< 4	4 to 6	> 6
INR	1.7	1.7 to 2.3	> 2.3
Encephalopathy	None	Grade 1 to 2 (lethargy, apathy)	Grade 3 to 4 (Somnolence, coma)
Grades	A (Well compensated)	B (Functional compromise)	C (Decompensated)
Total points	5 to 6	7 to 9	10 to 15
Mortality % (1 to 2 year)	0 to 15	20 to 40	55 to 65

Endoscopic banding or sclerotherapy is the definitive treatment for acute variceal bleeding.[29] Both telipressin and somatostatin analogues are as effective as endoscopic therapies, however, combination of both medical and endoscopic therapies are more beneficial to control bleeding.[30-32] Endoscopic therapies are associated with complications such as ulceration, mediastinitis, esophageal perforation as well as sepsis. Balloon tamponade is considered when medical and endoscopic approaches fail to achieve hemostasis or when there is a lack of expertise to perform endoscopic interventions. This is a temporary measure until definitive treatment can be undertaken. The common tubes used are the Sengstaken- Blakemore tube or the Minnesota tube. These tubes have gastric and esophageal bulbs to tamponade the varices and are effective in 30 to 90% of patients. The complications associated with their use include esophageal rupture and rebleeding.[33]

Trans-jugular portohepatic shunt can also be used as a temporary measure to decrease the portal venous pressure by creating a shunt between the hepatic and portal veins. In addition to controlling bleeding, prophylactic short-term antibiotics are recommended to prevent spontaneous bacterial peritonitis. Ceftriaxone or fluoroquinolones for 7 days are used in most of the studies.[34] Rebleeding is a significant problem and the risk factors are:

- Age > 60 years
- Child class C patients
- Large varices
- Renal failure
- Significant initial bleed (presence of hemodynamic instability)
- Hgb < 8 g/dL
- Hepatic venous pressure gradient > 20 mm Hg

Correction of coagulopathy and thrombocytopenia (platelets < 50 x 10^9/L) is vital in these patients, with careful attention to volume overload. There are few reports of using recombinant factor VIIa in severely fluid overloaded patients.

Other disorders associated with liver disease necessitating intensive care unit admission include lung disorders associated with liver failure. The major conditions are hepatopulmonary syndrome, hepatic hydrothorax and portopulmonary hypertension.

The hepatopulmonary syndrome (HPS) is a pulmonary vascular disorder characterized by pulmonary vascular dilatation, intrapulmonary arterio-venous shunting leading to ventilation-perfusion mismatch in the setting of liver disease. It has no association with the severity of liver disease.[35] Patients usually present with shortness of breath associated with platypnea and orthodeoxia (dyspnea and desaturation when position changes to sitting from recumbent position). The chest X-ray is usually normal or may show increased vascular markings, while the arterial blood gas (ABG) shows hypoxemia PaO_2 < 80 mm Hg with increased alveolar-arterial gradient (> 15 mm Hg).

Contrast echo-cardiography (microbubbles in left atrium within 3 to 6 cardiac cycles) or perfusion lung scanning using technetium labeled macroaggregates of albumin (presence of isotope in brain and kidney) are the preferred diagnostic tests. Liver transplantation is the treatment of choice.[36]

Portopulmonary hypertension occurs in patient with portal hypertension and is managed similar to Class 1 pulmonary hypertension.

Hepatic hydrothorax presents as massive pleural effusion mostly involving the right hemithorax. Its management is depicted in Figure 133.3.[37] The first step in management is therapy with low sodium diet (70 to 90 mEq/day) and diuretics. If there is no response to diuretics, therapeutic thoracentesis of approximately 2 liters can be attempted followed by diuretics at lower doses if possible. If patients do not respond to diuretics or develop complications, they should be considered for a transjugular intrahepatic portosystemic shunt (TIPS) placement. This measure may help as a bridge to liver transplantation. TIPS placement is best considered in patients younger than 60 years of age, without hepatic encephalopathy and/or those with child class A or B cirrhosis. For patients that cannot undergo TIPS placement, pleurodesis or diaphragmatic repair by thoracoscopy should be considered. Chest tube placement should be avoided as it is associated with severe complications.[38, 39]

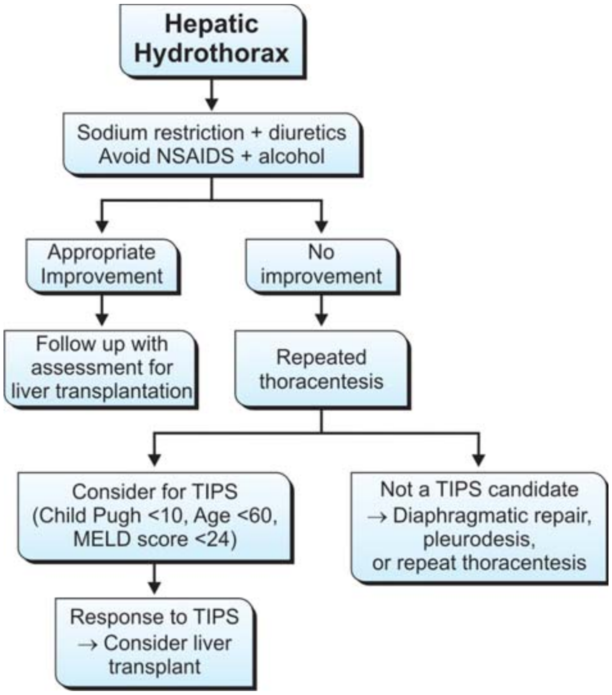
Hepatic Hydrothorax
Sodium restriction + diuretics Avoid NSAIDS + alcohol
Appropriate Improvement
No improvement
Follow up with assessment for liver transplantation
Repeated thoracentesis
Consider for TIPS (Child Pugh <10, Age <60, MELD score <24)
Not a TIPS candidate → Diaphragmatic repair, pleurodesis, or repeat thoracentesis
Response to TIPS → Consider liver transplant

Fig. 133.3: An algorithm outlining management of patients presenting with hepatic hydrothorax.
Abbreviations: NSAID – Non-Steroidal Anti-inflammatory Drug, TIPS-Trans-Esophageal Portosystemic Shunt, MELD – Model for End-stage Liver Disease.

Acute Liver Failure

Acute liver failure is defined as the onset of hepatic encephalopathy and coagulopathy within 26 weeks of jaundice in a patient with pre-existing liver disease.[40] Patients should be managed in a critical care unit at the onset of encephalopathy.

The treatment of liver failure according to the specific etiology is outlined in Table 133.8.[41]

Management of Complications

Hepatic encephalopathy is a reversible neurological dysfunction, occurring in patients with liver failure. Neurotoxins like ammonia, oxidative stress, production of false neurotransmitters and alteration in the blood brain barrier are implicated for its development. In addition to correction of precipitating factors, ammonia production in the gut is reduced with the use of lactulose and nonabsorbable antibiotics such as neomycin and rifaximin.[42] Infections contribute significantly to the mortality of these patients and should be treated aggressively.

Psychomotor agitation seen in patients with hepatic encephalopathy may be worsened by benzodiazepines and propofol through gamma amino butyric acid pathways. Flumazenil, a benzodiazepine antagonist, is reported to have short term benefit in patients with hepatic encephalopathy. For analgesia, fentanyl is used in these patients.[43] Even though these patients are coagulopathic, active bleeding is rare. The occurrence of upper GI bleeding is prevented by the use of either H2 blockers or PPIs.[44] Parental vitamin K is recommended for all patients with acute liver failure, however, routine fresh frozen plasma (FFP) administration is not recommended and cryoprecipitate is given when fibrinogen levels are less than 100 mg/dL. Recombinant factor VIIa is recommended if there is volume overload and fresh frozen plasma fails to correct coagulopathy or before invasive procedures with high risk of bleeding.[45] Further studies are needed to define the exact role of this agent. Nevertheless, factor VIIa should not be given to patients with acute myocardial infarction, stroke or other thromboembolic disorders.

Nutritional supplementation through the enteral route is preferred to parenteral nutrition in these patients.[46] However, patients with hypoglycemia should get intravenous glucose infusion.

TABLE 133.8: The etiology, treatment and transplant criteria for acute liver failure[41,51]

Etiology	*Treatment*	*Criteria for transplant*
	NAC oral: 140 mg load then 70 mg/kg every 4 hours	Arterial pH 7.3 or all of following: 1. PT > 100 sec (INR > 6.5) 2. Cr > 3.4 mg/dl 3. Grade 3 or 4 encephalopathy
	NAC IV: 150 mg/kg load then 12.5 mg/kg hourly X 4 hrs then 6.25 mg/kg hourly	Meld > 33, APACHE > 15
Amanita (mushroom)	Penicillin G: 1g/kg daily IV and NAC as above	PT > 100 sec (INR > 6.5) or any three of the following: 1. NANB/drug/halothane etiology 2. Jaundice to encephalopathy > 7 days 3. Age < 10 or > 40 yrs 4. PT > 50 sec (INR > 3.5) 5. Bilirubin > 17.4 mg/dl 6. Hepatocyte necrosis > 70%
HSV	Acyclovir 30 mg/kg daily IV	
AIH	Methylprednisolone 60 mg/day IV	
HBV	Lamivudine 100 to 150 mg/daily orally	
AFLP/HELLP	Delivery of fetus	

Abbreviations: NAC: N-acetylcysteine, PT: Prothrombin time, INR: International normalized ratio, Cr: Creatinine, MELD: Model for end-stage liver disease, APACHE: Acute physiology and chronic health evaluation, IV: Intravenous, NANB: Non-A, Non-B Hepatitis, HSV: Herpes Simplex Virus, AIH: Autoimmune Hepatitis, HBV: Hepatitis B Virus, AFLP: Acute Fatty Liver of Pregnancy, HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelets

Nonconvulsive seizures can also occur in these patients, however, routine seizure prophylaxis is not recommended. Electroencephalography monitoring is suggested for patients with grade III or IV encephalopathy, sudden deterioration of mental status or myoclonus.

Acute liver failure patients, who develop hypotension, should be treated aggressively, initially with fluids to correct volume status and subsequently with vasopressors if fluid administration alone does not correct the hypotension.

Cerebral edema and raised intracranial pressure increases the morbidity and mortality for these patients. Computerized tomography of the brain is recommended for patients with an advanced hepatic encephalopathy.[47] Placement of an intracranial pressure monitoring device for these patients is controversial at this time but should be considered for liver transplant candidates.[48] The management of patient with intracranial hypertension includes keeping the head of bed at 30° in the neutral position and the maintenance of euthermia; however, prophylactic hyperventilation is not recommended.[49] Conversely, acute hyperventilation can be given to patients with brain herniation. In addition, specific therapies such as mannitol are utilized when intracranial pressure (ICP) is > 25 mm Hg for > 10 minutes. The dose ranges from 0.25 to 1.0 g/kg over 30 minutes.[50] The dose can be repeated if serum osmolality is < 320 mOsm/L or ICP > 25 mm of Hg. Other treatment modalities include hypertonic saline, induction of moderate hypothermia, barbiturate coma and indomethacin infusion. Patients with acute liver failure are candidates for orthotopic liver transplantation. The criteria for transplantation are shown in Table 133.8.[51, 52]

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is an infection of ascitic fluid in the absence of an intra-abdominal source of infection.[53-56] It is a common and life-threatening complication of cirrhosis. SBP occurrence is rare in non-cirrhotic patients as opposed to cirrhotic ones. Bacterial translocation into ascitic fluid is commonly believed to be a causative factor for the development of SBP, however, current research shows that SBP is the result of the interplay of several factors such as prolonged bacteremia resulting from defective local and humoral immunity, intrahepatic shunting of blood, defective bactericidal action of ascitic fluid and transabdominal introduction of infection.[57] The microorganisms responsible for SBP are isolated in 60 to 70% of cases and colonic bacteria are cultured in 65% of cases with *Escherichia coli* and *Klebsiella* species being the common organisms isolated.

Clinical Features

SBP should be suspected in all cirrhotic patients with ascites, as the clinical manifestations can be very subtle as well as non-specific, with a broad range of clinical expression. Ascitic fluid analysis should be performed in all patients with ascites who are admitted to hospital, in addition to those presenting with abdominal pain, fever and encephalopathy.

Diagnosis and Management

SBP is identified when an ascitic fluid analysis demonstrates a polymorphonuclear cell count greater than 250 cells/mm^3. A positive culture of ascitic fluid is noted in only 30% of cases and is usually not required for diagnosis. Antibiotics, preferably a third generation cephalosporin, should be started immediately after a positive ascitic fluid tap.[58] Renal dysfunction can also occur in patients with SBP as a consequence of large-volume paracentesis. Intravenous albumin administration has been shown to reduce the risk of renal impairment taking place.[59] However, albumin has been proposed to be used in patients with serum creatinine > 1 mg/dl, blood urea nitrogen > 30 mg/dL and total bilirubin > 4 mg/dL.[60] Following a single episode of SBP, patients should receive long-term prophylaxis with either norfloxacin or trimethoprim/sulphamethoxazole.

Severe Acute Pancreatitis

Acute pancreatitis is an inflammatory condition of the pancreas resulting in abdominal pain and elevation of the serum levels of the pancreatic enzymes. It is a self-limited disease in most cases. About 20% of patients develop acute necrotizing pancreatitis, leading to multiorgan failure and death. The common etiologies include gallstones, alcohol consumption, hypertriglyceridemia, smoking, hypercalcemia, drugs, trauma, pancreatic divisum and infections.

Clinical Features

Pancreatic enzymes are activated within the acini causing damage to the pancreatic tissues and vasculature. In necrotizing pancreatitis the inflammation extends into the adjacent tissues. Patients present to the ICU with fever, tachycardia, shock and multiorgan dysfunction.

Diagnosis

A CT scan of the abdomen and Magnetic Resonance Pancreaticoduodenography (MRCP) are the best radiological tests for the diagnosis and staging of acute pancreatitis, though the MRCP gives a better image of the pancreatic and biliary duct system.[61-63] A number of scoring systems have been developed to assess the severity of pancreatitis. The most well-known scoring system is Ranson's criteria (Table 133.9).[64] Other scoring systems include APACHE II scores (> 8 is considered significant) and CT scan grading.

Management

A contrast enhanced abdominal CT-scan should be performed for patients with acute pancreatitis within

TABLE 133.9: Ranson's criteria for predicting the severity of acute pancreatitis. Each parameter is assigned a score of 1 if present. A higher score is associated with higher mortality (score: < 3 → < 3% mortality; 3-6 → 15% mortality; > 6 → 40% mortality)[64]

0 hours	
Age	> 55
White blood cell count	> 16,000/mm^3
Blood glucose	> 200 mg/dL (11.1 mmol/L)
Lactate dehydrogenase (LDH)	> 350 U/L
Aspartate aminotransferase (AST)	> 250 U/L
48 hours	
Hematocrit	Fall by ≥ 10%
Blood urea nitrogen	Increase by ≥ 5 mg/dL (1.8 mmol/L) despite fluids
Serum calcium	< 8 mg/dL (2 mmol/L)
Partial pressure of oxygen (pO_2)	< 60 mm Hg
Base deficit	> 4 mEq/L
Fluid sequestration	> 6000 ml

72 hours of admission to the ICU. Fluid resuscitation at a rate of 200 to 300 cc per hour of isotonic solution is required to prevent acute renal tubular necrosis. Hematocrit measurement can guide the adequacy of fluid resuscitation. Pain is managed with meperidine, morphine or fentanyl. Infections caused by enteric gram negative organisms increase the morbidity and mortality of these patients. The role of prophylactic antibiotics is controversial: the use of carbapenems as prophylactic agents for 2 weeks in patients with necrotizing pancreatitis is reported.[65] Anti-fungal agents are not given routinely for these patients. CT-guided aspiration and drainage of collections are performed in patients who do not improve with at least 1 week of antibiotics. Open necrosectomy is not favored.[66-68] Early enteral feeding via a nasojejunostomy tube is associated with decreased infectious complications and early recovery compared to parenteral nutrition.[69] In patients with gallstone pancreatitis, the need for an early Endoscopic Retrograde Cholangiopancreatography (ERCP) is dictated by the presence of acute cholangitis and jaundice. If the liver enzymes remain elevated or increasing, early ERCP is recommended. An algorithm for the management of acute pancreatitis is shown in Figure 133.4.

HEMATOLOGY IN CRITICAL CARE

Anemia

Anemia, acute or chronic is a frequent problem in critically ill patients admitted into Intensive Care Units (ICUs)[70,71] and can result from a number of causes (Table 133.10).[72] The proinflammtory state seen in critically ill patients result in a blunted erythropoietic response to anemia in addition to abnormalities in iron metabolism, further complicating the clinical course.[73-77] It has been reported that 63 and 29% of critically ill patients admitted into the ICU have an admitting Hgb concen-tration of less than 12.0 g/dL and 10.0 g/dL respectively with Hgb concentrations on average decreasing by approximately 0.5 g/dL/day in nonseptic patients (without active bleeding or hemolysis) during the first 3 days of ICU stay.[76,78,79] The Hgb concentration remains stable thereafter in these patients.[79] Conversely, in septic patients, Hgb concentrations on an average decrease by 0.8 g/dL/day during the first 3 days in the ICU and subsequently by 0.3 g/dL/day.[79] Historically, the lower limits of normal Hgb concentration in adults have been suggested to range from 12.7 to 13.7 g/dL in men and

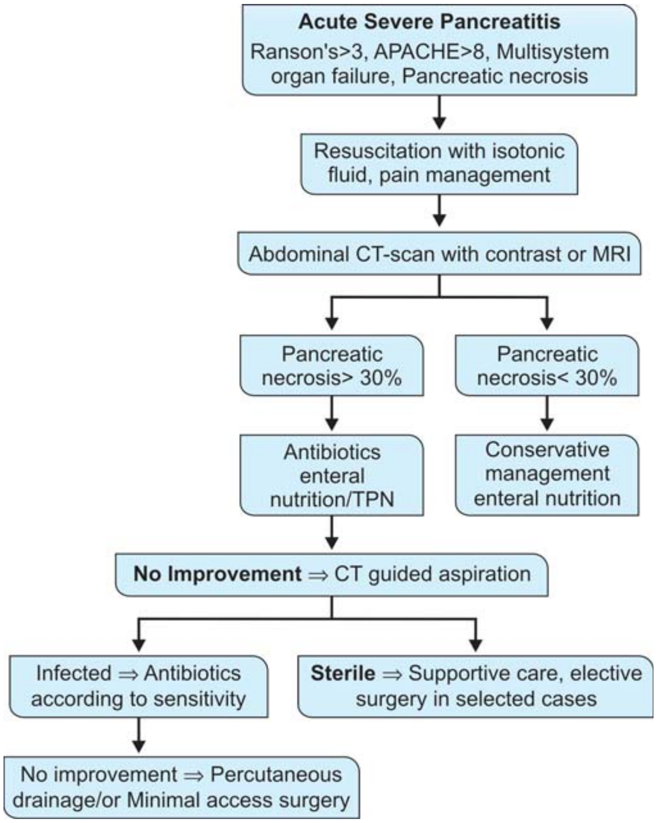
Acute Severe Pancreatitis
Ranson's>3, APACHE>8, Multisystem organ failure, Pancreatic necrosis
Resuscitation with isotonic fluid, pain management
Abdominal CT-scan with contrast or MRI
Pancreatic necrosis> 30%
Pancreatic necrosis< 30%
Antibiotics enteral nutrition/TPN
Conservative management enteral nutrition
No Improvement ⇒ CT guided aspiration
Infected ⇒ Antibiotics according to sensitivity
Sterile ⇒ Supportive care, elective surgery in selected cases
No improvement ⇒ Percutaneous drainage/or Minimal access surgery

Fig. 133.4: Demonstration of an algorithmic approach to the management of acute pancreatitis

Abbreviations: APACHE: Acute physiology and chronic health evaluation, CT-scan: Computerized tomographic scan, MRI: Magnetic resonance imaging, TPN: Total parental nutrition

TABLE 133.10: The different etiologies of anemia in the intensive care unit[72]

Mechanism	*Etiology*
Blood loss	Phlebotomy Gastrointestinal bleeding Other sources of bleeding Surgery and other invasive procedures
Diminished erythropoiesis	Decreased erythropoietin synthesis Erythropoietin resistance Iron deficiency Nutritional deficiencies Myelo-suppressive drugs or toxins Bone marrow disorders Endocrine disorders
Pre-existing chronic anemia	Anemia of chronic disease
Increased erythrocyte destruction	Defective production of Hgb sub-units Hemolysis Autoimmune diseases Drugs
Hemodilution	Aggressive fluid resuscitation

Abbreviations: Hgb-Hemoglobin

11.5 to 12.2 g/dL in women. According to recent data, maintaining Hgb concentration of 7.0 to 9.0 g/dL has been considered to be sufficient and red cell transfusion is considered when Hgb concentration is less than 7.0 g/dL.[71,80,81,82] Clinicians must weigh the potential benefits against the possible risks and complications of red cell transfusions.

Clinical Features

The clinical consequences of anemia will depend on the degree of anemia, the rate at which it has developed, the oxygen demands of the patient which tends to be high in the critically ill, as well as the ability of the patient to compensate for these changes. High-risk groups in which anemia is considered to be less tolerated and more vulnerable to adverse outcomes include the elderly, critically ill patients and patients with respiratory, coronary or cerebrovascular disease.[70] The symptoms and signs are nonspecific.

Diagnosis

Detailed clinical history and physical examination supplemented with laboratory evaluations will give some clues towards the etiology of anemia.[72,83] Laboratory tests include a complete blood count (CBC) including red blood cell indices and white blood cell differentials.[83] It is important to compare these results with prior CBCs so as to determine the onset of the anemia, as well as to identify trends and progression of disease. Other laboratory tests that can be performed as indicated to determine the etiology of anemia includes peripheral blood smear; iron profile studies, folate levels and vitamin B_{12} levels to evaluate nutritional deficiencies; bilirubin level, Lactate Dehydrogenase (LDH) levels, haptoglobin levels and Coomb's test to evaluate degree and type of hemolysis; hemoglobin electrophoresis; thyroid function tests; blood urea nitrogen and creatinine levels; and bone marrow examinations.[83, 84]

Management

Anemia of acute onset such as in gastrointestinal bleeding, is typically treated with the administration of physiologic crystalloids, colloidal fluids or red cell transfusions.[72] However, in patients with a more chronic evolution of anemia, treatment will depend on the underlying etiology.[72] Iatrogenic causes such as phlebotomy are common in the ICU and range from 40 to 70 mL/day.[71,76,79] Blood conservation techniques such as use of small volume phlebotomy tubes, point-of-care analysis and closed, no-waste sampling systems may contribute to the reduction in anemia.[78]

Approximately 70% of critically ill patients are transfused and receive their initial transfusion within the first 48 hours in the ICU.[76] For those patients staying greater than a week in the ICU about 73 to 85% of them will receive red cell transfusions.[71,76] The benefits of red cell transfusions must be weighed against such risks as immunosuppression, allergic reactions and infectious transmissions.[76] Higher transfusion rates have been reported to be associated with increased ICU length of stay, higher rates of coagulation abnormalities, more severe organ failure as well as increased mortality rates.[76,81,82] In light of these risks, alternative treatment strategies have been explored in critically ill patients such as the administration of exogenous human recombinant erythropoietin which has not been reported to result in a decrease in red cell transfusion. Erythropoietin is associated with more thrombotic events.[85-87] There are no widely accepted treatment guidelines for managing anemia in critically ill patients and practice varies between centers. Further research and understanding of anemia, in addition to innovative treatment strategies may promote improved clinical outcomes for critically ill patients.[75]

Indications for Red Blood Cell Transfusion in the ICU

In patients with hemorrhagic shock, initial resuscitation should be done using crystalloids. If the shock is not corrected after 2L of crystalloids, Packed Red Blood Cell (PRBC) transfusion is indicated to improve oxygen delivery to the tissues and should be guided by hemodynamic parameters rather than Hgb measurement.[88] Aggressive measures to control bleeding should accompany resuscitation. Blood lactate levels can be used to guide the adequacy of resuscitation.[89] In patients with hemodynamically stable anemia, transfusion is indicated if the Hgb level drops below 7g/dL and should be guided by the patient's condition rather than the absolute number.[82, 90] Transfusion to improve Hgb > 9 g/dL is not indicated in mechanically ventilated patients, patients with stable coronary disease and stable trauma patients. Transfusion to increase Hgb level > 8g/dL is indicated in patients with acute coronary symptoms. Whenever possible, transfusion should be given in single units.[91]

Massive transfusions, defined as transfusion to replace entire blood volume in 24 hours, are necessary in patients with hemorrhagic shock; however such transfusions are associated with hypothermia, metabolic acidosis and coagulopathy. Hypothermia occurs due to transfusion of stored cold blood and impairment of metabolism leading to delayed clearing of toxins and cytokines. Dilutional coagulopathy along with consumption coagulopathy occurs in these patients and this is further exacerbated by hypothermia that can occur with massive transfusions. A transfusion ratio of 1:1:1 (RBC, fresh frozen plasma, platelets) or whole blood is recommended in case of massive transfusions. Massive transfusions are also associated with hyperkalemia, hypocalcemia, hypomagnesemia, metabolic alkalosis and acidosis.[92] Transfusion associated acute lung injury (TRALI) occurs within 6 hours of transfusion with signs and symptoms of acute respiratory failure. The proposed mechanisms are reaction of donor antibodies against the recipient white blood cells (WBCs) and pulmonary vascular endothelial activation leading to WBC sequestration and endothelial damage.

Thrombocytopenia

Thrombocytopenia occurs frequently in critically ill patients and is the most common coagulation problem in this group of patients.[93,94] Approximately, 50% of critically ill patients may not present with thrombocytopenia at the time of admission into ICU, however, whether present on admission or developing during the ICU course, thrombocytopenia in critically ill patients suggests poor prognosis.[93,94] Depending on the cut off level utilized to define thrombocytopenia (i.e. $<150 \times 10^9$/L vs $< 100 \times 10^9$/L), the type of population being assessed (e.g. medical vs surgical/trauma) and the period of the ICU course (e.g. < 4 days vs ≥ 4 days) being studied, the incidence of thrombocytopenia has been reported to range from 15 to 60%.[94-96] The decreased risk of bleeding with platelet counts between 100 and 150×10^9/L has resulted in a cut off level of $< 100 \times 10^9$/L being proposed as the definition of thrombocytopenia in the critically ill.[94] In addition to increased bleeding risks and consequent necessity for transfusions, thrombocytopenia has also been associated with an increased length of ICU and hospital stay, as well as an increased mortality.[94,96] Not only has the severity of thrombocytopenia been independently associated with a poorer outcome, but the degree of decline in platelet count (i.e. 30 to 50%) over time has also been associated with a higher mortality, even if it remains within the normal range.[93,95,97] The relationship between a low or declining platelet count and mortality is doubtful to be causal but rather influenced by the disease or factors contributing to the development of thrombocytopenia.[93] These etiological factors include but are not limited to sepsis, organ failure, drugs, disseminated intravascular coagulation (DIC), nutritional deficiencies and tranfusion.[96] The mechanisms which may elucidate the development of thrombocytopenia are: spurious (e.g. laboratory error), disorders of distribution (e.g. splenomegaly) and dilution (e.g. massive transfusions), increased platelet destruction (e.g. DIC) and decreased platelet production (e.g. drugs).[94,96] Correction of the underlying cause may contribute to improving platelet counts and consequently prevent delays in required invasive procedures as well as limit the use of platelet transfusions.[94] Heparin induced thrombocytopenia (HIT), an antibody mediated reaction against platelet factor 4 occurs approximately 4 days after initiation of treatment and is associated with thrombotic rather than bleeding risk. Diagnosis is suspected when platelet count decreases by 50% from initial value. Treatment is with thrombin inhibitors– argatroban, hirudin or danaparoid– until platelet count reaches $> 150 \times 10^9$/L.[98]

Clinical Features

The signs and symptoms of thrombocytopenia tend to take place rapidly as platelets have a relatively short 10 day half-life.[83] The type of bleeding may be comparatively mild as in mucosal or cutaneous bleeding, e.g.

TABLE 133.11: The degree of thrombocytopenia and associated bleeding

Platelet count (cells × 10^9/L)	*Risk*
< 100	10-fold increased bleeding risk compared to platelet counts 100 to 150
< 50	Invasive procedures commonly avoided (Surgical bleeding uncommon if platelet counts >50)
< 20	Risk of spontaneous bleeding
< 10	Risk of severe, life-threatening bleeding

epistaxis, gingival bleeding and petechiae, or more severe as in spontaneous intracerebral hemorrhage.[83,94] The risk of bleeding depends on the degree of thrombocytopenia (Table 133.11).[94]

Diagnosis

The evaluation of a patient with thrombocytopenia involves a complete history and physical examination, assessing for what may be contributing to or causing the patient's low platelets such as splenomegaly, recent infections, co-morbidities or medications the patient may be taking or recently have taken. A peripheral blood smear can be essential in also determining the etiology of the patient's thrombocytopenia (Table 133.12).[94]

Management

Platelet concentrates are made by centrifugation of either whole blood or plasma and by apheresis of blood. Simply transfusing patients with platelets to raise levels may be unwarranted, ineffective and even contraindicated in some critically ill thrombocytopenic patients. It is essential to determine the typically multifactorial etiology of thrombocytopenia in these patients and subsequently correct the underlying cause (Table 133.13).[94] This usually results in the increase of platelet counts and possibly limits exposure to the risks of platelet transfusions as well as prevent delays in required invasive procedures.[94] Prophylactic platelet transfusion is given to patients who are actively bleeding with thrombocytopenia or when platelet counts fall below 10 × 10^9/L. The dose for prophylactic transfusion of platelets is controversial. In a recent study published in the New England Journal of Medicine, low, medium or high dose platelet transfusion did not differ in the incidence of bleeding.[99] Therapeutic transfusion is given to patients with thrombocytopenia associated with gross hemorrhage. Usually this bleeding is multifactorial and may not be corrected with platelet transfusion alone. In patients who require interventions, a platelet count > 50 × 10^9/L for trauma and general surgery and >100 × 10^9/L for neurological interventions is required.[100] Each platelet concentrate should produce an increase in platelet count of approximately 5 to 10 × 10^9/L

TABLE 133.12: Possible peripheral blood smear findings and their corresponding etiology and initial diagnostic step[94]

Smear	*Possible etiology*	*Diagnostic step*
Normal	Hypersplenism	Physical exam; imaging test
	Immune-mediated (drugs)	Review medications
	Idiopathic thrombocytopenic purpura (ITP)	Diagnosis of exclusion
Platelet clumping Platelet satellitism	Pseudo-thrombocytopenia	Re-draw specimen in heparin or citrate tube; repeat manual or automated count
Fragmented red blood cells (Schistocytes, helmet cells)	Microangiopathic hemolytic anemia*	Further evaluation based on suspected etiology
Atypical lymphocytes	Viral infection	Viral studies ± further evaluation based on suspected etiology
Oval macrocytes		
Hyperpigmented polymorphonuclear cells	Vitamin B_{12} deficiency Folate deficiency	Check vitamin B_{12} and folate levels
Leukoerythroblastosis	Myelophthisis	Bone marrow biopsy
Blasts	Leukemia	
	Myelo-dysplastic syndrome	Bone marrow biopsy
Dyserythropoiesis		
Dysgranulopoiesis	Myelo-dysplastic syndrome	Bone marrow biopsy
Dysmegakaryopoiesis		
White blood cell left shift	Sepsis	Septic work up

*Microangiopathic hemolytic anemia–Thrombotic thrombocytopenic purpura (TTP), Hemolytic uremic syndrome (HUS), Disseminated intravascular coagulation (DIC), Malignant Hypertension, Pre-eclampsia/eclampsia, HELLP syndrome (Hemolysis, elevated liver enzymes, low platelets), disseminated carcinoma, malfunctioning prosthetic heart valve, vasculitis, scleroderma renal crisis.

TABLE 133.13: The different causes, mechanisms and treatment of thrombocytopenia

Mechanism	*Pathophysiology*	*Etiology*	*Treatment*
Spurious	Clumping of platelets in specimen tube	Laboratory order	Specimen redrawn in heparin or citrate tube
Decreased platelet production	Bone marrow suppression	Nutritional deficiency Drugs; toxins Viral infections Metastases	Replete deficiencies Stop offending agent Supportive care Chemotherapy; radiation therapy
Increased platelet destruction	Non-immune-mediated	DIC	Treat underlying etiology; anticoagulation
		TTP	Plasma exchange
		HELLP	Delivery of infant
	Immune-mediated	Drugs	Stop offending drug
		Type 2 HIT	Stop heparin administration; start direct thrombin inhibitor
		ITP	Steroids; IV Ig; Splenectomy
Dilutional	Infusion of massive amounts of blood products and intravenous fluids	Transfusion for massive blood loss	Platelet transfusion; supportive care
Distributional	Increased platelet sequestration	Splenomegaly; portal hypertension	Supportive care; splenectomy

TTP: Thrombotic thrombocytopenic purpura, DIC: Disseminated intravascular coagulation, HELLP syndrome: Hemolysis, elevated liver enzymes, low platelets, HIT: Heparin-induced thrombocytopenia, ITP: Idiopathic thrombocytopenic purpura.
Adapted from Rice et al.[19]

in an average 70 kg adult. Refractoriness to platelet transfusion may be due to alloimmunization or non-immune factors. Alloimmunization can be prevented by giving ABO matched platelets and HLA compatible donors. Splenectomy may also improve thrombocytopenia in some cases. In patients with life-threatening bleeding and platelet refractoriness, giving frequent small transfusions, intravenous IgG administration, use of antifibrinolytic agents and transfusion of factor VIIa may be helpful.[101,102]

Risks of Transfusion

The administration of blood products is not without risk. These risks could be infectious or immune-mediated in nature (Table 133.14), but the greatest risk results from human error.[103-106] Although the incidence of infectious and immune-mediated events such as ABO incompatibililty has been on the decrease, in recent times the transfusion of blood products has been associated with organ dysfunction, immunosuppression, increased ICU stay and decreased survival.[73,76,82,94,96] Significant progress has been made in diminishing the risks, particularly infectious risks, associated with the transfusion of blood products. Early recognition of adverse events associated with transfusion is vital for patient's safety. Nevertheless, the accumulating body of clinical evidences suggest that the past assumptions of transfusions regularly providing effective therapy for anemia or thrombocytopenia can no longer be adhered to.[107] Transfusion practices vary from country to country and even from center to center within the same country. This has restricted advancement in identifying the best transfusion practice.[108]

Coagulopathy in the Intensive Care Unit

Coagulopathy occurs in critically ill patients due to the underlying illness or medications. There is no recommendation to transfuse patients with coagulopathy if they are not actively bleeding. Fresh frozen plasma is indicated for the replacement of single coagulation factor deficiency, multiple factor deficiencies, for patients with DIC associated with bleeding, during plasma exchange in patients with thrombotic thrombocytopenic purpura and for severe bleeding associated with warfarin-induced coagulopathy. Cryoprecipitate is given to patients when plasma fibrinogen levels are < 1 g/L. Recombinant factor VIIa is used in patients with hemophilia and factor VIII and factor IX inhibitors.

TABLE 133.14: The infectious and non-infectious complications of blood transfusion[105,106,108]

Infectious	HIV	**Non-infectious**	Febrile reactions
	Hepatitis A, B and C virus		Allergic • Urticarial/cutaneous reaction • Anaphylaxis
	Bacterial • *Yersinia enterocolitica* • *Staphylococcus aureus* • *Klebsiella pneumonia* • *Serratia marcescens* • *Staphylococcus epidermidis*		Hemolytic reaction • Acute • Delayed
	Parasites • Plasmodium • Babesia • Trypanosoma		Circulatory overload
	Other viruses • HTLV types I and II • CMV • EBV		Allo-immunization • Red blood cell mediated • Human leukocyte antigen mediated
	Emerging infections • Creutzfeldt-Jakob disease • West nile virus • B19 Parvovirus		TRALI GVHD Transfusion related iron overload Transfusion related Immunomodulation

Abbreviations: CMV – Cytomegalovirus, EBV – Epstein-Barr virus, TRALI – Transfusion associated lung injury, GVHD – Graft-versus-host disease, HIV–Human immunodeficiency virus, HTLV–Human T-cell lymphotropic virus.

RENAL DISEASE IN CRITICAL CARE

Acute Kidney Injury

A normally functioning kidney eliminates urea and other nitrogenous waste products, in addition to regulating fluid, electrolyte and acid-base equilibrium.[109] Conversely, renal dysfunction results in the build-up of uremic toxins and nitrogenous waste products (azotemia) as well as an imbalance in the fluid, electrolyte and acid-base equilibrium, as a consequence of reduction in the Glomerular Filtration Rate (GFR).[110] Acute Kidney Injury (AKI), formerly referred to as acute renal failure, is said to occur when renal dysfunction takes place suddenly and/or rapidly.[111,112] Various definitions for AKI have been reported in the literature,[113,114] resulting in wide-ranging incidence and mortality rates of 1 to 25% and 15 to 90% respectively in intensive care units.[109,115-123] The need for a consensus definition for AKI resulted in the development of the RIFLE classification (Table 133.15) by the Acute Dialysis Quality Initiative (ADQI) group,[114,124-126] which was later modified by the Acute Kidney Injury Network (AKIN) to comprise smaller increases in serum creatinine, introduction of a time frame (48 hours) to the diagnosis of AKI and the elimination of Loss and End-stage renal disease as categories (Table 133.15).[127] Both classifications are associated with increased mortality with worsening degrees of AKI. The change in nomenclature to AKI now encompasses a broader spectrum of disease with different levels of severity, ranging from minor renal dysfunction to total organ failure necessitating renal replacement therapy.[109,112,116]

The etiology of AKI has typically been separated into three categories:

1. Pre-renal
2. Intrinsic renal
3. Post-renal azotemia (Table 133.16)[111]

So, it guides the mode of therapeutic intervention. However, in ICU patients, etiology of AKI is usually a result of multiple factors which could easily fall into any or more commonly, a combination of the aforementioned categories, thus complicating the manner in which such patients can be treated successfully.[112]

TABLE 133.15: The RIFLE and AKIN classification of acute kidney injury

	GFR criteria	*Urine output criteria*
RIFLE category		
Risk	Increased serum creatinine × 1.5 or GFR decrease > 25%	UO < 0.5 ml/kg/h × 6h
Injury	Increased serum creatinine × 2 or GFR decrease > 50%	UO < 0.5 ml/kg/h × 12h
Failure	Increased serum creatinine × 3 or GFR decrease > 75% or serum creatinine ≥ 4 mg/dl (with acute rise ≥ 0.5 mg/dl)	UO < 0.3 ml/kg/h × 24h or Anuria × 12h
Loss	Persistent ARF → complete loss of renal function > 4 weeks	
ESRD	End-stage renal disease → complete loss of renal function > 3 months	
AKIN stage		
1	Increased serum creatinine ≥ 0.3 mg/dl (≥ 26.4 μmol/l) or increase ≥ 150% to 200% (1.5- to 2- fold) from baseline	UO < 0.5 ml/kg/h for > 6h
2	Increased serum creatinine > 200% to 300% (>2- to 3-fold) from baseline	UO < 0.5 ml/kg/h for > 12h
3	Increased serum creatinine > 300% (3-fold) from baseline or serum creatinine ≥ 4.0 mg/dl with an acute increase of at least 0.5 mg/dl	UO < 0.3 ml/kg/h for > 24 h or anuria for 12 hours

Abbreviations: GFR: Glomerular filtration rate; UO: Urine output; ARF: Acute renal failure; ESRD: End-stage renal disease; AKIN: Acute kidney injury network; RIFLE: Risk, injury, failure, loss, ESRD.
Adapted from Bellomo R et al.[126] and Mehta RL et al.[127]

TABLE 133.16: Various causes of acute kidney failure in intensive care unit[111]

Pre-renal		*Intrinsic*		*Post-renal*
	Acute tubular necrosis	Glomerulonephritis	Interstitial nephritis	
Sepsis*	Hypotension/shock	Post-infectious GN	Medications (NSAID, antibiotics, diuretics)	Bladder neck obstruction (prostate disease)
Low cardiac output state	Sepsis*	Vasculitis (Wegener's granulomatosis, lupus nephritis)	Infections	Ureteric obstruction (pelvic malignancy, renal calculi)
Medications (diuretics, NSAID)	Rhabdomyolysis	Goodpasture's syndrome	Immunologic causes	
Burns	Medications (antibiotics, antivirals, antifungals, radiocontrast dye)	Rapidly progressive GN		Neurogenic bladder
Surgery (cardiac, vascular)	Burns	Medications (NSAID, biphosphonates)		
Shock (anaphylactic, hemorrhagic, hypovolemic)	Transfusion reactions Hemolysis Tumor lysis syndrome			
Hepatorenal syndrome				
Abdominal compartment syndrome				

Abbreviations: GN: Glomerulonephritis; GI: Gastrointestinal; NSAID: Non-steroidal anti-inflammatory drug.
*Sepsis is the most common cause of acute kidney injury in the ICU in up to 50% of cases.
Adapted from Abuelo JG[111] and Bellomo R et al.[126]

Clinical Presentation

Acute kidney injury can affect multiple organ systems. The reduction in GFR and urine output can result in fluid overload which may further progress into congestive heart failure and hypotension, raised intra-abdominal pressure from retroperitoneal tissue edema and ascites, hypertension from intravascular volume overload as well as pulmonary compromise from congestion and pleural effusions.[128] Electrolyte abnormalities such as metabolic acidosis and hyperkalemia commonly occur predisposing to cardiac arrhythmias. Critically ill patients with AKI can also develop a compromised inflammatory and immune response which increases the risk for infection, pneumonia, shock or other multi-organ failure.[128] The uremic state in these patients can contribute to the development of anorexia, vomiting, encephalopathy, pericarditis, bleeding diathesis, polyneuropathy and anemia from increased erythrocyte destruction which can be further complicated by weakness and easy fatiguability.[128,129] These multiple adverse effects contribute to the increased mortality in critically ill patients with AKI.

Diagnosis

The diagnosis of AKI involves taking a detailed clinical history, physical examination and the performance of relevant tests which may aid in determining the etiology such as, Blood Urea Nitrogen (BUN), serum creatinine, urine microscopy, urine chemistry and renal ultrasound.[112,130] The serum creatinine is a commonly used tool in diagnosing AKI; however, it is important to note that like all approximations of GFR, it is not an accurate reflection of the latter in ICU patients who tend to be in a non-steady state. In such patients, it tends to underestimate the degree of renal dysfunction such that large changes in GFR are mirrored by only small changes in the serum creatinine.[112,118] Nonetheless, it is the change in serum creatinine that provides clinical benefit in diagnosing AKI. Urine chemistries such as the fractional excretion of sodium and urea (Table 133.17) may help in distinguishing pre-renal from renal causes of AKI (Table 133.18); although in ICU patients these tend to co-exist.[112,130] Finally, due to limitations of the aforementioned diagnostic tools, AKI biomarkers such as cysteine-rich protein 61, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, cystatin C and urine interleukin-18, are actively being investigated as alternatives for the earlier detection of AKI prior to functional deterioration.[109,112,130]

TABLE 133.17: The calculation formulas for the fractional excretions of sodium and urea

Fractional excretion of sodium

$FE_{Na} = \{(U_{Na} / P_{Na}) \div (U_{Cr} / P_{Cr})\} \times 100$

Fractional excretion of urea*

$FE_{Ur} = \{(U_{Ur} / P_{Ur}) \div (U_{Cr} / P_{Cr})\} \times 100$

Abbreviations: FE_{Na}: Fractional Excretion of Sodium; U_{Na}: Urine Sodium Concentration (mEq/L); P_{Cr}: Plasma Creatinine Concentration (mg/dL); U_{Cr}: Urine Creatinine Concentration (mg/dL); P_{Na}: Plasma Sodium Concentration (mEq/L); FE_{Ur}: Fractional Excretion of Urea; U_{Ur}: Urine Urea Concentration (mg/dL); P_{Ur}: Plasma Urea Concentration (mg/dL).

*Provides information similar to the fractional excretion of sodium, but in contrast, can be used in patients on diuretic therapy.

Management

The treatment of ICU patients with AKI can be challenging as the majority of these patients develop AKI from multiple precipitating factors and commonly have co-existing multiorgan failure.[110,112] Nonetheless, treatment strategies are initially targeted at correcting the suspected underlying cause. Such treatment may include but is not limited to fluid resuscitation with or without inotropic or vasopressor support to maintain hemodynamic stability and renal perfusion, correction of metabolic abnormalities, discontinuation of nephrotoxic agents or dosage adjustments of medications eliminated through the kidney, as well as the provision of adequate nutrition.[112,130]

With regards to fluid resuscitation, there is no difference in survival when comparing crystalloids with colloids (albumin).[131] In patients with head trauma, colloid resuscitations have been found to increase mortality.[132] In addition, synthetic colloids are associated with an increased incidence of kidney injury, especially

TABLE 133.18: Delineation of laboratory features for differentiating pre-renal and renal causes of acute kidney injury

Urinary diagnostic indices	*Pre-renal*	*Renal*
BUN:Cr ratio	> 20:1	< 20:1
Urine sodium (mEq/L)	< 20	> 40
FE_{Na} (%)	< 1	> 2
FE_{Ur} (%)	< 35	> 50
Urine osmolality (mOsm/L)	> 500	< 350
Urine microscopy	Normal (except for occasional hyaline casts)	Abnormal

Abbreviations: BUN: Blood urea nitrogen; Cr: Creatinine; FE_{Na}: Fractional excretion of sodium; FE_{Ur}: Fractional excretion of urea the large molecular preparations used for resuscitation.[133,134] Furthermore, though fluid resuscitation can be crucial in these patients, a positive fluid balance is also associated with an increased mortality.[135]

The role of diuretic agents in the treatment of AKI remains controversial.[112] Diuretics have not been found to improve overall mortality, need for renal replacement therapy or shorten the duration of AKI.[136] At the present time, there is no evidence supporting the routine use of diuretics in patients with AKI or to convert oliguric renal failure to nonoliguric renal failure. In addition, there is no consensus regarding the most appropriate time to start Renal Replacement Therapy (RRT) for AKI. However, severe hyperkalemia, severe metabolic acidosis, uremic complications such as encephalopathy, pericarditis, pleuritis or bleeding diathesis and volume overload are generally considered to be absolute indications for RRT, which could either be continuous or intermittent.[112]

Similarly, there is also no consensus regarding the dose of hemofiltration or the renal replacement modality, i.e. continuous versus intermittent. A detailed description of modes of renal replacement therapy is beyond the scope of this chapter.

Prevention of Acute Kidney Injury

Early recognition of underlying risk factors and prevention of additional injuries in high risk patients are particularly important. Maintaining adequate renal perfusion, prevention of hyperglycemia and avoidance of nephrotoxins are some of the strategies used for this purpose.

Radioiodine contrast-induced nephropathy can be prevented by using a low volume nonionic low osmolar or iso-osmolar agent in a well-hydrated patient. There is no significant advantage in using sodium bicarbonate over sodium chloride solution.[137] Prophylactic administration of N-acetyl cysteine to prevent renal failure is also controversial.[138,139] In patients who must undergo radiological studies utilizing contrast, adequate hydration, use of prophylactic N-acetyl cysteine, avoidance of other nephrotoxic agents and use of low volume non-ionic low or iso-osmolar agents are recommended.

Acute kidney injury is common in patients with hepatic failure admitted to ICUs. In cirrhotic patients requiring large volume paracentesis and in patients with spontaneous bacterial peritonitis, the administration of intravenous albumin decreases the incidence of AKI.[140] In patients with hepatorenal syndrome, use of a splanchnic vasoconstrictor like telipressin may improve kidney function.[141] Noradrenaline has also been reported to be as effective as telipressin in decreasing serum creatinine.[142] Similarly, other agents like octreotide and midodrine have been found useful in this condition.[143] Nonetheless, the definitive treatment for hepatorenal syndrome is liver transplantation.

In summary, acute kidney failure is common in critically ill patients and is associated with significant increase in mortality. Prevention of renal injury is important. Most of the treatment modalities are controversial and need further studies.

ENDOCRINE EMERGENCIES IN CRITICAL CARE

Patients with endocrine emergencies are uncommonly admitted to critical care units. The accurate and early diagnosis of these entities is absolutely important for better outcomes in these patients. In this section, we will discuss the clinical presentation, diagnosis and management of the common endocrine emergencies.

Thyroid Storm

Hyperthyroid patients present with palpitations, unexplained weight loss, diarrhea and intolerance to heat and muscle weakness. Thyroid storm is a hyperthyroid state where the symptoms are exaggerated and associated with 20 to 50% mortality. The common causes are Grave's disease, chronic and subacute thyroiditis, postpartum thyroiditis and excessive iodine intake. It can also be precipitated by stress, surgery, sepsis or cardiovascular events in a preexisting hyperthyroid patient.

Clinical and Diagnostic Features

Patients can present with cardiac arrhythmias, widened pulse pressure, congestive heart failure, systemic inflammatory response syndrome, hypotension, psychosis, delirium and coma. A scoring system based on the signs and symptoms seen in thyroid storm are shown in Table 133.19.[144] The laboratory findings specific to the thyroid gland include a low or undetectable Thyroid Stimulating Hormone (TSH) level and a high thyroxine (T4) level.

Management

The key is to start treatment as soon as the thyroid storm is clinically suspected. The therapeutic regimen involves the use of various agents. Patients should be stabilized with fluids if hypotensive or with diuretics in case of congestive heart failure. Adequate oxygenation should be maintained and often these patients may need mechanical ventilatory support. Fever should be controlled by cooling

TABLE 133.19: The scoring system for the clinical evaluation of a thyroid storm

Thermoregulatory dysfunction		**Cardiovascular dysfunction**	
Temperature		Tachycardia	
99-99.9	5	99-109	5
100-100.9	10	110-119	10
101-101.9	15	120-129	15
102-102.9	20	130-139	20
103-103.9	25	≥ 140	25
≥ 104.0	30	**Congestive heart failure**	
Central nervous system effects		Mild	5
Mild	10	Pedal edema	
Agitation		Moderate	10
Moderate		Bibasilar rales	
Delirium, Psychosis	20	Severe	
Extreme lethargy		Pulmonary edema	15
Severe		Atrial fibrillation	10
Seizure	30		
Coma		**Precipitant history**	
		Negative	0
		Positive	10
GI/Hepatic dysfunction		**Total score**	**Diagnosis**
Moderate			
Diarrhea, abdominal pain	10	≥ 45	More likely
Nausea/vomiting			
Severe	20	25 to 44	Suggestive
Unexplained jaundice		≤ 25	Less likely

Adapted from Burch HB et al.[144]

and the use of acetaminophen. Specific treatment initially involves the prevention of thyroid hormone synthesis by using thionamides. Either propylthiouracil or methimazole can be used. Propylthiouracil has the advantage of decreasing peripheral conversion of T4 to triiodothyronine (T3). Propylthiouracil is given at a dose of 200 mg every 4 hours and methimazole is given at a dose of 30 mg every 6 hours.[145] Unlike propylthiouracil, methimazole cannot be given in pregnancy. The serious side effects of thionamides are agranulocytosis (dose dependent), anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis and hepatic failure. The second step is to prevent the release of synthesized hormone from the thyroid gland. Lugol's iodine (10 drops, 3 times daily) or saturated solutions of potassium iodide [SSKI (5 drops every 6 hours)] is used for this purpose.[146] It is important to give iodine only after giving hormone synthesis blocking agents. Lithium carbonate also decreases the release of thyroid hormone but is rarely used due to its toxicity. The third step is to give agents to prevent conversion of T4 to T3. These include glucocorticosteroids and iodinated contrast solutions. The administration of beta- (β) blockers will counteract the sympathetic stimulation and propanolol is the drug of choice. It is given intravenously 1 mg/minute. Alternative agents are nadolol or esmolol. Patient with contraindications to β-blockers can be given calcium channel blockers as an alternative.

Myxedema Coma

Myxedema coma is a rare but life-threatening complication that results from severe untreated hypothyroidism or long standing hypothyroidism.[147] It can be precipitated by trauma, surgery, severe infection and cold stress especially with the usage of sedative, hypnotic and narcotic medications.[148]

Clinical and Diagnostic Features

Myxedema is characterized by distinct clinical features rather than by laboratory findings suggestive of

TABLE 133.20: The clinical features of myxedema coma based on the organ system involved

System	*Clinical features*
Neurological	Mental obtundation, delayed relaxation phase of reflexes
Cardiovascular	Bradycardia, hypotension, EKG changes, pericardial effusions
Endocrine	Hypoglycemia, hyponatremia, hypothermia
Respiratory	Hypoventilation, pleural effusions
Gastrointestinal	Paralytic ileus, ascites
Genitourinary	Atonic bladder, urinary retention
Integumentary	Alopecia, coarse dry skin, myxedema facies

hypothyroidism. Clinical features of myxedema coma are outlined in Table 133.20.

The role of laboratory findings is to confirm the diagnosis and delineate co-existing or precipitating conditions. Low TSH levels along with low total and free serum T4 and T3 levels are noted in primary hypothyroidism. High TSH levels with below normal levels of T3 are seen in secondary hypothyroidism. Low sodium levels with elevated levels of lactate dehydrogenase (LDH) and creatinine are also seen.

Management

Because of the high mortality associated with this condition, patients should be monitored in the ICU.[149] Supportive care, treatment of hypothermia, monitoring of the neurological and respiratory status should be emphasized along with the supplementation of thyroid hormones.[150,151] Treatment is outlined in Table 133.21. The optimal dose of thyroid replacement remains controversial.

Both thyroid storm and myxedema coma are associated with significant mortality and early recognition and treatment are important for a favorable outcome.

TABLE 133.21: The management of myxedema coma in a critical care setting

Supportive care	• Invasive mechanical ventilation to bypass mechanical obstruction caused by large tongue • Fluid and vasopressor administration for hypotension • Passive re-warming for hypothermia • Stress dose corticosteroids for possible co-existing adrenal insufficiency • Monitoring and correction of electrolyte abnormalities
Replacement of thyroid hormone	• Both T4 and T3 given intravenously • Bolus of 300-500 μg followed by 50-100 μg daily • Use caution in elderly patients and patients with myocardial injury • Pregnant patients may need higher doses
Management of co-existing conditions	• Panculture and initiation of broad-spectrum antibiotics

Acute Adrenal Insufficiency

Acute adrenal insufficiency is seen in patients with bilateral adrenal hemorrhage, undiagnosed adrenal insufficiency with stress, trauma, surgery, drugs especially etomidate and previous steroid therapy, and pituitary apoplexy.[152-154] The clinical and laboratory features associated with acute adrenal insufficiency or adrenal crisis are outlined in Table 133.22.

Diagnosis is difficult due to diurnal variation of cortisol secretion. Cortisol levels are higher in the morning and lower in the evening. A cortisol level of less than 3 mcg/dL in the morning is diagnostic of adrenal insufficiency and a level less than 10 mcg/dL is suggestive of the diagnosis.[155] The Adrenocorticotropic Hormone (ACTH) stimulation test is used to establish a definitive diagnosis. In cases of suspected adrenal crisis, treatment with hydrocortisone or dexamethasone should be started immediately and not delayed by confirmatory tests. The supportive measures include volume administration with isotonic fluids with glucose in case of hypoglycemia. Precipitating causes must be sought and treated. Management of adrenal insufficiency in patients with septic shock will be described elsewhere.

Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

Diabetic Ketoacidosis (DKA), hyperosmolar Hyperglycemic State (HHS) and drug-induced hypoglycemia

TABLE 133.22: The clinical and laboratory findings that can be seen in patients with adrenal crisis

- Dehydration, hypotension or shock out of proportion to severity of current illness
- Nausea and vomiting with a history of weight loss and anorexia
- Abdominal pain (acute abdomen)
- Unexplained hypoglycemia
- Unexplained fever
- Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia
- Hyperpigmentation or vitiligo
- Other autoimmune endocrine deficiencies, such as hypothyroidism or gonadal failure

are the major complications of diabetes mellitus. Both DKA and HHS are due to insulin deficiency and excessive counter-regulatory hormones. A detailed description of the pathogenesis is beyond the scope of this chapter, however, a synopsis is demonstrated in Figure 133.5.[156] The precipitating factors contributing to the development of DKA and HHS are also outlined in Table 133.23.[156]

Clinical and Diagnostic Features

DKA and HHS patients usually present with nausea, vomiting, abdominal pain, shortness of breath, polyuria and polydipsia. As the condition worsens they develop neurological symptoms which may progress to coma. The initial evaluation should assess hemodynamic status and airways. The investigations to be performed include WBC count, complete metabolic panel, plasma osmolality, urine analysis, serum and urine ketones, arterial blood gases, electrocardiogram (ECG) and Chest X-ray (CXR). The characteristic findings and differences are described in Table 133.24.[157] Metabolic acidosis is the hallmark of DKA. Other causes of metabolic acidosis are outlined in Table 133.25.[156]

Management

A management algorithm is described in Figure 133.6.[158] These patients should be managed in the ICU. If potassium is less than 3 mEq/L, replenish potassium to above 3.3 mEq/L before initiating insulin. Sodium bicarbonate is given only when the arterial pH is less than 7. The insulin infusion is typically continued until ketoacidosis is resolved. Blood glucose should be

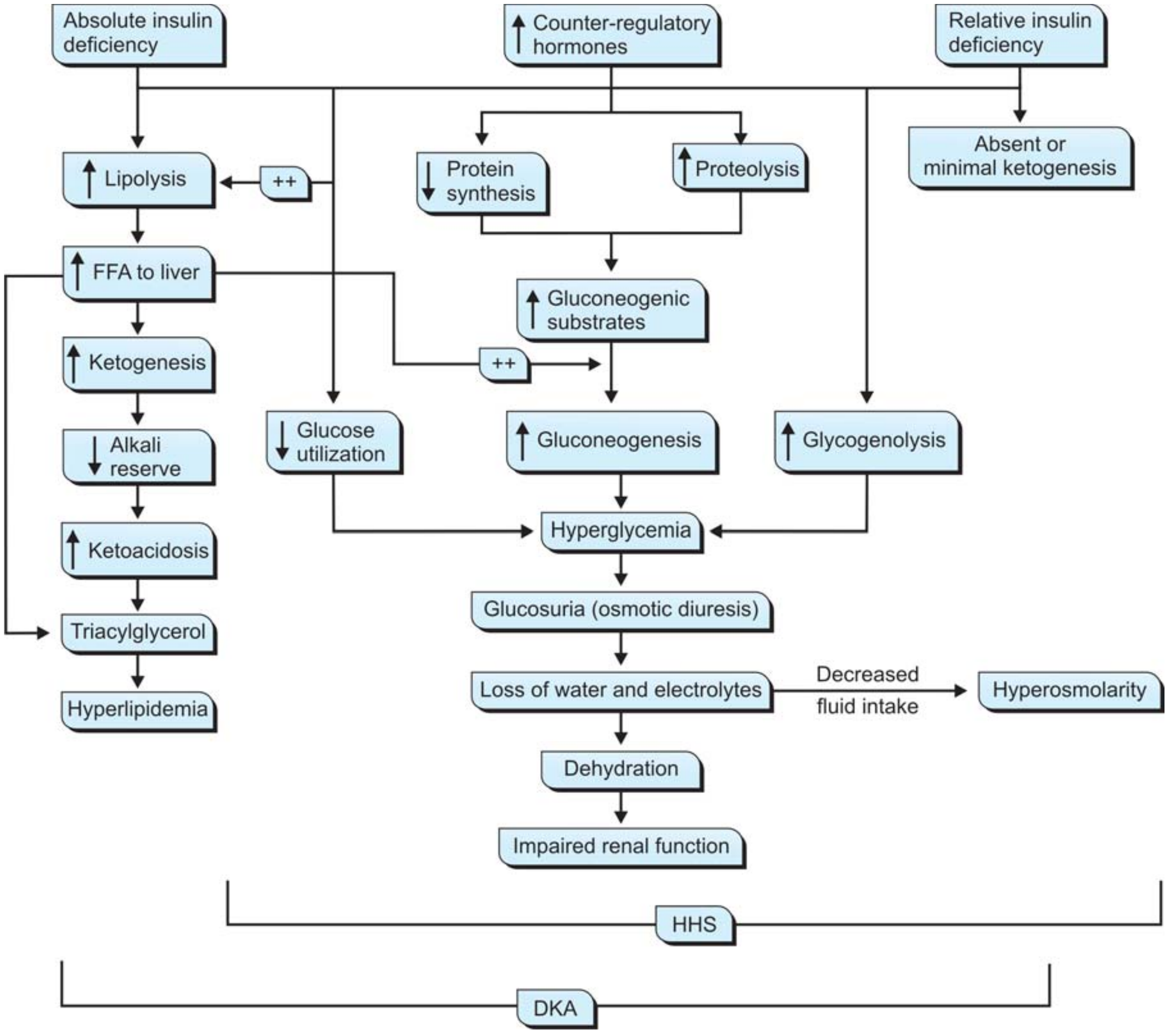
Absolute insulin deficiency
↑ Counter-regulatory hormones
Relative insulin deficiency
↑ Lipolysis
++
↓ Protein synthesis
↑ Proteolysis
Absent or minimal ketogenesis
↑ FFA to liver
↑ Gluconeogenic substrates
↑ Ketogenesis
++
↓ Alkali reserve
↓ Glucose utilization
↑ Gluconeogenesis
↑ Glycogenolysis
↑ Ketoacidosis
Hyperglycemia
Glucosuria (osmotic diuresis)
Triacylglycerol
Loss of water and electrolytes
Decreased fluid intake
Hyperosmolarity
Hyperlipidemia
Dehydration
Impaired renal function
HHS
DKA

Fig. 133.5: A flow diagram depicting the pathophysiology of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS).
Kitabchi AE et al[156]

TABLE 133.23: Some of the precipitating factors that can contribute to the development of a hyperosmolar hyperglycemic nonketotic syndrome and diabetic ketoacidosis

Inadequate insulin treatment or non-compliance	21 to 41%
Acute illness	32 to 60%
Infection	Pneumonia, urinary tract infection, sepsis
Neurological	CVA
Endocrine	Acromegaly, thyrotoxicosis, Cushing syndrome
Gastrointestinal	Peritoneal dialysis, mesenteric thrombosis, acute pancreatitis
Cardiopulmonary	Acute PE, MI
Other	Heat stroke, hypothermia, severe burns
Predisposing factors for DKA	
Inadequate insulin treatment or non-compliance	Most common cause
New onset diabetes	20 to 25%
Acute illness	Infection (30 to 40%), CVA, MI, acute pancreatitis
Drugs	

Abbreviations: UTI – Urinary Tract Infection, CVA – Cerebrovascular Accident, PE – Pulmonary Embolus, MI – Myocardial Infarction, Kitabchi AE, et al.[156]

Table 133.24: The criteria utilized in diagnosing diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS)

Parameter		*DKA*		*HHS*
	Mild	*Moderate*	*Severe*	
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10	>18
Urine ketones	Positive	Positive	Positive	Small
Serum ketones	Positive	Positive	Positive	Small
Effective serum osmolality (mOsm/kg)	Variable	Variable	Variable	>320
Anion gap	>10	>12	>12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/ drowsy	Stupor/ coma	Stupor/ coma

Kitabchi AE, et al.[157]

TABLE 133.25: The laboratory evaluation of the metabolic causes of acidosis and coma

	Starvation or high fat intake	*DKA*	*Lactic acidosis*	*Uremic acidosis*	*Alcoholic ketosis (starvation)*	*Salicylate intoxication*	*Methanol or ethylene glycol intoxication*	*Hyper osmolar coma*	*Hypoglycemic coma*	*Rhabdo myolysis*
pH	Normal	↓	↓	Mild ↓	↓ ↑	↓ ↑*	↓	Normal	Normal	Mild ↓ may be ↓↓
Plasma glucose	Normal	↑	Normal	Normal	↓ or normal	Normal or ↓	Normal	↑↑ >500 mg/dl	↓↓ <30 mg/dl	Normal
Glycosuria	Negative	++	Negative	Negative	Negative	Negative•	Negative	++	Negative	Negative
Total plasma ketones$^{\Delta}$	Slight ↑	↑↑	Normal	Normal	Slight to moderate↑	Normal	Normal	Normal or slight ↑	Normal or slight ↑	Normal
Anion gap	Slight ↑	↑	↑	Slight ↑	↑	↑	↑	Normal	Normal or slight ↑	↑↑
Osmolality	Normal	↑	Normal	↑	Normal	Normal	↑↑	↑↑ >330 mOsm/kg	Normal	Normal or slight ↑
Uric acid	Mild (starvation)	↑	Normal	Normal	↑	Normal	Normal	Normal	Normal	↑
Miscellaneous		May give false-positive for ethylene glycol	Serum lactate >7 mmol/l	BUN >200 mg/dl		Serum salicylate positive	Serum levels positive			Myoglobinuria, hemoglobinuria

Acetest and Ketostix measure acetoacetic acid only - values obtained may be misleading low because the majority of ketone bodies are β-hydroxybutyrate; + Positive; • Respiratory alkalosis/metabolic acidosis; ∆ May get false-positive or false-negative urinary glucose caused by the presence of salicylate or its metabolites.

Kitabchi AE et al.[156]

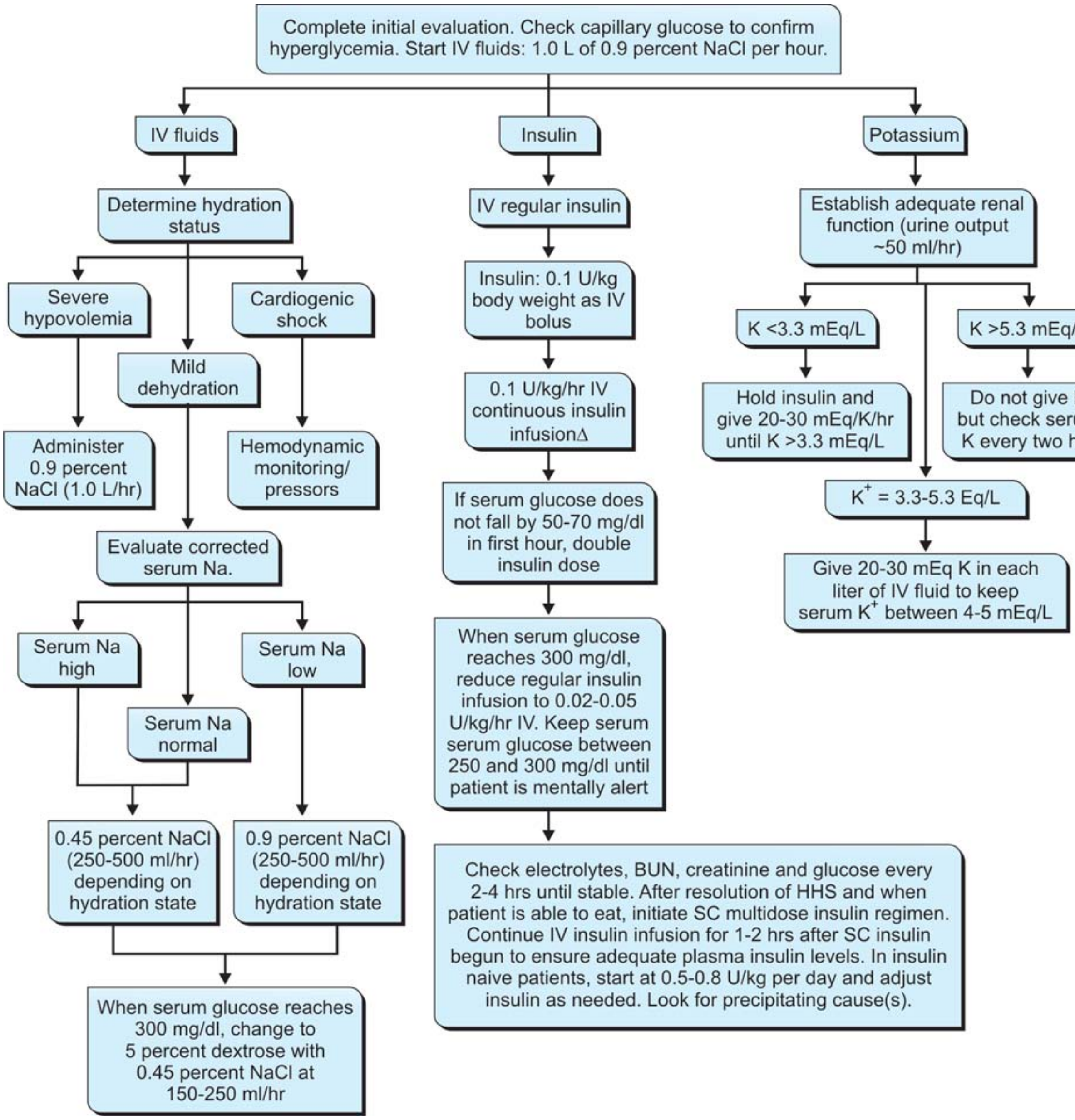
Complete initial evaluation. Check capillary glucose to confirm hyperglycemia. Start IV fluids: 1.0 L of 0.9 percent NaCl per hour.
IV fluids
Insulin
Potassium
Determine hydration status
IV regular insulin
Establish adequate renal function (urine output ~50 ml/hr)
Severe hypovolemia
Cardiogenic shock
Mild dehydration
Insulin: 0.1 U/kg body weight as IV bolus
K <3.3 mEq/L
K >5.3 mEq/L
Administer 0.9 percent NaCl (1.0 L/hr)
Hemodynamic monitoring/ pressors
0.1 U/kg/hr IV continuous insulin infusionΔ
Hold insulin and give 20-30 mEq/K/hr until K >3.3 mEq/L
Do not give K but check serum K every two hrs
If serum glucose does not fall by 50-70 mg/dl in first hour, double insulin dose
K⁺ = 3.3-5.3 Eq/L
Evaluate corrected serum Na.
Give 20-30 mEq K in each liter of IV fluid to keep serum K⁺ between 4-5 mEq/L
Serum Na high
Serum Na low
Serum Na normal
When serum glucose reaches 300 mg/dl, reduce regular insulin infusion to 0.02-0.05 U/kg/hr IV. Keep serum serum glucose between 250 and 300 mg/dl until patient is mentally alert
0.45 percent NaCl (250-500 ml/hr) depending on hydration state
0.9 percent NaCl (250-500 ml/hr) depending on hydration state
Check electrolytes, BUN, creatinine and glucose every 2-4 hrs until stable. After resolution of HHS and when patient is able to eat, initiate SC multidose insulin regimen. Continue IV insulin infusion for 1-2 hrs after SC insulin begun to ensure adequate plasma insulin levels. In insulin naive patients, start at 0.5-0.8 U/kg per day and adjust insulin as needed. Look for precipitating cause(s).
When serum glucose reaches 300 mg/dl, change to 5 percent dextrose with 0.45 percent NaCl at 150-250 ml/hr

Fig. 133.6: An algorithm on the management of patients with hyperosmolar hyperglycemic non-ketotic syndrome and diabetic ketoacidosis.
Abbreviations: IV: intravenous; SC: subcutaneous.
Umpierrez GE et al.[158]

monitored every hour while on an insulin infusion while other laboratory tests, i.e. basic metabolic profile are monitored every 3 to 4 hours. The complications of untreated DKA and HHS are cerebral edema particularly in children and noncardiogenic pulmonary edema.[157,159] Patients must be monitored for hypoglycemia and hypokalemia. Almost all patients with DKA develop a non-anion gap metabolic acidosis with treatment and phosphate repletion is not recommended for patients with DKA.[160]

Hypoglycemia in diabetic patients occurs either due to insulin excess or as a result of failure of the counter regulatory hormones. Symptoms and signs are usually non-specific. Severe hypoglycemia causes seizure and coma and should be treated with glucagon 0.5 to 1mg subcutaneous or intramuscularly as well as intravenous glucose (dextrose).

NEUROLOGICAL DISORDERS IN CRITICAL CARE

Acute Ischemic Stroke

A stroke is a focal neurological deficit that is typically of acute onset and results from a disruption of the cerebral blood flow. It usually occurs suddenly, but occasionally progresses in a more gradual fashion. The majority of stroke presentations result from cerebral ischemia, while hemorrhage (intra-cerebral or subarachnoid) cause the rest.[161] Acute ischemic stroke is being discussed here while intra-cerebral and subarachnoid hemorrhages are discussed in subsequent sections. The mechanisms causing ischemic strokes could be grouped into atherothrombotic, cardioembolic, lacunar and cryptogenic types (Table 133.26).[162,163] Strokes may result in permanent disability and prognosis tends to be poorer in older patients, as well as patients with underlying co-morbidities such as diabetes or heart disease.[161,164] Time is of the essence in the management of these patients. The advent and widespread utilization of thrombolytic therapy within 3 hours of developing ischemic stroke, has revolutionized the management of what was once considered a condition with few treatment choices.[165]

TABLE 133.26: The different pathophysiological mechanisms contributing to the development of ischemic stroke

Pathophysiology	*Frequency of ischemic stroke*
Atherosclerotic cerebrovascular disease	
Hypoperfusion	
Arteriogenic emboli	20%
Lacunar (small penetrating artery disese)	
Arterial thrombosis 2^o atheroma formation or lipohyalinosis	25%
Cardiogenic embolism	
Atrial fibrillation	
Valvular heart disease	
Atrial or ventricular thrombi	20%
Atrial myxoma	
Bacterial endocarditis	
Cryptogenic	30%
Other	
Prothrombotic states	
Dissections	5%
Arteritis	
Migraines/vasospasms	
Drug abuse	

Adopted from Albers et al.[162,163]

Clinical Features

Thrombotic strokes tend to present with clinical features that evolve over hours to days whereas embolic strokes have a sudden or rapid onset at maximum severity at the time or presentation. The pattern of neurological impairment will depend on the vascular territory involved (Table 133.27).

Diagnosis

It is essential to obtain a comprehensive history, particularly determining the time of symptom onset, any recent events like trauma, surgery, myocardial infarction or prior stroke, medication use such as anticoagulants, insulin or anti-hypertensives, and evaluation of other co-morbidities which are present.[166] A complete physical examination with emphasis on the neurological system should also be performed when a patient presents with a neurological deficit suggestive of an ischemic event.

TABLE 133.27: The clinical presentation of acute ischemic stroke in relation to the vascular region involved

Vascular territory	*Neurological deficit*
Anterior cerebral artery	Contralateral hemiparesis and hemisensory deficit (leg > arm), urinary incontinence, abulia, confusion, primitive reflexes (sucking, grasp), apraxia.
Middle cerebral artery	Contralateral hemiparesis and hemisensory deficit (face and arm > leg and foot), homonymous hemianopsia, ipsilateral gaze preference, aphasia (Broca's and Wernicke) with dominant (left-sided) hemisphere lesion, neglect with non-dominant (right-sided) hemisphere lesion.
Posterior cerebral artery	Contralateral hemiparesis and hemisensory deficit, altered mental status, ophthalmoplegia from 3rd cranial nerve palsy, macular-sparing homonymous hemianopsia, visual agnosia, visual hallucinations, alexia without agraphia, disorders of color perception, amnesia.
Vertebrobasilar	Deficits involve the medulla (medial or lateral medullary syndrome), pons (locked-in syndrome), midbrain and cerebellum; and consist of dysphagia, dysarthria, diplopia, dizziness, vertigo, nausea, vomiting, Horner's syndrome, cranial nerve palsies, limb and gait ataxia, motor and sensory deficits involving both parts of the body.
Lacunar	Pure hemiparesis, pure hemisensory deficit, ataxic hemiparesis, dysarthria-clumsy hand.

Certain conditions are known to mimic the clinical features of ischemic strokes and include but are not limited to intracranial bleeds, seizures with postictal paresis, syncope, systemic infection, brain tumors, complicated migraines, conversion disorders, hypertensive encephalopathy, hypothyroidism, hyperglycemia, hypoglycemia and hyponatremia.[161,165-167] It is important to distinguish these mimics from ischemic strokes so as to treat the patients appropriately. The National Institute of Health Stroke Scale (NIHSS) is a 42-point scale based on neurological deficits elicited on physical examination (Table 133.28).[168] It is commonly utilized to quantify the severity of the neurological deficit. Initial general tests to be performed include complete blood count, coagulation profile, serum electrolytes, serum glucose, renal function, electrocardiography and chest radiography.[161,165,167,169] Specific tests that are to be performed promptly are CT-scan or Magnetic Resonance Imaging (MRI) of the brain to distinguish the etiology and nature of the stroke, and later once the diagnosis is established, carotid duplex ultrasonography and transthoracic echocardiography with or without bubble contrast.[161,165,170]

Management

Time is of the essence and initial management at time of presentation involves stabilizing the patient, performing a prompt clinical evaluation, as well as laboratory and imaging studies, and thereby assessing the need for resuscitation, oxygen supplementation or intubation, fever, blood sugar or blood pressure control, and thrombolysis.[161,169] Fever, hyperglycemia and hypotension following an ischemic stroke have been associated with poorer outcomes and their treatment is being evaluated in randomized trials.[171-175] The National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) stroke trial demonstrated that ischemic stroke patients treated with thrombolysis using intravenous recombinant tissue plasminogen activator (rt-PA) i.e. alteplase within 3 hours after the onset of symptoms were 31 to 50% more likely to have a better clinical outcome at 3 months in contrast to the 20 to 38% in those who received placebo, although there was no difference in mortality.[176] However, there is an associated risk of intracranial hemorrhage associated with thrombolysis.[176] Prevention of this complication is of the utmost importance, therefore only carefully selected patients who fulfill certain criteria (Table 133.29) can receive thrombolysis.[166,170] Patients need to be monitored closely either in an ICU or stroke unit following thrombolysis, with vital sign checks every 15 minutes for 2 hours, then every 30 minutes for 6 hours and then every hour for 16 hours. Additionally, arterial punctures need to be avoided and all anti-platelet or anti-coagulation therapy should be withheld for the first 24 hours following rt-PA administration because of the increased risk of bleeding.[176] Stroke patients develop significant morbidity either as a result of the disease itself e.g. impaired swallowing, seizures, cerebral edema, infections such as pneumonia or urinary tract infection, or as a result of complications following treatment e.g. hemorrhagic transformation. The early recognition and appropriate treatment of these conditions, where possible, is essential in improving clinical outcome.

Subarachnoid Hemorrhage

Subarachnoid Hemorrhage (SAH) accounts for 10% of Cerebrovascular Accidents (CVAs) and is associated with significant morbidity and mortality (50%). Subarachnoid hemorrhage may be spontaneous or traumatic.[177] The spontaneous causes of SAH are delineated in Table 133.30. The risk factors for SAH include cigarette smoking, heavy alcohol consumption, uncontrolled hypertension, use of sympathomimetic drugs, cocaine abuse, estrogen deficiency and some hereditary conditions like polycystic kidney and Ehlers-Danlos syndrome.

Clinical Features

Patients present with unusual or severe sudden onset headaches. Warning bleeds and sentinel headaches are relatively uncommon. Physical examination may provide some indication to the location of the bleeding. Clinical features associated with SAH are delineated in Table 133.31.

Diagnosis

The initial screening test to confirm the diagnosis is a non-contrast CT-scan of the brain; however the diagnostic yield depends on the time that has elapsed between symptom onset to performance of the CT-scan (sensitivity 98% in first 12 hours and 54% at 5 days). Other conditions such as intracerebral hemorrhage, mass effect and hydrocephalus, which may present in a similar manner, can also be differentiated with the initial CT-scan. A false negative CT-scan can result from severe anemia or small volume hemorrhage. A lumbar puncture should be performed after an initial negative CT-scan and in SAH patients will display a high opening pressure, red blood cells in the CSF that do not clear and

TABLE 133.28: The NIH stroke scale (NIHSS). A score of ≥ 16 is associated with a high likelihood of severe disability or death, while a score of ≤ 6 is associated with a good prognosis

Entity	*Score*
1a. Level of Consciousness: A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 =Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close	0 =Answers both questions correctly. 1 =Answers one question correctly. 2 =Answers neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is a unilateral blindness or enucleation, visual fields in the remaining eye are scored.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient.	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion 5a. Left Arm 5b. Right Arm
6. Motor Leg: The limb is placed in the appropriate position: Hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation.	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion 6a. Left Leg 6b. Right Leg
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.

Contd...

Contd...

(arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss.	2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list.	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier,
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

Brott T et al.[168]

TABLE 133.29: The indications and contraindications for thrombolytic therapy in patients with acute ischemic stroke

Indications

- Ischemic stroke with symptom onset < 3 hours
- Measurable neurological deficit
  - Signs should not be clearing spontaneously
  - Signs should not be minor and isolated
  - Ideal candidates have NIHSS scores of 4–20 (estimation of risk/benefit ratio required)
  - Caution in patients with major deficits
- Patient and /or patient's designee/family comprehend potential risks and benefits of thrombolysis

Contraindications

- CT or MRI of brain demonstrates:
  - Intracranial hemorrhage
  - Hypodensity > one third of cerebral hemisphere
- Head trauma or stroke in the preceding 3 months
- Myocardial infarction in the preceding 3 months
- Gastrointestinal and urinary tract hemorrhage in last 21 days
- Arterial puncture at a non-compressible site in the last 7 days
- Major surgery in last 14 days
- Systolic blood pressure ≥ 185 mm Hg or diastolic blood pressure ≥ 110 mm Hg
- History of prior intracranial hemorrhage
- Evidence of active bleeding or acute trauma on physical examination
- Use of oral anticoagulation with INR > 1.7
- Use of heparin in last 48 hours with a prolonged aPTT level
- Platelet count ≥ 100 x 10^9/L
- Blood glucose level < 50 mg/dL
- Seizure with postictal residual neurological deficit

Abbreviations: NIHSS: National Institute of Health Stroke scale, CT: Computed Tomography, MRI: Magnetic Resonance Imaging, INR: International Normalized Ratio, aPTT: activated partial thromboplastin time.
Adapted from Adams et al.[166,170]

TABLE 133.30: The common and uncommon causes of spontaneous subarachnoid hemorrhage

Common	Cerebral aneurysms AVM
Uncommon	Neoplasms Dural AVM Venous angiomas Infectious aneurysms

xanthochromia which may persist for up to 2 weeks. A definitive diagnosis is made by angiography, which can identify the source of bleeding. Other tests which can be used are digital subtraction angiography or magnetic resonance angiography. The amount, location and extent of bleeding, correlates with prognosis.[178] A number of grading systems are used in practice to standardize the clinical classification of patients with SAH based upon the initial neurologic examination and the appearance of blood on the initial head CT.[179] They include the Glasgow Coma Scale (GCS) system, Hunt and Hess Grading System and The World Federation of Neurological Surgeons system.[180] The utility of these systems to predict prognosis is poor. Two of these grading systems are shown in Tables 133.32 and 133.33 respectively.

Management

The management of SAH is centered on three aspects which are delineated in detail in Table 133.34, namely:

- General management
- Definitive treatment (identifying and treating the causative lesion and preventing rebleeding)
- Treatment of complications.[180-185]

General management involves ICU monitoring, discontinuation of all antithrombotic medications and correction of any coagulopathy, if present. Blood pressure control is essential if elevated in these patients and may also be guided by monitoring of the patient's level of consciousness or intracranial pressure. The calcium channel blocker, nimodipine, has been shown to improve outcome in SAH patients, however the exact mechanism of this improvement is unknown and has been attributed

TABLE 133.31: The clinical symptoms and physical examination findings in subarachnoid hemorrhage (SAH)

Clinical history

Onset of headache: abrupt, maximal at onset, "thunderclap"

Severity: Very severe or worst of life

Associated signs and symptoms: Loss of consciousness, Diplopia, Seizure, focal neurological signs.

Physical findings

Finding	*Likely Location of aneurysm*
Diminished consciousness	Any
Nuchal rigidity	Any
Papilledema	Any
Retinal and subhyloid hemorrhage	Any
Third nerve palsy	Posterior communicating artery
Sixth nerve palsy	Posterior fossa
B/l weakness in legs or abulia	Anterior communicating artery
Nystagmus or ataxia	Posterior fossa
Aphasia, hemiparesis, left-sided visual neglect	Middle cerebral artery

TABLE 133.32: The Glasgow coma scale (GCS) which is scored between 3 and 15; 3 being the worst, and 15 the best. It is composed of three parameters: best eye response, best verbal response and best motor response. A score of 13 or higher is associated with mild brain injury; a score of 9 to 12 is associated with moderate injury; and a score of 8 or less represents severe brain injury

Eye opening	
Spontaneous	4
Response to verbal command	3
Response to pain	2
No eye opening	1
Best verbal response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	1
Best motor response	
Obeys commands	6
Localizing response to pain	5
Withdrawal response to pain	4
Flexion to pain	3
Extension to pain	2
No motor response	1

TABLE 133.33: The Hunt and Hess grading system for assessing the severity of sub-arachnoid hemorrhage

Grade	*Presentation*
1	Asymptomatic or mild headache and slight nuchal rigidity
2	Moderate to severe headache, stiff neck, no neurological deficit except cranial nerve palsy
3	Drowsy or confused, mild focal neurological deficit
4	Stupor, moderate or severe hemiparesis
5	Deep coma, decerebrate posturing

Mortality is minimum with grade 1 but maximum with grade 5.

TABLE 133.34: The steps involved in the management of sub-arachnoid hemorrhage

General management

- Admission to an intensive care unit
- Oxygen supplementation, mechanical ventilation if indicated
- Stool softeners, bed rest, analgesia to diminish hemodynamic fluctuations
- Correction of coagulopathy if any
- Control blood pressure
- Deep venous thrombosis (DVT) prophylaxis with pneumatic compression stockings; subcutaneous unfractionated heparin 5000 units three times daily can be added for prophylaxis, once the aneurysm is treated
- Monitor and treat elevated intracranial pressure
- Seizure prophylaxis

Identifying and treating the causative lesion and preventing rebleeding

- Team of experienced surgeons and endovascular practitioners
- To consider the neurologic grade and clinical status of the patient, the availability of expertise in surgical and endovascular techniques, the anatomic characteristics of the aneurysm, including the location and the size of the aneurysm and its neck
- Timing of surgery is controversial although early surgery is preferred
- Neurosurgical clipping is preferable over endovascular coiling

Treatment of complications

- **Treating hydrocephalus**
  Ventricular drain placement for deteriorating level of consciousness and no improvement in hydrocephalus within 24 hours
- **Treating and preventing vasospasm**
  Inflammatory reaction in the blood-vessel wall develops
  Between days 4 and 12 after subarachnoid hemorrhage
  Transcranial Doppler ultrasonography is performed either daily or every other day
  Treated with hypervolemia and induced hypertension
  May require treatment with temporary external ventricular drainage or the placement of a permanent shunt
- **Rebleeding**
  Manifests as worsening neurological state.
  Treat underlying cause.

to the prevention of vasospam.[186,187] The use of antiepileptic medication in SAH is controversial; therefore the routine use of antiepileptics is discouraged due to the poor neurologic outcome that has been reported with its use.[188] In addition, antifibrinolytic agents such as tranexamic acid and epsilon aminocaproic acid have been shown to decrease rebleed in SAH patients, but this is also without a significant effect on the general outcome of these patients.[189] This has been attributed to the development of generalized cerebral ischemia; hence these agents are not used routinely in SAH patients. The administration of glucocorticosteroids has also not been shown to be beneficial in these patients. The systemic factors contributing to the increased mortality include hypoxemia, metabolic acidosis, hyperglycemia and cardiovascular instability.[190]

TABLE 133.35: The complications of subarachnoid hemorrhage

Complication	*Features*
Hydrocephalus	May develop in 24 hrs due to obstruction to CSF flow by clotted blood
Seizures	Prophylaxis with anti-seizure medications
Raised intracranial pressure	Monitor closely
Re-bleeding	20% in 2 weeks with peak incidence on day 1 (4%) and 1.5% per day for 2 weeks
Vasospasm-	Arterial smooth muscle contraction
Neurological deficits	Cerebral ischemia
Hypothalamic dysfunction	Sympathetic stimulation leading to myocardial ischemia and labile blood pressure
Hyponatremia	SIADH
Pulmonary edema	Neurogenic and non-neurogenic causes
Complications from ICU stay	Identify and treat appropriately

Abbreviations: CSF: Cerebrospinal fluid, SIADH: Syndrome of inappropriate anti-diuretic hormone, ICU: Intensive care unit.

Definitive treatment involves either surgical clipping or endovascular coiling. There is a decreased mortality and a non-significant increase in rebleeding in patients treated with endovascular coiling as opposed to surgical clipping.[191] The timing of intervention is also controversial.

Complications of SAH are delineated in Table 133.35. Re-bleeding manifests with worsening neurological status and carries significant morbidity and mortality. The definitive therapy involves treatment of the aneurysm. Vasospasm starts approximately 3 days after the initial bleed and peaks after 7 to 8 days. It is associated with cerebral ischemia and neurological deficits, and the extent of vasospasm can be monitored using transcranial Dopplers. Irrigation of the cistern magna with urokinase following surgical or endovascular intervention has been shown to prevent vasospasm.[192] In addition, statins have also been shown to prevent vasospasm.[193] Triple H therapy (hemodilution, induced hypertension and hypervolemia) after definitive aneurysm treatment has been used in some centers to treat vasospasm. Furthermore, balloon angioplasty has been performed in patients with vasospasm that is refractory to triple H therapy.

Hydrocephalus is common in elderly patients with intraventricular bleeding, posterior circulation aneurysms and treatment with antifibrinolytic agents. Spontaneous resolution occurs in about 50% of cases. Hyponatremia can develop secondary to the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) or with cerebral salt wasting. Clear distinction between these two entities is important for proper management: SIADH patients are euvolumic while cerebral salt wasting patients are hypovolemic.

Intracerebral Hemorrhage

Intracerebral hemorrhage (bleeding within the skull) occurs within the brain parenchyma or surrounding meningeal spaces. Brain hemorrhage can occur from defects in the vessel wall, such as aneurysms, arterio-venous malformations, small vessel microaneurysms, coagulopathy, increased blood pressure or trauma.[194-197] Intracerebral hemorrhage (ICH) accounts for 10 to 30% of all stroke hospital admissions and is associated with high mortality.[198] ICH can be classified into primary or secondary depending on the underlying cause of bleeding as delineated in Table 133.36. The causes of intracerebral hemorrhage are further outlined in Table 133.37. ICH commonly occurs in the cerebral lobes, cerebellum, basal ganglia, thalamus and brain stem with extension into ventricles with large hematomas. Cerebral edema and neuronal damage in the surrounding parenchyma also occurs. There are several mechanisms of brain injury in ICH:

- Primary direct mechanical injury to brain parenchyma by the expanding clot
- Increased intracranial pressure (ICP)
- Herniation secondary to mass effect

TABLE 133.36: The classification of intracerebral hemorrhage based on the cause of the bleeding

Primary intracerebral hemorrhage	• Accounts for majority of cases. • Caused by spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy.
Secondary intracerebral hemorrhage	• Occurs in minority of patients. • Secondary to vascular abnormalities, tumors, and impaired coagulation.

TABLE 133.37: The various etiologies of intracerebral hemorrhage, with hypertension being the most common

- Hypertension
- Amyloid angiopathy
- Arteriovenous malformation
- Intracranial aneurysm
- Cavernous hemangioma
- Venous angioma
- Coagulopathy
- Vasculitis
- Intracranial neoplasm
- Hemorrhagic ischemic stroke
- Cocaine or alcohol usage

Clinical Features

The neurologic symptoms usually increase gradually over minutes to a few hours. Patients present with decreased level of consciousness as a result of increased ICP and direct compression of thalamic and brain stem Reticular Activating System (RAS). The majority of patients are hypertensive at time of presentation. Other symptoms include headache, seizures, vomiting which is more common with ICH than ischemic stroke. Stupor or coma in ICH is a warning sign with the exception of patients with thalamic hemorrhage, in whom involvement of the RAS is the cause of stupor rather than diffuse brain injury. These patients often recover after reabsorption of blood. Neurological signs vary depending on location of hemorrhage. In cases of severe intracerebral bleeding, herniation can take place. The clinical signs of the herniation syndromes are shown in Table 133.38.

Diagnosis

ICH is a neurologic and medical emergency as it is related with a high-risk of ongoing bleeding, progressive neurologic deterioration, permanent disability and death. Although rapid onset of abnormalities and decreased level of consciousness suggest the diagnosis, imaging with CT scan of brain is needed to confirm the diagnosis.[199] CT-scan of the brain is the initial diagnostic test and a cerebral angiography usually does not provide any further information, especially in elderly patients.[200] In addition to the CT-scan, patients should get CBC, coagulation profile and comprehensive metabolic panel. MRI can be useful in identifying large Arteriovenous Malformations (AVMs) and may be used in selected patients.[201]

TABLE 133.38: The herniation syndromes that can be seen with intracerebral bleeding

Type	*Causes*	*Clinical hallmark*
Lateral transtentorial (uncal)	Temporal lobe mass lesion	Ipsilateral CN 3 palsy Contralateral or bilateral motor posturing
Central transtentorial	Diffuse cerebral edema; hydrocephalus	Progression from bilateral decorticate to decerebrate posturing Rostral-caudal loss of brainstem reflexes
Subfalcine	Frontal or parietal mass lesion	Asymmetric motor posturing (contralateral > ipsilateral) Preserved oculocephalic reflex

Abbreviations: CN 3 – Third cranial nerve

Management

All patients with ICH should be monitored closely in the ICU.[202-205] Initial management of these patients includes evaluation of the airways, breathing and circulation (Table 133.39). Mechanical ventilatory support is usually recommended for patients with GCS of less than 8, but should be guided by the clinical presentation. The secondary effects of ICH include expansion of the hematoma, increased ICP, perihematomal edema, intraventricular hemorrhage and hydrocephalus. Treatment involves a combination of both medical and surgical interventions. Elevated blood pressure is common in patients with ICH and is feared to contribute to the expansion of hematoma.[206] Aggressive management of blood pressure to keep the mean arterial pressure (MAP) < 110 mmHg should be started immediately. The management of hypertension and hypotension is depicted in Table 133.40. Raised ICP contributes to the mortality of these patients and should be managed expediently. It is defined as a pressure more than 20 mmHg for >5 minutes. As soon as raised ICP is suspected, the head of the bed should be raised to 30° keeping the head at midline. Hypovolemia should be treated expediently to prevent postural hypotension.

TABLE 133.39: The steps involved in the management of intracerebral hemorrhage

1. **General management**
    - Reversal of anticoagulation
    - Treatment of fever source
    - Prevent and address hyperglycemia and hypoglycemia
    - Adequate treatment of pain
    - Seizure prophylaxis and treatment
    - DVT prophylaxis
    - Supplemental oxygen or intubation as indicated
2. **Intracranial pressure monitoring (ICP)**
    - Elevate head of bed
    - Hypovolemia should be treated
    - Ventriculostomy and CSF drainage for hydrocephalus
    - Osmotic therapy with mannitol, hypertonic saline
    - Sedation and paralysis as needed
    - Maintain ICP 5-20 (aggressive measures to decrease ICP)
    - Maintain cerebral perfusion pressure > 70 mm Hg
3. **Maintainence of optimum blood pressure**
    - MAP < 110 (some suggested medications are shown in Table 133.40)
4. **Address metabolic and nutritional needs**
    - Early administration of TPN worsens ICH
    - Start TPN after 2-3 days with high concentration of calories from lipids

Abbreviations: DVT: Deep vein thrombosis, CSF: Cerebrospinal fluid, MAP: Mean arterial pressure, TPN: Total parenteral nutrition, ICH: Intracerebral hemorrhage.

TABLE 133.40: The management of hypotension and hypertension in acute intracerebral hemorrhage

High blood pressure	
1. If SBP is >200 mm Hg, or MAP >150 mm Hg on 2 readings 20 minutes apart	Start intravenous labetalol, esmolol, enalapril, or other smaller doses of easily titratable intravenous medications such as diltiazem, lisinopril, or verapamil
2. If SBP is >180 mm Hg and MAP <130 mm Hg with elevated ICP.	Start intravenous antihypertensives (Agents shown below)
3. If SBP is >180 mm Hg and MAP <130 mm Hg with no elevation of ICP	Intermittent or continuous antihypertensives can be used. The goal is to keep SBP< 160 mmHg and MAP ~ 110 mm Hg
Labetalol	5–100 mg/h by intermittent bolus doses of 10–40 mg or continuous drip (2–8 mg/min)
Esmolol	500 µg/kg as a load; maintenance → 50–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Nitroprusside	0.5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Hydralazine	10–20 mg every 4–6 h
Enalapril	0.625–1.2 mg every 6 h as needed
Low blood pressure	
Volume replenishment is the first line of approach. If hypotension persists after correction of volume deficit, continuous infusions of pressure should be considered, particularly for low systolic blood pressure such as < 90 mm Hg.	
Phenylephrine	2–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Dopamine	2–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Norepinephrine	Titrate from 0.05–0.2 $\mu g.kg^{-1}$. min^{-1}

Abbreviations: SBP: Systolic blood pressure, MAP: Mean arterial pressure, ICP: Intracranial pressure.

Osmotic therapy with mannitol decreases the swelling of an edematous brain, decreases the viscosity of blood and increases cardiac preload thus increasing the Cerebral Perfusion Pressure (CPP). The target osmolality is 310 to 320 osmols. Mannitol is given in a dose of 0.5 to 1 g/kg every 4 to 6 hours. Side effects include volume overload and osmotic renal failure. The effect of mannitol is seen within 30 minutes to 1 hour and is guided by clinical improvement. Hypertonic saline, either as a 3% saline 150 mL bolus every 6 hours or as a continuous infusion of 0.5 ml to 1 ml/kg/hr, is also recommended for the treatment of raised ICP. Frequent serum sodium moni-toring is required with hypertonic saline administration. Alternatively, 7.5% saline as a 250 mL bolus or 23.4% saline in doses of 30 to 60 mL over 20 minutes can be used when other modalities are unsuccessful. Sudden increases in sodium can contribute to the development of coma and seizures. Steroids are not recommended for cerebral edema secondary to CVA.

Hyperventilation has an immediate and transient effect on cerebral circulation. It lowers CPP by cerebral vasoconstriction and may be associated with exacerbations of ischemia in local regions of the brain. It is recommended to lower the $PaCO_2$ to 30 to 35 mmHg in situations of an intractable rise in CPP.[207] Hyperthermia worsens neurological damage by increasing the metabolism in ischemic brain tissues. Therapeutic cooling to a temperature of 30° to 32° C and gradual rewarming may improve outcomes.[208] The role of ventriculostomy and CSF drainage has not been studied prospectively, but is an effective method of decreasing ICP, especially in the phase of hydrocephalus.[209] Inter-ventricular hemorrhage and infection are notable complications of this procedure.[210]

In addition to these specific treatments, patients should be treated adequately for pain. Sedation and neuromuscular blockade may be needed for patients who are intubated. Also, blood glucose should be lowered to less than 150 mg/dL, but hypoglycemia should be avoided.[211] Since most of the seizures are nonconvulsive in nature, prophylactic seizure medications must be used initially.[212]

Patients with ICH have a high incidence of venous thromboembolism and should receive prophylaxis initially with pneumatic compression stockings and later subcutaneous heparin 5000 units every 8 hours after day 4 of ICH onset.[213] Patient who developed venous thromboembolism should be treated with an Inferior Venacaval (IVC) filter.[214] Warfarin treatment increases the incidence of ICH and the risk is proportional to the degree of anticoagulation and the presence of amyloid vasculopathy. The anticoagulant effect is rapidly reversed using Vitamin K 10 mg intravenously, Fresh Frozen Plasma (FFP), prothrombin complex concentrate and recombinant factor 7a (rFVIIa).[215] The reinstitution of warfarin therapy should be carefully assessed on an individual basis. ICH associated with antifibrinolytic therapy carries a worse prognosis than warfarin associated ICH and is treated with platelets and cryoprecipitate.[170]

Surgical treatment is not beneficial except in certain selected conditions.[216] The stroke association recommendations for surgery are as follows:

1. Cerebellar hematoma > 3 cm especially with neurological deterioration, brainstem compression or hydrocephalus should be removed as soon as possible
2. Patient with lobar clots within 1 cm of the surface of the brain, evacuation of supratentorial ICH by standard craniotomy may be considered
3. The usefulness of urokinase infusion into the clot or minimally invasive evacuation of the clot or routine decompressive craniotomy is currently unknown.[203] In one small study, decompressive craniotomy had a better outcome in young patients.[217]

Prognosis

A simple six-point clinical grading scale called the ICH score has been devised to predict mortality after ICH.[218] This scale incorporates several clinical components that may be independent predictors of outcome. The ICH score is determined by adding the score from each component (Table 133.41).

TABLE 133.41: The six-point ICH scoring used to predict mortality after the development of ICH. A cumulative ICH score is obtained by adding the points from each component

Scale	*Points*
GCS score	
3-4	2
5-12	1
13-15	0
ICH volume	
≥ 30 cm^3	1
≤ 30 cm^3	0
Intraventricular extension of hemorrhage	
Present	1
Absent	0
Infratentorial origin	
Yes	1
No	0
Age	
≥ 80 years	1
< 80 years	0

Abbreviations: ICH: Intracerebral hemorrhage, GCS: Glasgow coma scale.

Status Epilepticus

Seizures are a common condition seen in 3.3 to 34% of ICU patients.[219] They can result from either a primary neurological pathology such as a stroke, brain tumor or Central Nervous System (CNS) infection, or develop as a neurological complication of critical illness as in patients with metabolic abnormalities, drug/substance toxicity or withdrawal, or hypoxemia.[219,220] Status epilepticus is said to occur when seizures are recurrent or refractory lasting more than 5 minutes or repetitive in nature without regaining consciousness in between episodes.[219,221] It is a life-threatening emergency that necessitates urgent diagnosis and treatment, and is classified as either being convulsive or nonconvulsive. The convulsive form tends to be the more severe and common type, and is characterized by repeated seizure episodes associated with a postictal state, while the nonconvulsive form is characterized typically by an altered mental status and a lack of obvious physical manifestations.[220,222] Common causes of status epilepticus are outlined in Table 133.42.

Clinical Features and Diagnosis

Patients with convulsive status epilepticus are easy to recognize as they present with classic motor manifestations. Conversely, patients with nonconvulsive status epilepticus often go unrecognized because of the lack of obvious signs. The use of Electroencephalography (EEG) is therefore an essential tool in the diagnosis of the nonconvulsive type. The basic diagnostic work up also includes a rapid assessment of glucose levels, CBC, electrolytes, liver function, arterial blood gas analysis, toxicology screen, in addition to imaging studies like CT-scan or MRI of the brain. A lumbar puncture may also be performed in selected patients to evaluate the CSF for possible secondary causes of the seizure episodes. The prompt diagnosis and treatment of status epilepticus is essential, as prolonged or recurrent seizure episodes are associated with worsening neurological injury and systemic complications such as lactic acidosis, hyperthermia, arrhythmias, aspiration, rhabdomyolysis, renal failure and trauma.[220]

TABLE 133.42: The different etiologies associated with the development of status epilepticus

- Antiepileptic drug noncompliance
- Alcohol related
- Cerebrovascular accidents
- Vascular malformations
- Drug toxicity
  (Cephalosporins, penicillins, ciprofloxacin, tacrolimus, cyclosporin, theophylline and cocaine)
- CNS infections (Meningitis, encephalitis, abscess)
- CNS tumors (Primary or secondary)
- Metabolic disturbances
  (Electrolyte abnormalities, sepsis and uremia)
- Head trauma
  Surgery
- Cerebral anoxia/hypoxia
- Hypoglycemia or hyperglycemia
- Vasculitis

Abbreviation: CNS: Central nervous system.

Management

The EEG not only serves as a diagnostic tool, but also aids in monitoring response to treatment, as patients may still be actively seizing even though motor signs have subsided. Treatment involves eliminating seizure activity as well as preventing the development of further episodes.[220] The general and pharmacological strategies employed in the management of status epilepticus are shown in Figure 133.7.[221] The initial step in treatment involves evaluating the respiratory and cardiovascular status of the patient. Patients are frequently intubated in order to preserve the airway and enhance oxygenation.[219] A rapid blood glucose test is usually performed at bedside and treated for levels < 60 mg/dL and at the same time blood is sent off for blood tests as listed earlier.[219,220] Benzodiazepines are the initial drug of choice. Intravenous lorazepam 1 to 2 mg, midazolam 2 to 5 mg or diazepam 10 to 20 mg can be given at first but these doses can be increased up to 5 to 10 mg, 5 to 20 mg or 20 to 40 mg over 5 minutes in cases of recurrent or refractory seizures.[219] In patients not responding to the increased doses of benzodiazepines, second line agents that have been used include phenytoin (loading dose 20 mg/kg at 50 mg/minute) or fosphenytoin (20 mg/kg at 150 mg/minute).[219,220] Other alternative second line agents that can be used include intravenous medications like levetiracetam and valproic acid.[223,224] In patients who still continue to have seizure episodes (> 60 minutes), induction of a pharmacological coma may be necessary with infusions of phenobarbital, propofol or midal-zolam.[219,225-227] Continuous EEG monitoring is also preferred, particularly in patients with nonconvulsive status epilepticus. Status epilepticus is a serious condition in critically ill patients and is associated with a mortality

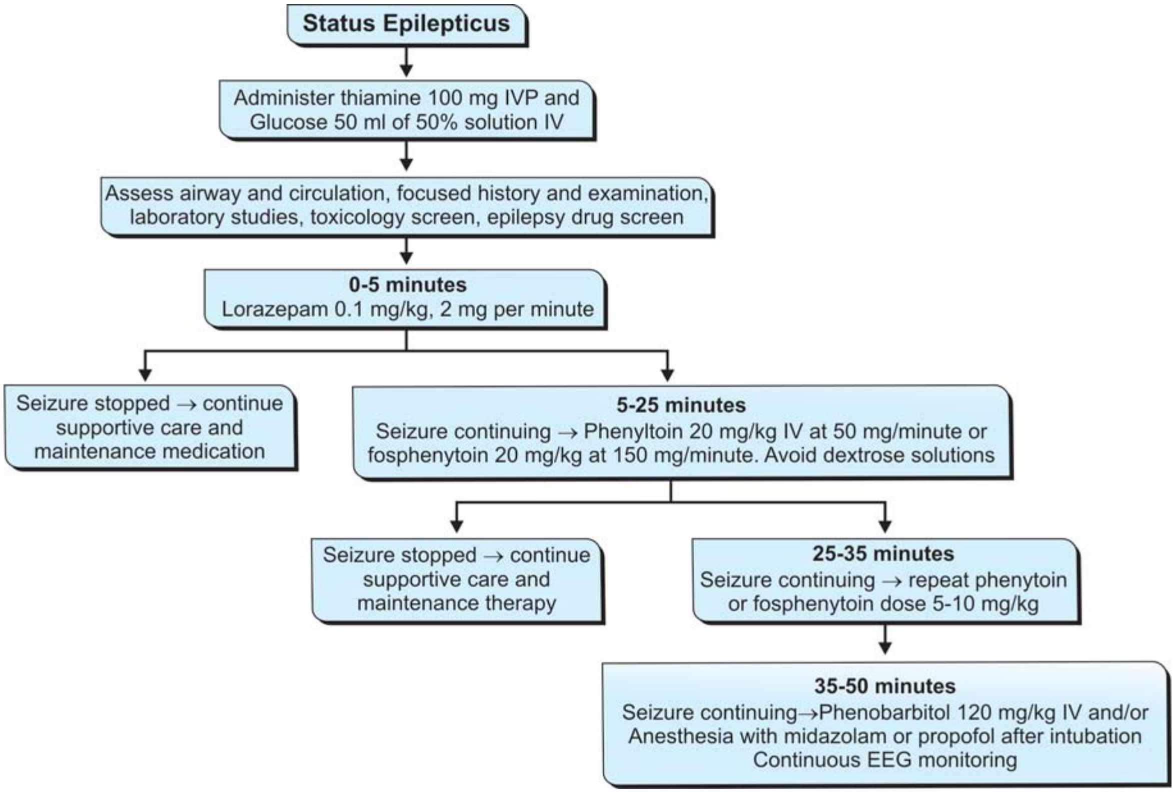
Status Epilepticus
Administer thiamine 100 mg IVP and Glucose 50 ml of 50% solution IV
Assess airway and circulation, focused history and examination, laboratory studies, toxicology screen, epilepsy drug screen
0-5 minutes
Lorazepam 0.1 mg/kg, 2 mg per minute
Seizure stopped → continue supportive care and maintenance medication
5-25 minutes
Seizure continuing → Phenyltoin 20 mg/kg IV at 50 mg/minute or fosphenytoin 20 mg/kg at 150 mg/minute. Avoid dextrose solutions
Seizure stopped → continue supportive care and maintenance therapy
25-35 minutes
Seizure continuing → repeat phenytoin or fosphenytoin dose 5-10 mg/kg
35-50 minutes
Seizure continuing→Phenobarbitol 120 mg/kg IV and/or Anesthesia with midazolam or propofol after intubation
Continuous EEG monitoring

Fig. 133.7: An algorithmic approach to the management of status epilepticus.
Abbreviations: IVP – Intravenous push, IV – Intravenous, EEG – Electroencephalogram

of approximately 20%.[228] Early recognition and treatment is necessary to prevent the potentially severe neurological consequences.

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Poisoning, Envenomation and Environmental Injuries

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INTRODUCTION

A large number of patients admitted in the hospitals for nonpulmonary problems, such as poisonings, snake envenomation, trauma, environmental injuries or with tropical infections like malaria, leptospirosis, tetanus and others with or without the involvement of lungs or respiratory muscles or both need intensive respiratory care where life is seriously threatened. In our own multidisciplinary Intensive Care Unit (ICU), 72% of 459 admissions in 2009 were due to the nonpulmonary causes of critical illnesses with 23% due to poisoning and neuroparalytic snake envenomation, 11% due to primary neurological conditions and 38% due to tropical infections (malaria, typhus, etc.), polytrauma, endocrinological emergencies, obstetrical and postsurgical critical illness.

POISONING

Acute poisoning is an important medical emergency needing admission in critical care units. Poisoning is an event where a living organism is exposed to a chemical that adversely affects the functioning of that organism.[1] The exposure to the toxin, which could be occupational, environmental, recreational or medicinal can occur through various portals of entry, but predominantly the oral route. A poison may affect the body in many different ways. It may inhibit, or alter the normal cellular function, change normal organ function, or may change the normal uptake or transport of substances into or within the organism.[2]

The nature of poisons which are used varies in different parts of the world and even in different parts of the same country depending on the socioeconomic factors and cultural diversities.[3] Self-poisoning, including of pesticides accounts for about one-third of the world's suicides. Official data from India probably underestimate the incidence of suicides.[4] The proportion of all suicides using pesticides varies from 4% in the European region to over 50% in the Western Pacific region. It is the pattern of pesticide use and the toxicity of the product, not the quantity used, that influences the likelihood that they will be used in the acts of fatal self-harm.[5] In general, accidental poisoning is more common in children, whereas suicidal poisoning is more so in young adults.[6,7]

It is important for the intensivists to know the pattern of poisoning in their area. Across India, pesticides (organophosphates and organochlorine) and fumicide (aluminium phosphide) are the common poisons used for self-harm in rural and semi-urban areas, whereas household products and drugs are commoner in the metropolitan/city areas.[8] Epidemiological studies demonstrating the patterns of poisoning in critical care are scanty. It is believed that the major share of poisoning in critical care units is contributed by pesticides and fumicides across the country since they cause most of the cases of severe intoxication[6-9] and deaths due to poisoning.[10]

Toxic ingestion presents variably. Patients often arrive with known drug overdose or toxic exposure, such as in the setting of illicit drug use, suicidal attempt or accidental exposure. In others, history is unclear, particularly when there is associated trauma or alterations in mental status. Clinical features may be specific for a toxic syndrome (or toxidrome), but just as often nonspecific and suggestive of other disorders.

The protean manifestations of intoxication mandate a higher index of suspicion to facilitate decisive and immediate treatment. General supportive measures supersede all other considerations. For the effective management of acutely poisoned victim the following should be considered:

I. Resuscitation and stabilization.
II. Diagnosis of poisoning and drug overdose (history, physical examination, use of toxicological screening tests, including other common laboratory tests).
III. Treatment and prevention of further drug absorption, elimination of absorbed drugs and antidotes.
IV. Specific approaches for evaluation and treatment of commonly encountered drugs, toxins and envenomations in the intensive care unit.

Resuscitation and Stabilization

The initial step is to identify and treat immediate life-threatening problems, which revolves around the pneumonic A B C D (Airway; Breathing; Circulation; Drugs and Decontamination).

Airway

With cervical precautions in place, airway patency and stabilization must be established. In comatose patients, upper airway obstruction by the tongue may be treated initially with jaw thrust maneuver, followed by the either placement of oral or nasal airway or an endotracheal tube. The choice of airway depends upon the level of sensorium, vigor of protective reflexes, degree of respiratory depression, and the initial response to the pharmacological therapy. In the nonintubated patients, the left side down, head-down position allows the tongue to drop forwards and decreases the risk of aspiration of oral secretions and stomach contents.

Breathing

It includes the maintenance of adequate oxygenation and ventilation. In the case of doubt regarding patient's ability to handle secretion or the maintenance of spontaneous respiration, endotracheal intubation should be done immediately. Intubation allows for the administration of high concentration of supplemental oxygen in hypoxemic patients and for assisted ventilation in patients with ventilatory failure.

Hypoxemia should be corrected immediately to avoid anoxic damage to brain, myocardial ischemia and cardiac arrhythmias. If the intubation is done solely for airway protection or to provide supplemental oxygen, then it must be connected to a T-piece. For patients with ventilatory failure, ventilation is achieved by mechanical ventilation. The initial settings of the ventilator are as per the clinicians comfort and the one which achieves greatest degree of synchrony between the patient and the machine. The initial ventilator mode should provide adequate backup minute ventilation.

Circulation

After ensuring adequate airway patency, oxygenation and ventilation, circulatory status of the patient should be assessed. Circulatory manifestation of poisoning can range from hypotension, hypertension, bradycardia, tachycardia to cardiac arrest.

Drugs and Decontamination

Give an antidote when there is reasonable certainty of a specific diagnosis. The indications and dosages are discussed subsequently. Decontamination consists of skin, eyes and gastrointestinal decontamination and facilitation for increased drug removal.

Decontamination of skin: Decontamination means separation of patient from the contaminant, i.e. poison in this instance. Many toxins, such as organophosphates and organochlorines are readily absorbed through the skin, systemic absorption can be prevented only by rapid action.

Wash the affected areas with the copious amounts of lukewarm water or saline. Wash carefully behind the ears, under the nails, and the skin folds. For oily substances (pesticides), wash the skin at least twice with plain soap and shampoo the hair. Specific decontaminating solutions or solvents (alcohol) are rarely indicated and in some cases may paradoxically enhance the absorption.

Gastrointestinal decontamination:[11,12] Removal of ingested poisons was a routine part of emergency treatment for decades. However, prospective clinical trials have failed to show improved outcomes after gastric emptying. For small and moderate ingestion of most substances, oral-activated charcoal alone without prior gastric emptying is recommended. Exceptions are the large ingestions of anticholinergic compounds and salicylates, which often delay gastric emptying, and ingestion of sustained release or enteric-coated tablets, which may remain intact for several hours.

Gastric emptying is **not recommended** for ingestion of corrosive agents or petroleum distillates, because further esophageal injury or pulmonary aspiration may result. It is also contraindicated in stuporous or comatose patients with absent gag reflexes unless their airway is secured beforehand.

Increased drug removal: Different ways of increased drug removal includes:

i. *Urinary manipulation:* Renal excretion can become a major route of excretion under conditions of forced diuresis. Forced diuresis is hazardous; the risk of complications (pulmonary edema, electrolyte imbalance) outweighs its benefits, and is usually not recommended. It is used commonly in the toxicity of acidic drugs (e.g. salicylates, phenobarbital) as they are more rapidly excreted with alkaline urine. Urinary alkalinization is usually achieved by the administration of intravenous sodium bicarbonate (1 to 2 mEq/kg every three to four hours); this may be administered as two 50 ml ampoules of 8.4% sodium bicarbonate (each containing 50 mEq of $NaHCO_3$) per liter of 5% dextrose in water infused at 250 ml/hour with aim to keep urinary pH above seven.[13] Complications of this therapy include alkalemia (particularly in the presence of respiratory alkalosis), volume overload, hypernatremia and hypokalemia. It is particularly important to avoid hypokalemia, which prevents the excretion of alkaline urine by promoting distal tubular potassium reabsorption in exchange for hydrogen ion. Addition of potassium chloride to the bicarbonate infusion is commonly required and is used prophylactically to prevent this complication.[14]

ii. *Hemodialysis:* The indications for hemodialysis are as follows: (a) Known or suspected potentially lethal amounts of dialyzable drug (Table 134.1), (b) Poisoning with deep coma, apnea, severe hypotension, fluid and electrolyte or acid-base disturbance, or extreme body temperature changes that cannot be corrected by conventional measures, (c) Poisoning in patients with severe kidney, cardiac, pulmonary or hepatic disease who will not be able to eliminate toxin by the usual mechanisms.

Continuous renal replacement therapy is of uncertain benefit for the elimination of most poisons, but has been used successfully in the management of lithium poisoning.[15]

iii. *Repeat dose charcoal:* Repeated doses of activated charcoal, 20–30 g orally or via gastric tube every 3-4 hours, may hasten the elimination of some drugs (phenytoin, carbamazepine, dapsone) by absorbing drugs excreted into the gut lumen (gut dialysis). However, clinical studies have failed to prove better outcome using multiple dose charcoal.[15,16]

TABLE 134.1: Drugs which can be removed by hemodialysis

Poison	*Indication*
Carbamazepine	Seizures, severe cardiotoxicity; serum levels > 60 mg/l
Ethylene glycol	Acidosis, serum level > 50 mg/dl
Lithium	Severe symptoms; level > 4 mEq/l more than 12 hours after last dose
Methanol	Acidosis, serum levels > 50 mg/dl
Phenobarbital	Intractable hypotension, acidosis despite maximal supportive care
Salicylate	Severe acidosis, CNS symptoms, Level > 100 mg/dl (acute overdose) or > 60 mg/dl (chronic intoxication)
Theophyllines	Serum level > 90-100 mg/l (acute) or seizures and serum level > 60 mg/l (chronic)
Valproic acid	Serum level > 900-100 mg/l or deep coma, severe acidosis.

Diagnosis of Poisoning

Because of its protean manifestations, poisoning and drug overdose should be considered in the differential diagnosis of all patients in an acute care setting. The identity of the ingested substance is usually unknown. The history is the single most important indicator of toxic ingestion, but for in a comatose patient or if the patient is unable or unwilling to give a coherent history. By performing a directed physical examination and ordering common clinical laboratory tests, the clinician can often make a tentative diagnosis, which allows for the management of the patient (Fig. 134.1).

Treatment of Symptomatic Patient

In symptomatic patients, treatment of life-threatening complications takes precedence over in-depth diagnostic evaluation. Every effort should be made to keep the patient alive. Patients with mild symptoms may deteriorate rapidly, which is why all potentially significant exposures should be observed in acute care facility. The following complications may occur, depending upon the type of poisoning.

Coma

Coma is commonly associated with the ingestion of the large number of drugs and toxins (Table 134.2). The most common cause of death in a comatose patient is respiratory failure, which may occur abruptly. Pulmonary aspiration of gastric contents may also occur, especially in victims who are obtunded or having seizures. Thus, the protection of the airway and assisted ventilation are the most important treatment measures for any poisoned patient in coma.

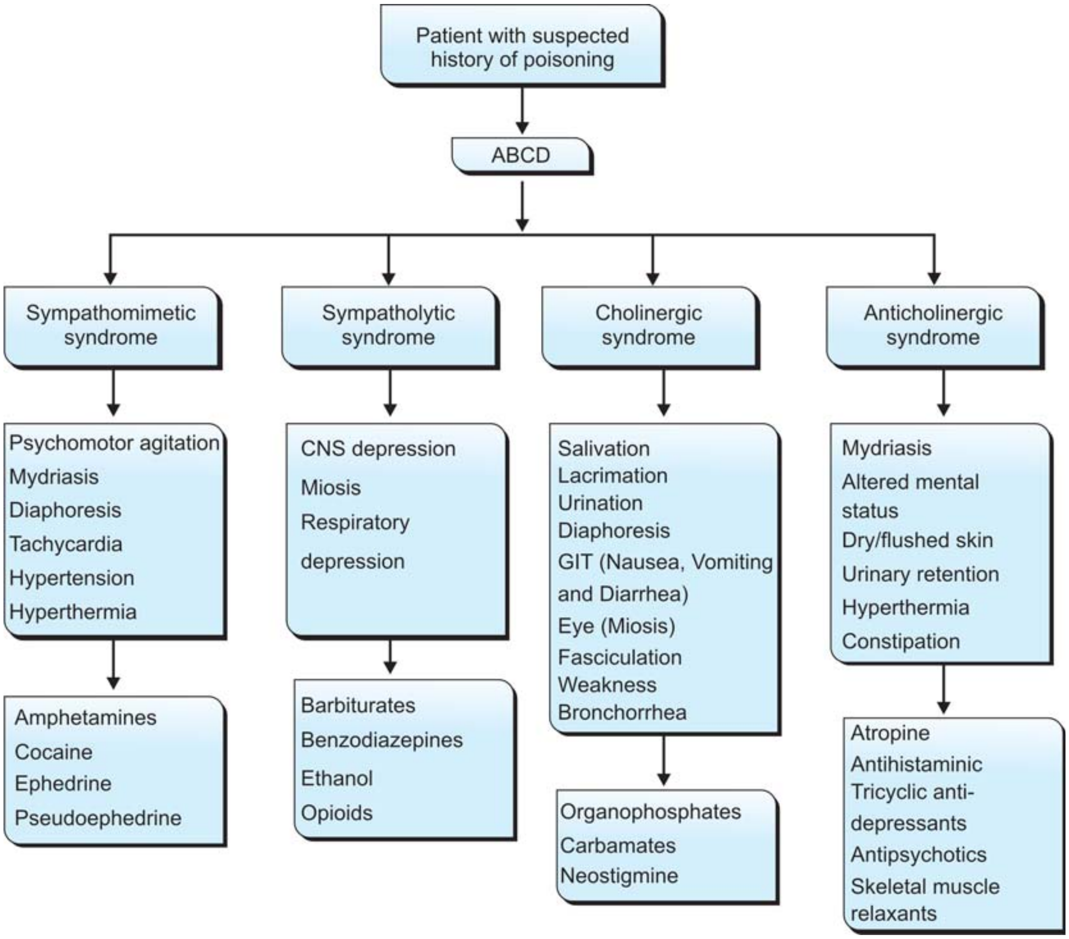
Patient with suspected history of poisoning
ABCD
Sympathomimetic syndrome
Sympatholytic syndrome
Cholinergic syndrome
Anticholinergic syndrome
Psychomotor agitation
Mydriasis
Diaphoresis
Tachycardia
Hypertension
Hyperthermia
CNS depression
Miosis
Respiratory depression
Salivation
Lacrimation
Urination
Diaphoresis
GIT (Nausea, Vomiting and Diarrhea)
Eye (Miosis)
Fasciculation
Weakness
Bronchorrhea
Mydriasis
Altered mental status
Dry/flushed skin
Urinary retention
Hyperthermia
Constipation
Amphetamines
Cocaine
Ephedrine
Pseudoephedrine
Barbiturates
Benzodiazepines
Ethanol
Opioids
Organophosphates
Carbamates
Neostigmine
Atropine
Antihistaminic
Tricyclic anti-depressants
Antipsychotics
Skeletal muscle relaxants

Fig. 134.1: Toxidromic approach to the diagnosis of poisoning
(ABCD = Airway maintenance, Breathing, Circulation, Drugs and Decontamination)

TABLE 134.2: Common causes of coma due to an exogenous agent

Hypoxia
Carbon monoxide

Depression of CNS
Alcohol, benzodiazepines, antidepressants, antihistamines, barbiturates, opiates, anticonvulsants

Acidosis
Ethylene glycol, alcohol, methanol, salicylates

Hypoglycemic agents
Alcohol, exogenous insulin, oral hypoglycemic agents (sulfonylureas)

Enzyme inhibitors
Heavy metals (arsenic, lead, etc.), organophosphates, salicylates, cyanide

Post ictal
Amphetamines, cocaine, hallucinogens, opiates, organochlorines, lead, phenothiazines, drug withdrawl

Other causes
Snake bites

Treatment: The initial emergency management of coma is on the lines of A B C. Immediately after stabilizing, a "coma cocktail" of thiamine, dextrose and naloxone should be administered. All comatose or convulsing patients should receive 50–100 ml of 50% dextrose. In alcoholic or severely malnourished patients, 100 mg of thiamine intravenously over 2–3 minutes should be administered prior to glucose. Naloxone, 0.4–2 mg intravenously, may reverse opioid-induced respiratory depression and coma. It is often given empirically in all coma patients. If however, opioid poisoning is strongly suspected, the additional dose of 5 to 10 mg may be required to reverse the effects. Flumazenil, 0.2–0.5 mg intravenously repeated every 30 seconds or as needed up to a maximum of 3 mg, may reverse benzodiazepine-induced coma.

Agitated or Convulsing Patient

Agitated, violent or acutely psychotic patients unresponsive to verbal feedback and reduction in environmental stimuli require pharmacological treatment or physical restraints to establish patient safety. Organic causes of agitation other than drug overdose should be considered like drug withdrawal, head trauma with subdural hematoma, intracerebral hemorrhage, hypoglycemia, etc.

Seizures are a major cause of drug-related morbidity and mortality. They are caused by multiple drugs and toxins (Table 134.3). Prolonged or repeated seizures may lead to hypoxia, metabolic acidosis, hyperthermia and rhabdomyolysis and hence require early active intervention.

Treatment: In an agitated patient haloperidol (1 to 5 mg) may be repeated every 30 to 60 minutes to a total dosage not exceeding 100 mg. Haloperidol lowers seizure threshold and is associated with tardive dyskinesia. For seizures, administer lorazepam, 2–3 mg, or diazepam, 5–10 mg, intravenously over 2 to 3 minutes. If seizures are not controlled consider phenobarbitone, 15–20 mg/kg slowly over no less than 30 minutes; or phenytoin 15 mg/kg intravenously not exceeding 50 mg per minute. For drug-induced seizures phenobarbitone is generally preferred over phenytoin. Propofol infusion has also been reported effective for some resistant drug-induced seizures.[17]

TABLE 134.3: Common compounds causing seizures

- Amphetamines
- Antihistamines
- Antipsychotics
- Carbamates
- Organochlorines
- Carbon monoxide
- Cocaine
- Ethylene glycol
- Cyclic antidepressants
- Isoniazid
- Salicylates
- Withdrawal from alcohol or sedative-hypnotics
- Organophosphates

In patients with seizures, the absence of visible muscular convulsive movements may give a false impression that brain seizure activity has ceased; however, this must be confirmed by electroencephalogram, wherever possible.

Temperature Alteration

Many drugs and toxins have the potential to alter body temperature through a number of different mechanisms. Both hypothermia and hyperthermia are common with intoxication. Hypothermia is caused by peripheral vasodilatation, inhibition of shivering, depression of metabolic activity, and loss of consciousness in cold environment. Hyperthermia occurs due to excessive generation of heat from sustained seizures, muscle rigidity, increased metabolic rate as in cocaine intoxication, or due to impaired dispersion of heat secondary to decreased sweating as in anticholinergic ingestion. Hyperthermia can also occur due to central causes that alter hypothalamic activity.

Treatment: Significantly abnormal temperature must be identified immediately and treated aggressively to prevent life-threatening complications. For hypothermic patient, gradual rewarming is preferred except in case of cardiac arrest. Hyperthermia should be managed aggressively by removing all clothes, spraying with tepid water and fanning the patient. If this is not rapidly effective, as shown by normal rectal temperature within 30–60 minutes or if there is significant muscle rigidity or hyperactivity, induce neuromuscular paralysis with a nondepolarizing neuromuscular blocker (rocuronium, vecuronium). Once paralyzed, the patient must be intubated and mechanically ventilated. Dantrolene (2–5 mg/kg intravenously) may be effective for hyperthermia associated with muscle rigidity that does not respond to neuromuscular blockade (i.e. malignant hyperthermia). Bromocriptine, 2.5–7.5 mg orally daily, has also been recommended for neuroleptic syndrome. Cyproheptadine, 4 mg orally every hour for three or four doses, has been used to treat serotonin syndrome.[18]

Circulatory Manifestation

Circulatory manifestations of drug overdose are common and varied, including cardiac arrest, atrial and ventricular arrhythmias, and hypotension and hypertension (Table 134.4).

Treatment: Hypertension should be treated if the patient is symptomatic or if diastolic blood pressure is greater than 105-110 mm Hg especially if there is no prior history of hypertension. Hypertensive patients who are agitated or anxious may benefit from a sedative such as lorazepam, 2-3 mg intravenously. For persistent hypertension, administer phentolamine, 2-5 mg intravenously, or nitroprusside sodium, 0.25-8 mcg/kg/min intravenously. Beta-blockers should not be given alone that may paradoxically worsen hypertension as a result of unopposed alpha-adrenergic stimulation.[19]

For hypotension, most patients respond to empiric treatment with repeated 200 ml intravenous boluses of 0.9% saline or other isotonic crystalloid (up to a total of 1-2 liter). **If fluid therapy** is not successful, dopamine at a dose of 5–15 mcg/kg/min by intravenous infusion may be given. Pulmonary artery catheterization may be done if hypotension persists. Hypotension due to certain drugs may need specific treatment. For example, in tricyclic antidepressant poisoning sodium bicarbonate (50–100 mEq by intravenous bolus injection) reverses hypotension; norepinephrine (4–8 mcg/min) is more effective then dopamine; for beta-blockers, glucagon (5–10 mg intravenously) may be more value; for calcium channel blocker overdose, calcium chloride at a dose of 1–2 g intravenously (repeated doses) may be administered. Intralipid 20% lipid emulsion has been reported to improve hemodynamics in intoxication by highly lipid soluble drugs, such as bupivacaine, verapamil, bupropion and clomipramine.[20]

TABLE 134.4: Factors associated with hypotension and hypertension

Hypertension and tachycardia	Amphetamines, cocaine, phencyclidine
Hypotension with bradycardia	Phenelzine, monoamine oxidase inhibitors, levodopa, organophosphates, tricyclic antidepressants
Hypertension with normal or slowed pulse	Phenylpropanolamine
Malignant hypertension with intracranial hypertension	Amphetamine, cocaine, phencyclidine, phenylpropanolamine
Hypotension and tachycardia	Theophyllines, cyanide, carbon monoxide, aluminium phosphide
Tachycardia with little change in blood pressure	Lomotil, Marijuana, thyroxine
Muscarinic syndrome	Organophosphates, pilocarpine, bethanechol

Arrhythmias are often caused by hypoxia or electrolyte imbalance, and these conditions should be sought and treated. If ventricular arrhythmias persist, administer lidocaine or amiodarone at usual antiarrhythmics doses. Class 1a agents should be avoided as they may worsen tricyclic antidepressant intoxication. Torsades de pointes associated with prolonged QT interval may respond to intravenous magnesium (2 g intravenously over 2 minutes) or overdrive pacing.[21]

Pupil Size

Pupil size can be of help in diagnosis of intoxications (Table 134.5).

TABLE 134.5: Drugs causing pupillary alterations

Miosis	*Mydriasis*	*Nystagmus*
Narcotics	Deep coma	Barbiturate
Phenothiazine	Alcohol	Phenytoin
Barbiturate	Atropine	Phencyclidine
Organophosphates	Anticholinergics	Alcohol
	Glutethimide	
	Diphenhydramine	
	Cocaine	

Laboratory Evaluation

Clinical laboratory data includes the assessment of three "gaps" of toxicology: the anion gap, the osmolal gap, and the arterial oxygen saturation gap.

a. *Anion gap:* Metabolic acidosis associated with an elevated anion gap is usually due to the accumulation of lactic acid or other acids. There are various causes of disturbed anion gap (Table 134.6). It is measured by:

$$[AG = Na^+] - [Cl^-] - [HCO_3^-]$$

The normal value is 12±4 mEq/L.

b. *Osmolal gap:* Certain drugs and toxins of low molecular weight produce discrepancy between measured and calculated plasma osmolality.[22] Osmolality is calculated by:

Calculated osmolality =
$2\,[Na^+] + [BUN]/2.8 + [glucose]/18 + [ethanol]/4.6.$

TABLE 134.6: Drugs associated with anion gap disturbance

Increased anion gap
- Carbon monoxide
- Cyanide
- Ethanol*
- Ethylene glycol*
- Formaldehyde
- Methanol*
- Salicylates

Decreased anion gap
- Hyperkalemia
- Hypercalcemia
- Acute lithium intoxication
- Bromide
- Hypermagnesemia

*Also have an increased Osmolal gap

Methanol and ethylene glycol are unique in producing both severe metabolic acidosis with elevated anion gap and an elevated osmolal gap (Table 134.6).

c. *Oxygen saturation gap:* Carbon monoxide and methemoglobin are associated with an elevated arterial oxygen gap (> 5% difference of the calculated from the arterial blood gas determination and saturation measured by co-oximetry). These toxins interfere with the oxygen binding to hemoglobin and thereby significantly decrease oxygen content without lowering PaO_2. Oxygen saturation measured by pulse oximetry is falsely high in the setting of these toxins.

d. *Toxicology screening:* Toxicology screening provides the direct evidence of ingestion, but it rarely impacts initial management, and initial supportive measures should never await the results of such analysis. If toxicology screen is required, urine is the best specimen (Table 134.7). Quantitative blood analysis of suspected drugs can be useful for diagnostic and therapeutic reasons, particularly in overdoses involving alcohols, acetaminophen, salicylates, and cyclic antidepressants.

Treatment of Specific Intoxications

Certain drugs or toxins can be managed by specific antidotes (Table 134.8).

Acetaminophen

Acetaminophen is the most popular "available over-the-counter" analgesic. It is the commonest poisoning in the western world especially in UK. However, it is uncommon in Indian subcontinent and other developing world. The toxic dose is > 150–200 mg/kg, or 8–10 grams in an average adult. Acetaminophen is primarily metabolized by liver through sulfation (20 to 46%) and glucuronidation (40 to 67%). A small percentage is oxidized to a toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQ1), by cytochrome P-450, which is quickly detoxified by the hepatic stores of glutathione to a nontoxic acetaminophen–mercaptate compound that can be eliminated through renal excretion. During toxic overdose a larger proportion is metabolized by cytochrome P-450 to NAPQ1, depleting glutathione.[23]

Clinical features: The evolution of acetaminophen toxicity is divided into four phases:[24,25]

TABLE 134.7: Drugs detected in urine

Drugs detected within 30 minutes
- Amphetamines
- Barbiturates
- Benzodiazepines
- Cocaine
- Opioids
- Phencyclidine

Drugs detected within 2-3 hours
- Acetaminophen
- Cannabinoids
- Phenothiazine
- Morphine
- Propranolol
- Ephedrine

TABLE 134.8: Specific antidotes for drugs and toxins

Drug/poison	*Antidote*
Acetaminophen	N-acetylcysteine
Anticholinergics	Physostigmine
Anticholinesterases	Atropine
Benzodiazepines	Flumazenil
Beta-blockers	Glucagon
Calcium channel blocker	Calcium chloride, glucagon
Cyanide	Amyl-nitrite, sodium nitrite, sodium thiosulfate
Digoxin	Digoxin specific antibodies
Ethylene glycol	Ethanol
Heavy metals	Dimercaprol(bal), edta, penicillamine
Opioids	Naloxone
Hypoglycemic agents	Dextrose, glucagon

Phase I refers to the first 24 hours after ingestion. Patients generally remain alert, but may experience nausea, vomiting, anorexia, malaise, pallor or diaphoresis.

Phase II occurs 24 to 72 hours after untreated ingestion. During this period, patient may develop the right upper quadrant pain and minor abnormalities of the liver function consisting of elevation of hepatic enzymes, prothrombin time and bilirubin.[26]

Phase III (72 to 96 hours after untreated ingestion) is characterized by continued hepatic necrosis, hepatic encephalopathy, disseminated intravascular coagulation and jaundice. Liver function abnormalities typically peak during phase III. The liver enzymes may rise to 10,000 IU/L or higher. Rare phase III sequel include hemorrhagic pancreatitis, renal failure and myocardial necrosis.[26]

Phase IV occurs four days to two weeks after ingestion, during which recovery occurs, with the return of enzymes to the normal range and without the development of chronic liver damage.

In some patients, there is a rising trend of prothrombin time, ammonia and bilirubin even though the levels of hepatic enzyme decline indicating fulminant hepatic failure.

Diagnosis: The diagnosis of acetaminophen toxicity depends upon serum levels and the time elapsed after ingestion. The interpretation of acetaminophen toxicity depends up on plotting of Rumack-Matthew nomogram.[26] The nomogram applies to an acetaminophen level measured after four hours following ingestion and before 24 hours after ingestion. Patients with four hours level of 200 µg/ml nomogram have a 60% risk of developing hepatotoxicity and a 5% risk of death.[27] Patients with four hour levels of 300 µg/ml have a 90% risk of developing hepatotoxicity.[28]

Treatment: Charcoal should be given within one to two hours of ingestion. One must treat if the serum acetaminophen level is above the nomogram line, i.e. four hour level of ≥ 200 µg/ml. If the precise time of ingestion is unknown, then a lower threshold of 100 µg/ml at four hours may be taken for treatment. Treatment with N-acetylcysteine is most effective if started within eight hours of ingestion.

The antidote N-acetylcysteine can be given orally or intravenously. Oral treatment begins with a loading dose of 140 mg/kg followed by 70 mg/kg every 4 hours for 72 hours or 17 doses. The intravenous regimen includes a loading dose of 150 mg/kg over 1 hour followed by 4 hours infusion of 50 mg/kg, and a 16 hours infusion of 100 mg/kg.[29-33]

Amphetamine and Cocaine

Cocaine and amphetamines are widely abused for their euphorigenic and stimulant properties. Both drugs may be smoked, snorted, ingested or injected. Amphetamines and cocaine produce central nervous system (CNS) stimulation and a generalized increase in central and peripheral sympathetic activity.[34] The toxic dose of each drug is highly variable and depends on the route of administration and individual tolerance. The onset of effects is most rapid after intravenous route or smoking.[35] Amphetamine derivatives and related drugs include methamphetamine (Crystal Meth, Crank), MDMA (Ecstasy), ephedrine (Herbal-ecstasy), and methcathinone (Cat).

Toxic effects of cocaine stem from excessive central nervous system stimulation and inhibition of neuronal uptake of catecholamine. Clinical features include anxiety, tremulousness, tachycardia, hypertension, diaphoresis, dilated pupils, agitation, muscular hyperactivity and psychosis.[36] Muscle hyperactivity may lead to metabolic acidosis and rhabdomyolysis. In severe intoxication, seizures and hyperthermia, may occur.[37] Sustained or severe hypertension may result in intracranial hemorrhage, aortic dissection or myocardial infarction.[38] Hyponatremia has been reported after MDMA use. Respiratory complications include status asthmaticus, upper airway obstruction, pulmonary hypertension, barotrauma, pulmonary edema and alveolar hemorrhage.[35,39]

Treatment: The diagnosis is supported by finding amphetamines, cocaine, or the cocaine metabolite benzoylecgonine in the urine. Blood screening is generally not sensitive enough to detect these drugs. Emergency treatment includes the A B C care. Rapidly lower the body temperature in patients who are hyperthermic. Treat agitation, psychosis or seizures with a benzodiazepine, such as lorazepam, 2–3 mg intravenously. Add phenobarbitone 15 mg/kg intravenously for persistent seizures.

Hypertension should be treated with a vasodilator agent, such as phentolamine (1–5 mg intravenously) or a combined alpha- and beta-blockers such as labetalol (10–20 mg intravenously). A pure beta-blocker, such as propranolol should not be used as it may result in paradoxical worsening of hypertension due to unopposed alpha-adrenergic effect.[40]

Tachycardia or tachyarrhythmias should be treated with a short-acting beta-blocker like esmolol (25–100 mcg/kg/min by intravenous infusion).

Aluminium Phosphide Poisoning

Aluminium phosphide is a very common cause of poisoning in North-West and Central India.[41-46] It is available as tablet (3 gram), which contains 56% aluminium phosphide and 44% ammonium carbonate. Toxicity of aluminium phosphide is due to phosphine, which is released when it comes in contact with moisture or hydrochloric acid. The precise cellular mechanism of phosphine is not clear. However, it is stipulated that it acts by preventing the uptake of oxygen by mitochondria.[47] Clinically, a myriad of symptoms are produced by the ingestion of aluminium phosphide. Immediately after ingestion all patients develop nausea, vomiting, retrosternal burning, and in the case of significant poisoning hypotension and shock.[41,43,44,46] Oliguria develops in a few patients. Adult respiratory distress syndrome develops in patients with severe intoxication.[48] Most patients develop myocarditis manifested by variable ECG changes ranging from bradyarrhythmias to tachyarrhythmias. Other complications include disseminated intravascular coagulation, intravascular hemolysis, congestive cardiac failure, hepatic failure and rarely pericarditis. Patients generally remain conscious till cerebral anoxia due to shock supervenes, resulting in drowsiness, delirium and coma.[41,43,49]

Management: The diagnosis is made by the history of ingestion. The diagnosis of aluminium phosphide poisoning can be made by detecting phosphine in exhaled air or in stomach contents.[50] There is no specific antidote for this poisoning and the treatment is supportive. Gastric lavage should be done with potassium permanganate within one hour of ingestion. For management of hypotension, intravenously fluids should be given judiciously as central venous pressure (CVP) is generally high in these patients. If the hypotension does not respond, then dopamine/dobutamine may be used to maintain the systolic BP above 80 mm Hg. Magnesium sulfate, a membrane stabilizer, which can reverse arrhythmias, has been used. Though arrhythmias improve, mortality does not decline. In severe cases, compromised adrenal function has been reported. Though corticosteroids have been administered, the outcome remains poor.[51]

Carbon Monoxide (CO) Poisoning

Carbon monoxide poisoning is seen regularly in clinical practice. It is the third leading cause of unintentional poisoning death in the USA.[52] Precise incidence of CO toxicity in developing countries is not available. Nonfatal incidences far more frequent and misdiagnosis is common.[52] CO poisoning occurs as a result of exposure to internal combustion engines in ill-ventilated places, fires and associated smoke inhalation and industrial accidents. Incidence tends to increase during winter months.

Pathophysiology: CO has 220 times more affinity to hemoglobin (Hb) than oxygen. It binds reversibly to Hb and its dissociation curve runs parallel to oxygen dissociation curve, however they move in opposite directions, i.e. CO curve shifts to right whereas oxygen dissociation curve shifts to left resulting in significant tissue hypoxia.[52,53] It also has higher affinity for myoglobin thereby enhancing myocardial ischemia. CO leads to the activation of platelets and neutrophil, as well as free oxygen radical injury and lipid peroxidation predominantly of the nervous tissue. Therefore, it is not surprising that presenting symptoms of CO toxicity are predominantly neurological and cardiovascular.

Clinical features: Symptoms of toxicity are variable and nonspecific. Careful history of exposure is important. Common patient's complaints include fatigue, nausea, vomiting, dizziness and headache. As the severity increases they develop ataxia, nystagmus, impaired judgment and unconsciousness. They can also develop dysrhythmia, myocardial dysfunction leading to hypotension and metabolic acidosis. Retinal hemorrhage though uncommon, if present strongly indicates CO poisoning. Patients can also have cyanosis and cherry red color of the skin. In pregnant patients, there is an increase risk of fetal death. Later on patients may develop either persistent or delayed neurologic sequelae.

Diagnosis: The diagnosis is confirmed by CO oximetry of the blood, which shows elevation of carboxyhemoglobin (COHb) levels beyond 10%. Severe poisoning is usually associated with levels more than 40%. Pulse oximeter usually gives falsely high values of saturation and must not be relied on in CO toxicity.[54]

Treatment: First of all, patient must be removed from the environment. Rescuer must take all precautions before evacuation. If person is not unconscious, then 100% oxygen with a tight mask with a flow rate of at least 10 L/min should be given. In case the patient is unconscious, he should be intubated and ventilated with 100% oxygen till COHb level reaches 5%. Wherever facility exists/available, hyperbaric oxygen should be preferred in severely poisoned cases.[52,53]

Insecticide Poisoning (Organophosphates, Carbamate, Organochlorine, Herbicide)

There are two major classes of insecticides in usage in commercial agriculture and home gardening, the organophosphates (malathion, parathion) and the carbamate (carbaryl, aldicarb). Insecticides can be absorbed from mouth, skin, conjunctiva, gastrointestinal tract and the respiratory tract. The cause of poisoning varies from suicidal attempt to accidental exposure. Signs and symptoms of acute poisoning generally occur within the first 12 to 24 hours after the exposure.

Organophosphate Poisoning (OP)

Commonly used organophosphates include malathion, parathion, chlorpyrifos, dichlorophos, and phorate. Organophosphates act by inhibiting the enzyme cholinesterase leading to the accumulation of acetylcholine at neuromuscular junction and nerve terminal resulting in the overstimulation of acetylcholine receptors. This initial overstimulation is followed by the paralysis of cholinergic transmission in the central nervous system, in autonomic ganglia, at parasympathetic and some sympathetic nerve endings and in some somatic nerves. A cholinergic crisis results in central and peripheral syndrome. Organophosphates bind irreversibly to cholinesterase, thus inactivating the enzyme through the process of phosphorylation. The aging that is the permanent binding of the organophosphates to the enzyme requires 24 to 48 hours to occur. Once ageing occurs only new enzymatic resynthesis must occur over a period of weeks before the clinical symptoms resolve and normal enzymatic function returns. Organophosphate poisoning can manifest with the varying combinations of symptoms attributed to muscarinic, nicotinic and central disturbances (Table 134.9).

An intermediate syndrome may occur one to four days following an acute organophosphate poisoning.[55] The patient appears to be recovering from acute poisoning when this manifests. Clinically, there is the paralysis of neck flexor muscles, muscles innervated by cranial nerves, proximal limbs and respiratory muscles to the extent that some patient may require respiratory support. Deep tendon reflexes are either absent or markedly diminished. EMG may assist in diagnosis by indicating a problem at neuromuscular junction. Symptoms usually resolve within 4 to 18 days.

TABLE 134.9: Signs and symptoms of organophosphate poisoning

Muscarinic	*Nicotinic*	*Central*
Salivation	Fasciculation	Anxiety
Lacrimation	Paresis/paralysis	Confusion
Urination	Hypertension	Seizures
Diarrhea	Tachycardia	Psychosis
GI cramps		Ataxia
Emesis		
Blurred vision		
Miosis		
Bradycardia		
Wheezing		

Diagnosis: In most of the developing countries, diagnosis of OP poisoning is largely clinical. However, it can be confirmed by the assays of plasma and Red Blood Cell (RBC) cholinesterases. Plasma cholinesterase assays are more readily available though the estimation of RBC cholinesterases is preferred over serum cholinesterases. Serum and RBC cholinesterase are usually depressed at least 50% below baseline in severe intoxication.

Treatment of organophosphate poisoning: Primarily treatment of OP poisoning includes decontamination, supportive therapy, including mechanical ventilation and definitive therapy in the form of antidotes like atropine and oximes.

i. *Decontamination:* OP compounds are highly lipophilic and are readily absorbed from skin, gut and lungs. Clothes should be removed and patient given a thorough wash with soap and water. Gastric lavage is done routinely, but is not of great help. Activated charcoal single or multiple doses, though found to be effective in animal models of OP poisoning and used routinely preferably within the first hour, is not effective in humans.[56] Airway protection should be a routine whenever lavage is done.

ii. *Supportive therapy:* Large proportion of these patients develops respiratory failure secondary to depolarizing muscle paralysis and overwhelming bronchorrhea. Airway must be protected early (preferably rapid sequence) followed by the control of breathing and circulation. Oxygenation should be started with an aim to have saturations more than 90%. Threshold for the initiation of mechanical ventilation should be low. In the case of seizures, preferred treatment is benzodiazepines (Lorazepam/Diazepam/Midazolam in usual doses) along with atropine.[57]

Respiratory muscle weakness may persist and cause difficulty in weaning, in spite of an apparent improvement in general condition and resolution of symptoms. Therefore, during weaning from ventilator or otherwise in wards, patients need close observation, especially of respiratory and heart rate. Fall in SpO_2 or rise in $PaCO_2$ are the late signs.

iii. *Specific therapy:* Atropine is the specific antidote in organophosphate poisoning. It is usually given in

2–5 mg IV bolus (0.05 mg/kg IV in children). Escalate (double) dose every 3–5 minutes until bronchial secretions and wheezing stops. Once the patient is fully atropinized, i.e. heart rate is more than 80 and secretions are dry; atropine infusion is set up by giving every hour 20 to 30% of the total amount that was required to atropinize the patient initially. The infusion dose is maintained for two to three days for full atropinization, then the infusion dose is daily reduced by 1/4th to 1/3rd of the previous day's dose.[58] Atropine is associated with anticholinergic side effects, including psychosis. Aim of the therapy is to have heart rate more than 80 with the drying of secretions and not dilatation of pupils and gut paralysis (observe abdominal sounds). Glycopyrronium bromide (Glycopyrrolate) can be used in place or together with atropine or if CNS side effects of later develop.[57]

Oximes: Theoretical and experimental basis of the use of oximes in OP poisoning are strong.[59] In humans especially in the case of self-harm, the data for their use is conflicting.[57-61] It has been argued that the efficacy of oximes depends not only on the amount, but also on the nature of compound consumed (dimethyl vs diethyl, former being more resistant), dosages, time of their administration, aging and reactivation kinetics implying there is a therapeutic window during, which oximes may be effective. The window in turn depends on the extent and rate of aging of Acetylcholinesterase (AChE). Further the type of oxime used is also a decisive factor in addition to their dosage (Obidoxime is nine times more active than Pralidoxime). Oximes have their own side effects too. Rapid administration of oxime can cause respiratory arrest in patients having shallow respiration.[62] In the presence of OP compounds they get converted into stable phosphoryl oximes. This further leads to the restriction of their ability to reactivate phosphorylated cholinesterase's and have been blamed for the variable response of oximes in OP toxicity.

In summary, at present evidence on the effectiveness and use of oximes in organophosphate poisoning is mixed. Therefore, it is difficult to contradict the WHO guidelines to give high dose oximes in OP poisoning. As of today, the recommended dosages are Pralidoxime chloride–30 mg/kg bolus followed by 8–10 mg/kg/hr or Obidoxime 250 mg bolus followed by 750 mg/24 hours, until at least 12 hours after the stopping of atropine.[57]

Carbamate Poisoning

Carbamates are cholinesterase inhibitors that are structurally related to the organophosphates. Commonly used carbamates are Sevin, Baygon and Lannate. They transiently and reversibly inhibit cholinesterase enzymes, unlike organophosphates. Regeneration of the ezyme occurs within few hours by the dissociation of the carbamyl-cholinesterase complex. Clinical features of carbamate poisoning are similar to that of organophosphate poisoning, but are of shorter duration. Carbamates do not penetrate the CNS readily, and hence less CNS effects are seen.

Treatment: Cholinesterase levels, thus enzymatic activity usually return to normal within four to six hours, therefore measurement of RBC cholinesterase level is not useful. Initial treatment is similar to that of organophosphate poisoning. Atropine is the antidote of choice and is administered for muscarinic symptoms. There is little need for 2-PAM in carbamate poisoning.[63]

Organochlorine Poisoning[64]

Organochlorine compound includes dichlorodiphenyl-trichloroethane (DDT), chlordane, hexachloro-cyclohexane, eldrin, etc. Organochlorines are well absorbed on ingestion by inhalation and minimally through skin. These agents are CNS stimulants and work by inhibiting GABA and glycine pathways. This leads to the inhibition of chloride channel preventing influx of Cl^- resulting in neuroexcitation, i.e. inhibitory control is lost.[65]

OCL are highly lipid soluble, therefore there is a slow redistribution, prolongation of elimination half life and increased duration of toxicity. Clinical features include the predominance of neurological symptoms ranging from hyperexcitability, irritability, delirium, myoclonus, and facial paresthesias in mild toxicity to seizures and status epilepticus in severe toxicity. In addition, these agents may produce myocardial irritability with ventricular fibrillation.

Management: History is important for making the diagnosis. Laboratory evaluation is generally not helpful, but these agents can be detected in serum and urine. Treatment includes oxygen administration with intubation to treat hypoxia secondary to seizures, aspiration and respiratory failure. Seizures are treated with benzodiazepines (lorazepam 0.04 mg/kg, midazolam 0.05 mg/kg or diazepam 0.2 mg/kg). Phenobarbitone or anesthesia with sodium thiopental may have to be used if the seizure persist. EEG monitoring if available, should be routinely done in these cases to observe seizure activity.

Atropine and epinephrine should be avoided for the control of dysrhythmia in organochlorine sensitized myocardium. Cholestyramine, a bile salt binding substance has been found to be helpful in reducing the absorption of these compounds (4 gm 4 times/day for at least 2–3 days in ingestional poisoning).[66]

Herbicide Poisoning

Herbicides are pesticides used to kill weeds. Herbicides are classified as chlorophenoxy, bipyridyl and urea-substituted compounds. Chlorophenoxy compounds dioxins and furans are the common chemicals under this group. Other agents are 2,4- dicholorophenoxyacetic acid (2,4-D), 4-chloro-2-methylphenoxyacetic acid (MCPA), etc.

The metabolic pathway or mechanism related to toxicity is unknown. Skeletal muscle toxicity can result in respiratory failure or rhabdomyolysis. Toxicity can result from inhalation or ingestion. Clinical features include the eye and mucous membrane irritation. After ingestion, nausea, vomiting and diarrhea occur. Cardiovascular findings include hypotension, tachycardia and dysrhythmias. Muscle toxicity manifests by muscle tenderness, fasciculation and myotonia with resulting rhabdomyolysis.[67]

Treatment: Diagnosis is based on the history of exposure. There is metabolic acidosis and hepatorenal dysfunction. Myoglobinuria and elevated creatinine levels indicate rhabdomyolysis. Treatment is supportive, including decontamination measures and respiratory support. Alkalinization is of any proven benefit however, may be tried in severe toxicity.[68]

Bipyridyl Compound

Paraquat and diquat are nonselective herbicided included in this class. Ingestion is responsible for maximum paraquat-related deaths. Paraquat is distributed to most organs with maximum concentration in the lungs and the kidneys. Acute exposure causes liver and renal necrosis that is followed in weeks by pulmonary fibrosis. Paraquat accumulates in the alveolar cells of the lungs where it is transformed to reactive oxygen species, the superoxide anion. This anion is responsible for lipid peroxidation causing the degradation of the membranes. Paraquat and oxygen enhance each other's toxicity by sustaining the redox cycle. Myocardial injury and necrosis of adrenal gland may occur. Paraquats caustic effects cause local skin irritation and ulceration of the mucous membranes. Hypovolemia occurs due to gastrointestinal losses and decreased oral intake. Cardiovascular collapse may occur early in severe toxicity. Multisystem effects then occur, including gastrointestinal corrosion, acute tubular necrosis and extensive pulmonary injury. Seizures, hepatic failure, gastrointestinal perforation and hemorrhage may occur. Pulmonary fibrosis leading to refractory hypoxemia occurs five days to several weeks later. Metabolic (lactic) acidosis is common as a result of pulmonary effects (hypoxemia) and multisystem failure.[69,70]

Treatment: Early diagnosis and treatment are essential. Diagnosis is based on the history. Qualitative and quantitative analyses for paraquat in serum and urine can help in diagnosis. A 10 hours level of greater than 0.4 mg/l carries a high probability of death.[71] Early treatment is supportive. An attempt at early and vigorous decontamination should be made to prevent superoxide radical formation by using low inspired oxygen to produce a therapeutic hypoxemia with the goal of reducing pulmonary toxicity. The use of low oxygen mixtures ($FiO_2 < 21\%$) with positive pressure ventilation reduces pulmonary toxicity. It is suggested that a higher FiO_2 may only be used when arterial oxygen pressure is less than 40 mm Hg.[72] Maintaining intravascular volumes and urine output are important to prevent prerenal failure. Immediate gut contamination with activated charcoal must be done.[69] Immunosuppressive therapy (cyclophosphamide with dexamethasone) has shown possible benefit in anecdotal reports.[73,74]

Opioids

The term opioids is an all-inclusive term for antagonists, endogenous and exogenous substances that possess morphine like activity. The most commonly abused opioids are heroin and methadone. Prescription and illicit opioids (morphine, codeine, oxycodone, fentanyl, etc.) are popular drugs of abuse and the cause of frequent hospitalizations for overdose.[75-77] These drugs have widely varying potencies and the durations of action; some of the illicit fentanyl derivatives are up to 2,000 times more potent than morphine. All these agents decrease central nervous system activity and sympathetic outflow by acting on opiate receptors in the brain. Mild intoxication is characterized by euphoria, drowsiness and constricted pupils. More severe intoxication can cause hypotension, bradycardia, hypothermia, coma and respiratory arrest. Pulmonary edema may occur.[78] Death is usually due to apnea or pulmonary aspiration of gastric contents. Propoxyphene may cause the seizure and prolongation of QRS interval.[79] Methadone has been associated with QT interval prolongation and torsades de pointes. With meperidine, the metabolite, normeperidine probably causes seizures and is most likely to accumulate after repeat dosing in patients with chronic kidney disease.[80]

Treatment: Naloxone is a specific opioid antagonist that can rapidly reverse the signs of narcotic intoxication. Although it is structurally related to opioids, it has no agonist effects of its own. It is given at a dose of 0.4–2 mg intravenously and a repeat dose may be given to awaken the patient. Very large doses (10–20 mg) may be required for patients intoxicated by some opioids (propoxyphene, codeine, fentanyl derivatives). The duration of the effect of naloxone is only 2–3 hours and repeated doses may be necessary for patients intoxicated by long-acting drugs, such as methadone. Continuous observation for at least three hours after the last dose of naloxone is mandatory.[81] In severest forms associated with respiratory depression, intubation and ventilation may be required.

STINGS AND ENVENOMATION

Snake Envenomation

Snake envenomation is an occupational hazard of farmers, plantation and agriculture workers. Exact incidence in India is not clear, however it is estimated that 35,000–50,000 snake bite deaths occur in India annually.[82] In India, the big four, i.e. Cobra (Naja naja), Common krait (Bungarus coeruleus), Russell's viper (Daboia russelii) and Saw scale viper (Echis carinatus) are responsible for nearly all the reported cases of severe envenomation, as well as death due to snake bites.

Snake venom is a combination of procoagulant enzymes, hemorrhagins, cytolytic or neurotoxins, hemolytic and myolytic phospholipases A_2 and pre/post-synaptic neurotoxins in isolation or in combinations. The net result is myonecrosis, consumption coagulopathy, neuroparalysis leading to life-threatening respiratory paralysis, myocarditis and hypotension, as well as renal failure.[82,83] This explains the diversity of clinical symptoms of the snake envenomation. However, certain patterns are species or genus specific thereby allowing clinical identification and treatment.

Cobra and common krait belong to family elapidae and their bites are primarily responsible for neuroparalytic presentation. Cobra venom acts predominantly postsynaptically whereas Krait venom acts presynaptically and dysautonomia is common. Viperine bites (Russell's viper and saw scale viper) cause severe coagulopathy leading to hemorrhagic manifestations, cardiac toxicity, capillary leak and acute renal failure.[83] There occurs significant local necrosis leading to compartment syndrome. In addition, it is not uncommon to see marked myonecrosis, but it is more common in sea snake bites. In south India and Sri Lanka, neuroparalysis may also be associated with Russell's viper. Cobra bites are associated with significant local necrosis like viperine bites and occasionally with hemolysis.

Clinical Features[82]

Clinical presentation primarily depends on the type of snake and amount of venom injected.

Majority of patients with clinically significant toxicity will have malaise, nausea, vomiting, abdominal pain, drowsiness, weakness and prostration.

Local symptoms are minimal or nearly absent in krait bite. In cobra and viperine bite, there is a swelling at the site of bite, which may expand rather rapidly (Fig. 134.2). It is not uncommon to have regional lymphadenopathy.

Systemic manifestations are usually preceded by significant nausea and abdominal pain. In elapidae bites, patient complains of blurring of vision, double vision, and inability to keep eyes open, drooping of the eyelids followed by difficulty in swallowing, speech and complete bulbar paralysis. The progression of paralysis follows roastrocaudal distribution leading to the development of respiratory and flaccid areflexic paralysis. There occurs complete internal, as well as external ophthalmoplegia (Figs 134.3 and 134.4). In its full blown form, it can mimic brain death with widely dilated nonresponsive pupils. In the Indian subcontinent, snake bite should always be considered as the cause of this presentation especially when it presents acutely even in the absence of history or fang marks as krait usually has little or no local reaction.[84] Recovery occurs in reverse fashion.

Bleeding from the site of bite may be the first manifestation of coagulopathy. Patients can bleed from

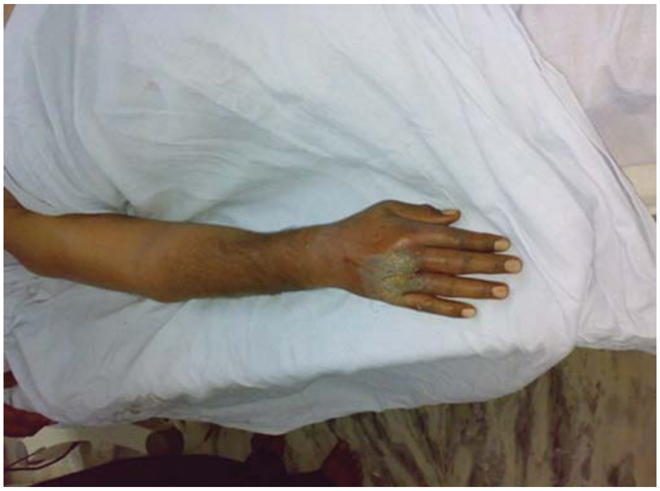

Fig. 134.2: Local signs in cobra bite

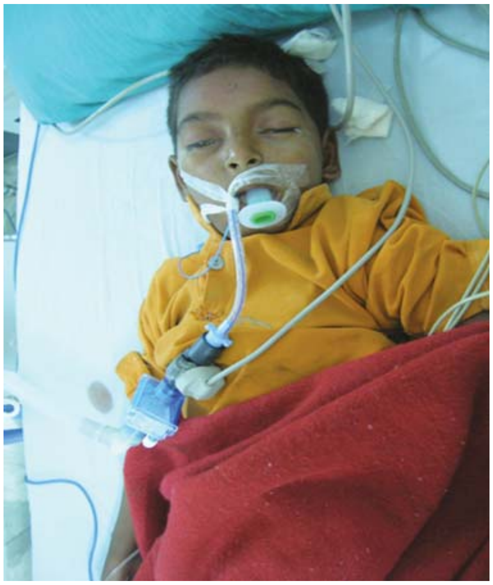

Fig. 134.3: Patient of neuroparalytic snake envenomation with ptosis

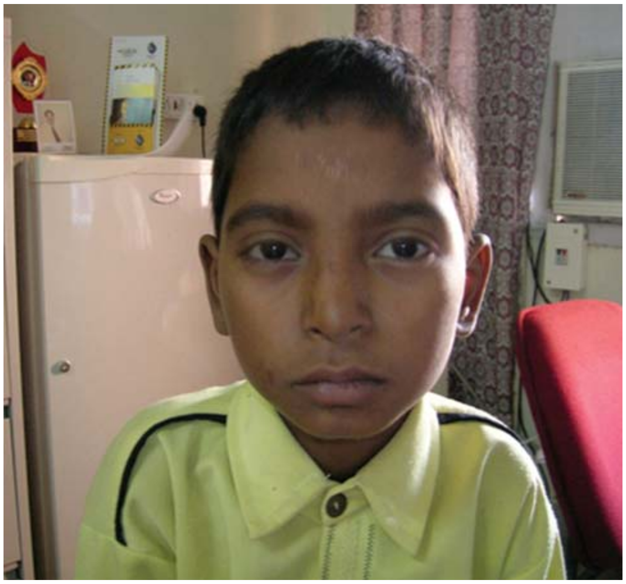

Fig. 134.4: Same patient after recovery

any site, the most dreaded is the intracranial hemorrhage. Due to bleeding, patients can have pituitary apoplexy or acute Addisonian crisis leading to refractory hypotension. Hematuria may be associated with loin pain. Hypotension, cardiac arrhythmias and pulmonary edema are also seen frequently because of the associated toxic myocarditis.

In South India and Sri Lanka, snake bite is a common cause of acute renal failure. It is multifactorial in origin and is characterized by oligoanuria and features of uremia.

Patients may complain of severe muscular pain. Misdiagnosis of acute abdomen has been made in the absence of history. Muscles become tender to touch and rigid. Myoglobinuria, if occurs is characterized by cola colored urine without the evidence of the presence of RBCs.

Investigations

Complete hemogram with platelet counts, Bleeding and Clotting Times (BT and CT) must be done in all patients. Urine should be examined for RBCs in the absence of hematuria. WHO recommend 20 minutes Whole-Blood Clotting Test (WBCT). Failure of blood to clot within 20 minutes signifies significant toxicity. Alternately where facility exists, Prothrombin Time Index (PTI), PTTK, fibrinogen level, creatinine kinase, etc. be done. If urine is smoky and RBCs are absent, myoglobulin should be looked into to rule out myoglobinuria. Electrolytes, blood urea and serum creatinine levels should be regularly monitored in patients with renal failure. Arterial puncture is contraindicated in the presence of coagulopathy.

Treatment

Snake bite is an emergency and usually happens in rural settings where medical facilities are minimal. However, once in the hospital, if severe envenomation is present, the patient should ideally be managed in intensive care (Table 134.10).

The first principal of management is to **do no harm**. Reassure and calm the patient. The limb should be immobilized preferably with a splint and bandage (pressure bandage, if available). Do not apply the bandage if there is a swelling at the site of bite and do not raise the limb. Never-ever open the bandage

TABLE 134.10: Potentially lethal conditions associated with snake bite and its treatment needing

- Circulatory shock, cardiac dysfunction, pulmonary edema
- Hemorrhage, hypovolemia
- Coagulopathy, disseminated intravascular coagulation (DIC)
- Coma, seizures, intracranial hemorrhage
- Cranial nerve dysfunction
- Rhabdomyolysis, renal failure, hyperkalemia
- Gastrointestinal bleeding
- Respiratory failure
- Anaphylaxis (to component of venom or antivenom)

quickly, especially in the absence of life support equipment, as it can lead to sudden deterioration in patient's condition.

The only **specific treatment** for snake envenomation is monovalent or polyvalent antisnake venom (ASV) prepared from horses sera. In India, only polyvalent ASV in both liquid, as well as lyophilized form is available. One ml of reconstituted antivenin neutralizes 0.6 mg venom of Indian cobra and Russell's viper and 0.45 mg of common krait and saw scale viper. Indications for its use are: coagulopathy, neuroparalysis, hypotension/ cardiovascular toxicity, acute renal failure, severe myonecrosis leading to myoglobulinuria and local swelling more than half of the bitten limb (provided not related to ligature) or the local swelling is rapidly enlarging.

Sensitivity must be checked prior to ASV infusion, preferably intradermally. Usually patients are given 50–100 ml of reconstituted ASV in serious envenomation as an infusion over one hour, after premedication with chlorpheniramine maleate (5 mg) and ranitidine (50 mg). It can also be given as a bolus with rate not more than 2 ml/min, especially when the patient is bleeding profusely. Whole blood CT should be repeated every four to six hourly or until the bleeding stops. Recurrence of bleeding after the initial improvement is not uncommon. ASV should be given until clinical bleeding stops and CT normalizes.

ASV will not have a dramatic effect in neuroparalysis. Airway must be protected if patient develops bulbar palsy or has difficulty in swallowing or speaking. Patient must be intubated before giving ASV and ventilated if respiration is shallow or tachypneic. Principles of resuscitation as enumerated in poisoning should take precedence. Low dose ASV is as effective as high dosage in neuroparalytic snake envenomation.[85] Majority of patients usually recover within 48 hours. Mechanical ventilation has reduced the mortality significantly in neuroparalytic envenomation, provided given at appropriate time. In the absence of a ventilator, patient should be managed with manual resuscitators.[86] Anticholinesterase drugs like edrophonium and neostigmine have also been recommended in the treatment of neuroparalytic snake envenomation. They should be given 10 mg of edrophonium or 0.5 mg of neostigmine over 2–3 minutes with atropine to take care of their harmful effect. In case patient improves, he should be managed with neostigmine/atropine over the next 24 to 48 hours.[82,87]

ASV is a foreign protein. Therefore, allergic reactions, including anaphylaxis are not uncommon. True incidence of anaphylaxis is not known as any death or complication is attributed to snake envenomation. Adrenaline syringe should always be kept ready before infusing ASV. In case of anaphylaxis or urticaria, stop the infusion of ASV. It should be followed by adrenaline: usual recommended dosage is 0.5 mg of 1:1000 dilution s/c. Additional dosages of H_1 (Chlorpheniramine maleate) and H_2 (Ranitidine) receptor blockers with hydrocortisone 100 mg, should be given simultaneously. Adrenaline can be repeated up to 2–3 dosages or an infusion can be started in dilution of 1:50,000. Hypotension is also treated with fluids. Inotropes may be required in patients with overt myocardial dysfunction.[82]

Patients developing renal failure need hemodialysis. Hyperkalemia should be looked for and managed aggressively. All patients should be given tetanus immunization. Antibiotics may be given to cover gram-negative organisms and anaerobes (gentamicin and metronidazole or amoxicillin), whenever there is an intense local reaction and swelling.

Snake envenomation, if recognized early and treated aggressively, usually has a good outcome.

Scorpion Sting and Envenomation

Scorpion bite is a common problem in tropics and subtropics. It is commonly associated with outdoor activity. There are more than 90 species of scorpions whom venom is lethal and nearly 50% of them are found in India. In Maharashtra and South Western India, the envenomation is seen entirely after the stings of Mesobuthus tamulus (known as red scorpion), whereas in eastern India it is secondary to Heterometrus bengalensis.[88,89] It is difficult to make any guess estimate of mortality and morbidity in India secondary to scorpion envenomation, but in Mexico more than 1,000 patients are reported to die in a year.[90]

Pathophysiology[91-93]

Unlike snake venom, scorpion venom acts on gated channels primarily the sodium channels leaving them open thereby leading to constant stimulation. Similarly, they also have an effect on calcium dependent K^+ channels in various cells and organs. Venoms effect on presynaptic membranes leads to cholinergic, as well as adrenergic hyperstimulation resulting in the massive release of catecholamines and the stimulation of angiotensin-rennin axis. The autonomic storm is associated with intense vasoconstriction, cardiac stimulation with increased myocardial oxygen demand and marked metabolic abnormalities as in pheochromocytoma crisis ending up in myocardial necrosis and failure. In addition, the activation of cholinergic stimulation also takes place. Therefore, it is not surprising that clinical syndrome is dominated by the features of autonomic crisis, including severe cardiovascular effects and cholinergic stimulation.

Clinical Features

Clinical signs and symptoms depend primarily on the amount of venom released in the body. If accidentally the venom is injected in the veins, presentation of envenomation can occur in as little as 5–10 minutes. There occurs intense severe pain at the site of sting. It worsens on taping at the site of bite (Tap sign) and may be associated with burning and paresthesiae. Systemic envenomation is characterized in the initial stages by tachycardia and hypertension. There may be sweating, lacrimation and fasciculations. In severe envenomation, patient develops pulmonary edema, dysrhythmias, hypotension, which becomes refractory later. Muscle paralysis and priapism are also not uncommon to see.

Investigations

EKG: The most common abnormality is sinus tachycardia, which is universal. Overtime, one can see QTc prolongation, and ST-T changes, including T inversions. In 10 to 12% of patients, conduction blocks may also be present.

Echocardiography: In patients with moderate to severe toxicity, it shows global left ventricular hyperkinesias, which return to normal after recovery.

Pulmonary artery (PA) studies: Demonstrate elevated systemic vascular resistance (SVR), which may be increased up to four times with low cardiac index and elevated filling pressures.

CXR: Shows cardiomegaly with evidence of pulmonary edema.

Biochemical: Hyperglycemia and elevated levels of FFA are common.

Coagulation parameters and blood gases should be done when necessary.

Treatment

Scorpion bite is an emergency and patients with systemic manifestations must preferably be managed in critical care units.

i. *Local:* Immobilize the affected part and keep it below the heart. Lymphatic venous compression may be applied an inch proximal to the bite to prevent venoms absorption. Like snake envenomation, it should be removed when one is in position to provide life-sustaining support.[90]

   Pain can be relieved by giving ice packs, as well as analgesics. Ice packs are most effective when applied earlier, preferably within two hours of sting.

ii. *Systemic:* General: Primary aim is to resuscitate and stabilize. One must follow the principles of resuscitation, i.e. establish airway, breathing, and circulation and shift the patient to intensive care for monitoring. Administer oxygen and maintain saturations to more than 90%. Fluids should be administered to prevent hypovolemia, which is not uncommon in these seriously sick patients.

Specific

Antivenin is the treatment of choice and should be administered at the first opportunity after stabilization of the patient. The usual starting dose is 10 ml of the reconstituted ASV and can vary from 10 to 30 ml or more depending on the severity and evolution of toxicity; 1 ml neutralizes approximately 13–17 mg of crude venom.[93] Antivenom neutralizes only the free venom therefore ongoing toxicity may continue. Either one has to use more ASV or preferably use prazosin (which is a postsynaptic alpha-2 blocker), which reverses most of the effects of the venom.

Combination of sympathetic alpha-blocker (Prazosin) with beta-blocker is most effective in reversing the effect of venom in patients who primarily have hyperdynamic cardiovascular changes manifested by tachycardia and hypertension.[90] Beta-blockers must never be used alone. Golden rule is to treat the condition like pheochromocytoma crisis. Prazosin alone has decreased the mortality from 30 to 40% to less than 3%. Therefore, if ASV is not available then patient must preferably be treated with Prazosin.[94]

Insulin-glucose-K^+ infusion, as well as other antihypertensive like nifedipine, captopril and others have also been used. People have also used nitroprusside and nitroglycerin to reduce the after-load. All patients must receive antitetanus prophylaxis.

ENVIRONMENTAL INJURIES

Environmental injuries are commonly seen in medical practice. While hypothermia is common during winters and at high altitudes, hyperthermia is commonly seen during the summer months in humid tepid and warm working environment when temperature may go as high as 45° centigrade. Increased outdoor activities, such as excursions, swimming, travel and accidents add to the growing number of people involved in injuries requiring life supporting treatment. Environmental injuries may also result from occupational hazards, such as in armed forces personnel posted at high altitude in deserts.

Hypothermia

Definition

Primary or accidental hypothermia can be defined as unintentional decrease in core body temperature probably due to cold environment exposure.[95] It can also be defined as core temperature less than 35ºC (95.0ºF). Hypothermia is further defined as mild (35–32ºC), moderate (32–28ºC) or severe (<28ºC).

Epidemiology

People in extremes of age, military combatants and winter sport participants are common risk population. Dehydration, malnutrition and certain common drugs like β-blockers, calcium channel blockers, antibiotics can also contribute to cause hypothermia. It may also be seen in endocrinopathies like hypothyroidism, postoperative states and alcohol intoxication.

Pathophysiological Changes

Hypothermia is caused when normal heat generating mechanism by posterior pituitary and heat conservation mechanism by anterior pituitary are disturbed by extreme cold exposure. Every organ shows changes due to the effects of hypothermia.

The initial response of cold stress on cardiovascular system is peripheral vasoconstriction with tachycardia and increased myocardial oxygen consumption. There is also associated increase in blood pressure.[96] As temperature goes down to 28°C, myocardial depression ensues resulting into bradycardia, decrease in cardiac output and index (with resultant QRS broadening and prolongation of QT segment) and hypotension. Atrial and ventricular arrhythmias occur with profound hypothermia. J wave or Osborn wave,[97-98] present at the junction of QRS and ST segment, marked in lead II and V6, is diagnostic of hypothermia when temperature goes down to 32ºC.

Cerebral metabolic activity decreases linearly as hypothermia sets in.[99] Cognitive functions are the first to be affected. EEG activity slows as temperature goes down and is totally silent by 19–20ºC. Triphasic waves are characteristic in electroencephalogram of hypothermia.

Initial hyperventilation is followed by hypoventilation, increased secretions, ventilation perfusion mismatch, noncardiogenic pulmonary edema, acute respiratory distress syndrome and lastly respiratory arrest. Below 30ºC, respiratory rate is generally slow at 5–10/min.

Renal system responds by cold diuresis probably due to the inhibition of ADH release.

Coagulopathies are frequent during hypothermia. Prolongation of activated partial thromboplastin time with normal prothrombin time and normal international normalized ratio occur up to temperatures of 30ºC whereas below this temperature, picture of disseminated intravascular coagulopathy with thrombocytopenia sets in. Leukocytosis with hemoconcentration occurs secondary to volume contraction from diuresis.

Treatment

Principles of resuscitation, i.e. ABC should take precedence followed with careful rewarming under observation.

Rewarming: Method of rewarming depends on the severity of hypothermia and should be accompanied with adequate cardiac and hemodynamic monitoring. Passive external rewarming, active external rewarming or active core rewarming are the accepted methods.[100] Removing the stable patient from cold exposure forms passive external rewarming.[101,102] This method is generally employed at the prehospital scene.

Active external rewarming is done by creating heated environment around the patient by using heating pads, warm blankets, infrared lights or immersion in warm water. It raises the body temperature by 0.5–0.6ºC/hour. This method is controversial as it results into a phenomenon called core temperature after drop, which is decrease in core temperature due to sudden peripheral vasodilatation resulting at times into life-threatening arrhythmias.

Active core rewarming is the method of choice in severe hypothermia and is done by infusing warm intravenous fluids of up to 42ºC, body cavity warm lavages, inhalation of heated air or by extracorporeal circuit. This method is best in increasing body temperature to the magnitude of 1–2ºC/hour.

Associated conditions must be identified and treated. In the cases of myxedema coma leading to hypothermia, thyroxine along with steroids must be given.

In spite of aggressive management, mortality with hypothermia continues to be high.

Hyperthermia

Hyperthermia is defined as increase in body temperature with abnormal thermoregulation. There is a wide spectrum of heat-related illnesses extending from heat cramps or miliaria rubra to life-threatening heat exhaustion and heat stroke.

Heat exhaustion is generally present in individuals who sweat profusely during extreme environment heat load, thus become hypovolemic.[103] The symptoms are generally vague, such as general irritability, fatigue, increased thirst, decreased urine output and light headedness. Muscle cramps occur later in the course of the illness. Temperatures are generally elevated, readings up to 40ºC have been seen. Rhabdomyolysis does not occur in heat exhaustion. Treatment consists of exposing the individual to cool environment and aggressive fluid resuscitation.[104] Encourage oral intake in conscious patients, if patient has vomiting, then intravenous fluids should be administered.

Heat stroke is a medical emergency. It can be differentiated from heat exhaustion by temperature elevation of more than 40.6ºC and associated CNS symptoms. Another peculiar symptom is the absence of sweating. This syndrome is also associated with multiorgan failure with rhabdomyolysis, Disseminated Intravascular Coagulation (DIC) and renal failure. These patients have classical CNS symptoms[105] like agitation, delirium, hallucinations, convulsions and lastly coma. They have cerebral edema on autopsy. Tachycardia is a universal finding; low cardiac output with hypotension refractory to volume loading and vasopressors is characteristic.[106,107] High-grade fever stimulates respiratory center leading to hyperventilation, respiratory alkalosis, hypocalcemia and tetany. Acute renal failure and the elevation of hepatic enzymes are seen in approximately 25 to 30% of patients probably due to thermal cell injury. Vomiting and diarrhea are common. Patches of gut ischemia can occur due to compensatory mesenteric vasoconstriction.[108] Thrombocytopenia with DIC resulting into petechial hemorrhages, hematuria, and alveolar hemorrhage is a common feature of heat stroke.

Heat stroke is of two types—classic heat stroke is due to environment exposure and exertional heat stroke is after strenuous exercise, mostly in hot humid environment. Exertional heat stroke is the severe form and has higher incidence of multiorgan dysfunction and mortality.

Management

After addressing to airway and breathing, fluid resuscitation should be done. Cold intravenous fluids can be used.[109] Cooling of the patient should be undertaken. The aim of any cooling method is to bring down the temperature to 39ºC.[110] External cooling is the most common and the easiest method. This is achieved by placing the patient in cool environment and by putting ice packs in groins, axillae and over the chest. Pouring tap water over the body and fanning the patient will also decrease temperature by evaporative cooling. Cool water immersion[111] is one of the commonest methods of cooling. Internal cooling can be done by lavages of body cavities by cool water. Blood samples to check for multiorgan dysfunction should be taken.[112]

Drowning and Near Drowning

World Health Organization defines drowning as "the process of experiencing respiratory impairment from submersion or immersion in liquid."[113] Some of the important situations, which have been identified to lead to drowning include unattended children, alcohol abuse, restricted swimming capability, exacerbation of pre-existing conditions (seizure, myocardial infarction), risky behavior, exhaustion and others.[114] Children form the major bulk of patients.

Drowning is a continuum of events, which occur when the victim's airway lies below water.[115-117] It starts with breath holding leading to laryngospasm and resultant respiratory acidosis and hypoxemia. This progresses to the respiratory efforts and drinking of large quantities of water in lungs causing severe acid-base changes and finally respiratory arrest. Drowning is associated with cerebral edema and raised Intracranial Pressure (ICP), acute respiratory distress syndrome, noncardiogenic pulmonary edema, myocardial dysfunction, cardiac arrhythmias, acute tubular necrosis, hepatocellular damage and hypothermia. These patients generally have hypoxic-ischemic injury.

Management

Basic cardiopulmonary resuscitation after drowning/near drowning and the treatment of pulmonary edema remains the mainstay of treatment.

Treatment starts at the site of submersion injury. The main objective of prehospital management is to restore normal ventilation, circulation and acid-base balance.[118] Cardiopulmonary resuscitation should be started by the bystander until health care personnel arrive. Cardiopulmonary resuscitation has the same principles as for other patients.[119] Cold wet clothes should be removed from the victim's body. Airway and breathing should be addressed immediately. Cervical spine immobilization should be undertaken. If patient does not breathe adequately, then breathing should be controlled by intubation and ventilation. Once the patient reaches the hospital, controlled ventilation with the low levels of Positive End Expiratory Pressure (PEEP) should be used initially. Generally, these patients have pulmonary edema, so noninvasive ventilation with Continuous Positive Airway Pressure (CPAP) can also be used.[120] Invasive monitoring is generally not required. Methods to measure core temperatures should be employed. ICP monitoring has a limited role in management. Antibiotics become useful only for those patients who become febrile after drowning in sea water.

Inhalational Injury

Inhalational injuries and smoke inhalation are not common. It is of more serious nature in burns in children.[121] The combination of burn injury and inhalational injury increase mortality by 44%. Inhalational injuries should be identified early, which can be due to: i. direct injury to the airways; ii. carbon monoxide poisoning; iii. toxic fumes, like cyanide; or iv) acute asphyxia.

Pathophysiology

Inhalational injury generally follows a three phase course:

Initial phase: There are signs of carbon monoxide poisoning (headache, nausea, irritability, decreased visual aquity, confusion, seizure) with features of toxic fume poisoning. Pulmonary edema with airway obstruction is not uncommon.

Second phase: Features of ventilation-perfusion mismatch and hypoxemia start appearing and patient may develop acute respiratory distress syndrome.

Final phase: Pneumonias and pulmonary embolism may occur after the initial phases.

Management

These patients pose a real challenge as far as their airway management is concerned. A normal looking patient after a burn injury can suddenly develop respiratory distress. Dry heat produces edema of the oral cavity and larynx leading to respiratory obstruction. All inhalational injury patients presenting with stridor should be immediately intubated in the view of impending respiratory failure. Patients with inhalational injury should be given 100% oxygen to treat carbon monoxide poisoning.[122,123] If arterial saturation is not maintained above 90%, conventional ventilation should be initiated and treatment protocol of ARDS should be started.[124-127] For patients who are refractory to conventional ventilation, extracorporeal oxygenation[128] or nitric oxide inhalation can be tried.

Tracheobronchial toilet with fiberoptic bronchoscope should be done to clear out burn debris and sloughed mucosa. Strategies[129] to prevent pneumonia (e.g. head elevation of the bed by 30°), stress ulcer and deep vein thrombosis prophylaxis must be initiated from the very beginning. There is no role of prophylactic antibiotic administration. Corticosteroids whether inhaled or intravenous are detrimental in burn patients as they increase the chances of superadded infections.

Summary

Environmental hazards can manifest after natural or man-made disasters and can lead to huge resource utilization. The presentation and management of each injury has a characteristic course and if timely protocolized management in followed the results can be awarding.

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Obstetric Critical Care

Hrishikesh S Kulkarni, Dilip R Karnad, Kalpalatha K Guntupalli

INTRODUCTION

Critically ill patients comprise nearly 7% of all admissions to Indian intensive care units (ICUs).[1] Studies in Asian ICUs show that 120 to 730 obstetric patients are admitted to the ICU per 100,000 deliveries.[2] Poor preexisting nutritional status of the patient and anemia, low socioeconomic status of the family, lack of access as well as delay in receiving appropriate antenatal health care, unhygienic deliveries and increasing numbers of operative interventions lead to unique problems in the developing countries. Managing critically ill obstetric patients is a challenge for the intensivist, who needs to ideally ensure the well-being of both the mother and the fetus. Among other things, the intensivist needs to consider the physiological changes of pregnancy while interpreting the results of diagnostic tests. The intensivist also needs to assess the safety profile of prescribed medications, and needs to modify the dose where appropriate due to the different pharmacokinetics (absorption, distribution, metabolism and elimination) during pregnancy. A database of the safety profile of different medications in pregnancy is available online at http://www.safefetus.com.[3]

The causes of ICU admissions in pregnant patients can be divided into obstetric (defined as "those admissions that would not have occurred in a nonpregnant patient") and medical (Table 135.1).[4]

TABLE 135.1: Conditions requiring intensive care unit admission in critically ill obstetric patients in developing countries

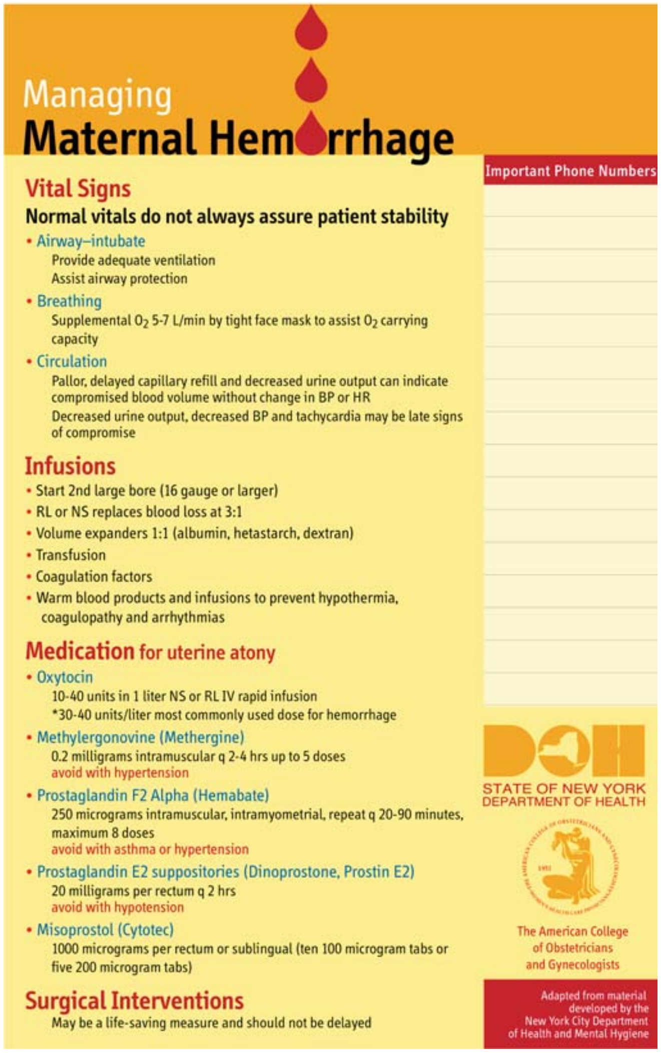
Obstetric	*Incidence (%)*	*Medical*	*Incidence (%)*
Pre-eclampsia/eclampsia	45.5	Malaria	10
Postpartum hemorrhage (PPH)	15.3	Viral hepatitis	6.2
Intrauterine fetal death (IUFD)	12.5	Cerebral venous thrombosis	3.5
Postabortal/puerperal sepsis	6.5	Community-acquired pneumonia	3.1
HELLP syndrome	5.6	Aspiration pneumonia	3.1
Abruptio placentae	5.7	Cardiac arrest prior to ICU admission	2.8
Acute fatty liver of pregnancy (AFLP)	4.4	Rheumatic heart disease	2.1
Antepartum hemorrhage	3.6	Diabetes mellitus	2.1
Abortions	2.4	Bacteremia	1.7
Abnormal adherence of placenta	1.1	Attempted suicide (poisoning/drugs)	1.7
Uterine rupture	0.8	Hematologic disorder	1.6
Chorioamnionitis	0.9	Intracranial hemorrhage	1.2
Peripartum cardiomyopathy	0.5	Endocrine	1.1
Amniotic fluid embolism	0.5	Central nervous system infection	0.8
		Tetanus, leptospirosis, typhoid	0.7
		Deep vein thrombosis/pulmonary embolism	0.7
		Chronic renal failure	0.5

Severity scores, such as the APACHE II and SAPS II often overestimate the risk of mortality in critically ill obstetric patients, especially in those with "obstetric disorders." Interestingly, among ICU patients with similar conditions (e.g. sepsis), pregnant patients often do better than the nonpregnant patients.[2] Precedence should be given to maternal well-being, resuscitation and stabilization of the mother often results in the external manifestations of fetal distress (like persistent fetal tachycardia, decreased variability and late decelerations on external cardiac monitor) returning to normal, and improves fetal survival. The next few pages briefly describe what the intensivist can do in the management of critically ill obstetric patients, while coordinating with the obstetrician and neonatologist, to improve maternal and fetal outcomes.

OBSTETRIC HEMORRHAGE

Obstetric hemorrhage occurs either antepartum (4 to 10% of pregnancies) or postpartum (10 to 20% of deliveries).[2,4,5] Common antepartum causes include placenta previa, abruptio placentae, vasa previa, ruptured ectopic pregnancy and uterine rupture.[6] Postpartum bleeding is most commonly due to uterine atony, retained placenta, uterine rupture, uterine inversion or genital ulcerations.[5] Postpartum bleeding is significant when there is over 500 mL of blood loss within 24 hours of delivery, a drop of more than 10% in the hematocrit since admission, or when the blood loss leads to hemodynamic instability.[5]

Obstetric hemorrhage should be managed immediately because the patient's condition can deteriorate rapidly.[7] Clinicians underestimate the degree of loss, and the clinical signs and symptoms should be used to guide the management (rather than the amount of external bleeding).[7] For every 1 mL of blood loss, 3 mL of fluid needs to be given through one or two large bore intravenous cannulae (14 or 16 gauge). Colloids can possibly worsen coagulation.[8] The American College of Obstetricians and Gynecologists and the New York State Department of Health have developed a poster that is useful in the initial management of obstetric hemorrhage (Fig. 135.1).[9] As the patient is being resuscitated, the obstetrician and neonatologist need to be informed immediately. These patients also need continuous cardiac monitoring, because the hemorrhage can precipitate myocardial ischemia.[10] If the fetus has yet not been delivered, start continuous electronic fetal monitoring as soon as possible.



Managing

Maternal Hemorrhage

Important Phone Numbers

Vital Signs

Normal vitals do not always assure patient stability

- Airway–intubate
  - Provide adequate ventilation
  - Assist airway protection
- Breathing
  - Supplemental O_2 5-7 L/min by tight face mask to assist O_2 carrying capacity
- Circulation
  - Pallor, delayed capillary refill and decreased urine output can indicate compromised blood volume without change in BP or HR
  - Decreased urine output, decreased BP and tachycardia may be late signs of compromise

Infusions

- Start 2nd large bore (16 gauge or larger)
- RL or NS replaces blood loss at 3:1
- Volume expanders 1:1 (albumin, hetastarch, dextran)
- Transfusion
- Coagulation factors
- Warm blood products and infusions to prevent hypothermia, coagulopathy and arrhythmias

Medication for uterine atony

- Oxytocin
  - 10-40 units in 1 liter NS or RL IV rapid infusion
  - *30-40 units/liter most commonly used dose for hemorrhage
- Methylergonovine (Methergine)
  - 0.2 milligrams intramuscular q 2-4 hrs up to 5 doses
  - avoid with hypertension
- Prostaglandin F2 Alpha (Hemabate)
  - 250 micrograms intramuscular, intramyometrial, repeat q 20-90 minutes, maximum 8 doses
  - avoid with asthma or hypertension
- Prostaglandin E2 suppositories (Dinoprostone, Prostin E2)
  - 20 milligrams per rectum q 2 hrs
  - avoid with hypotension
- Misoprostol (Cytotec)
  - 1000 micrograms per rectum or sublingual (ten 100 microgram tabs or five 200 microgram tabs)

Surgical Interventions

May be a life-saving measure and should not be delayed

STATE OF NEW YORK
DEPARTMENT OF HEALTH

The American College
of Obstetricians
and Gynecologists

Adapted from material
developed by the
New York City Department
of Health and Mental Hygiene

Fig. 135.1: Management of obstetric hemorrhage

While stabilizing the vital signs, look for the cause by initially examining the external genitalia. In the case of postpartum hemorrhage, first check the tone of the uterus. Handling of the uterus needs to be done by an experienced physician/obstetrician, because the unnecessary kneading of a firm uterus can lead to the worsening of the bleeding.[11] If the uterus is contracted, rule out genital lacerations by inspecting the vagina, cervix and uterus. These are the most common causes of postpartum bleeding.[5] Massive bleeding from genital lacerations suggests the involvement of a major vessel. In rare cases, genital lacerations may lead to unexplained hemodynamic instability. In these cases, rule out a retroperitoneal hematoma. Some of these patients may even need an exploratory laparotomy.[5] Patients with retroperitoneal hematomata generally present with fever, thigh pain, leg edema and/or ileus within 24 hours of delivery. [12] The alternate possibility in a patient with a contracted uterus is a retained placental fragment.[11]

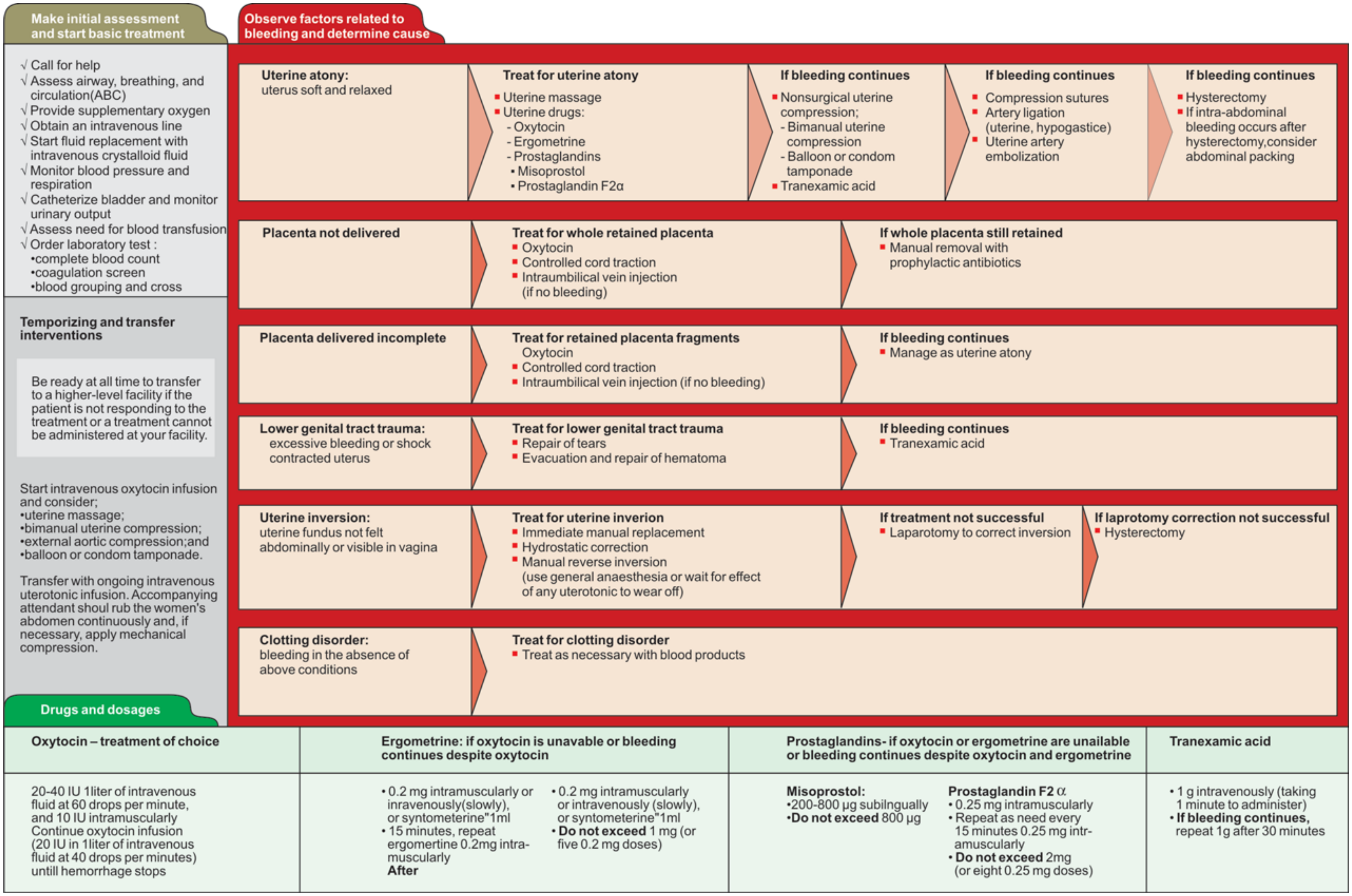
Always be wary of precipitating a massive hemorrhage when exploring the uterus for a retained placental fragment.[5]

If the uterus is atonic, first discontinue uterine relaxants like tocolytics, inhalational anesthetics and empty the patient's bladder.[10] Prompt, yet carefully monitored initiation of an uterotonic agent like oxytocin is essential. Further management of the different etiologies and the recommended drug doses are described in Figure 135.2. In addition to the steps in Figure 135.2, alert the blood bank and have at least four units of typed and cross-matched blood, two units of fresh frozen plasma and one ten-pack of platelets ready for transfusion (if necessary); the lab should always stay four units ahead of blood use.[13] The first unit of cross-matched blood should be obtained within 30–45 minutes. [14] Table 135.2 gives a list of blood products. Meanwhile, O negative red blood cells (RBCs) can be used on an emergency basis, because continued dependence on fluids can dilute the coagulation factors.[14] Every unit should have a readily available tray containing the essential drugs for the management of primary postpartum hemorrhage (PPH).[7] If the bleeding continues in spite of medical management, uterine massage, followed by temporary tamponade can be achieved (before the obstetrician arrives) by passing the balloon of a Foley's catheter or a Sengstaken-Blakemore tube past the cervical canal and inflating it (generally with 60–80 mL of saline) till the bleeding stops.[15,16] This is also a useful diagnostic test to decide if the patient needs an emergency laparotomy.[17] The maximum time the balloon can be left inflated is 48 hours. Thrombophilias like von Willebrand's Disease (vWD) may be unmasked in pregnancy.[18] Treat such patients using tranexamic and/or deamino-delta-D-arginine vasopressin (DDAVP), followed by factor replacement (Table 135.2). Recombinant-activated factor VII (initial bolus dose of 90 mcg/kg followed by a second identical dose if no response is seen) has shown promise as an adjunctive measure in obstetric hemorrhage, but the lack of randomized control trials precludes its routine use.[10,19]

Placental abruption occurs when the normally implanted placenta separates (partially or completely) from its basal layer before the delivery of the fetus. Placental abruption may lead to either frank or concealed hemorrhage and uterine atony that when untreated, leads to hypovolemia-induced end-organ damage (e.g. acute kidney injury, Sheehan's syndrome) and disseminated intravascular coagulation.[5] Increasing uterine tenderness, uterine contractions, maternal tachycardia and the evidence of hemodynamic instability are warning signs.[6] An emergent vaginal ultrasound can help delineate the degree of separation; however, only 50% of the hemorrhages due to abruptio placentae can be detected by ultrasound—hence, it is more of use for ruling in than ruling out. Stable patients with placental abruption can be managed conservatively, waiting for normal vaginal delivery if the pregnancy is less than 36 weeks. [6] However, deteriorating maternal or fetal status may warrant an emergency cesarean section. In nonresponsive cases, a hysterectomy is the last resort. Placental abruption used to carry 20 to 40% mortality, but this has reduced in recent years to 5 to 10%.[20,21] Yet, placental abruption can lead to adverse neurologic sequelae in the infant.[22]

Placenta previa, in which the placenta abnormally implants over the lower uterine segment, leads to painless frank antepartum bleeding because the progressive cervical dilatation and lengthening causes shearing of the placenta.[5] It may also be precipitated by minor trauma or sexual intercourse.[6] Most cases stop spontaneously, but hemodynamically unstable mothers may need cesarean section. An increased incidence of abnormal fetal positions may occur —another reason for the obstetrician to be involved early. Careful monitoring of the mother is necessary even after the bleeding has stopped, because it may recur at any time. Vasa previa involves bleeding from the vessels that cross the internal os before entering the placenta. The bleeding is entirely fetal and generally happens when the membranes rupture; thus these patients will generally not present in the medical intensive care unit (MICU) unless there is preterm labor in an already admitted patient. However, if it occurs, consider an emergency cesarean section followed by fetal transfusions and volume resuscitation by the neonatologist if the fetus is alive.[6] Patients having a ruptured ectopic pregnancy may not necessarily have torrential bleeding; however, an acute abdomen in the presence of any amount of vaginal bleeding should prompt the physician to explore this diagnosis. Diagnosis is by emergency transvaginal ultrasound and if confirmed, immediate surgical repair is warranted.[23]

Uterine rupture occurs in those patients having a history of uterine scarring (e.g. cesarean section, myomectomy), especially in that subset who attempt a vaginal delivery or in whom uterotonic agents are used. However, it may occur in a primigravida as well.[10] A part or whole of the fetus enters the peritoneal cavity. Severe abdominal pain may be deceptively absent, and the blood loss is moderate; therefore, a nonreassuring fetal heart rate pattern that is eventually lost should alert the attending physician to this



Make initial assessment and start basic treatment

√ Call for help
√ Assess airway, breathing, and circulation(ABC)
√ Provide supplementary oxygen
√ Obtain an intravenous line
√ Start fluid replacement with intravenous crystalloid fluid
√ Monitor blood pressure and respiration
√ Catheterize bladder and monitor urinary output
√ Assess need for blood transfusion
√ Order laboratory test :
•complete blood count
•coagulation screen
•blood grouping and cross

Temporizing and transfer interventions

Be ready at all time to transfer to a higher-level facility if the patient is not responding to the treatment or a treatment cannot be administered at your facility.

Start intravenous oxytocin infusion and consider;
•uterine massage;
•bimanual uterine compression;
•external aortic compression;and
•balloon or condom tamponade.

Transfer with ongoing intravenous uterotonic infusion. Accompanying attendant shoul rub the women's abdomen continuously and, if necessary, apply mechanical compression.

Observe factors related to bleeding and determine cause

Uterine atony: uterus soft and relaxed

Treat for uterine atony
- Uterine massage
- Uterine drugs:
  - Oxytocin
  - Ergometrine
  - Prostaglandins
    - Misoprostol
    - Prostaglandin F2α

If bleeding continues
- Nonsurgical uterine compression;
  - Bimanual uterine compression
  - Balloon or condom tamponade
- Tranexamic acid

If bleeding continues
- Compression sutures
- Artery ligation (uterine, hypogastice)
- Uterine artery embolization

If bleeding continues
- Hysterectomy
- If intra-abdominal bleeding occurs after hysterectomy,consider abdominal packing

Placenta not delivered

Treat for whole retained placenta
- Oxytocin
- Controlled cord traction
- Intraumbilical vein injection (if no bleeding)

If whole placenta still retained
- Manual removal with prophylactic antibiotics

Placenta delivered incomplete

Treat for retained placenta fragments
Oxytocin
- Controlled cord traction
- Intraumbilical vein injection (if no bleeding)

If bleeding continues
- Manage as uterine atony

Lower genital tract trauma: excessive bleeding or shock contracted uterus

Treat for lower genital tract trauma
- Repair of tears
- Evacuation and repair of hematoma

If bleeding continues
- Tranexamic acid

Uterine inversion: uterine fundus not felt abdominally or visible in vagina

Treat for uterine inverion
- Immediate manual replacement
- Hydrostatic correction
- Manual reverse inversion (use general anaesthesia or wait for effect of any uterotonic to wear off)

If treatment not successful
- Laparotomy to correct inversion

If laprotomy correction not successful
- Hysterectomy

Clotting disorder: bleeding in the absence of above conditions

Treat for clotting disorder
- Treat as necessary with blood products

Drugs and dosages

Oxytocin – treatment of choice	Ergometrine: if oxytocin is unavable or bleeding continues despite oxytocin	Prostaglandins- if oxytocin or ergometrine are unailable or bleeding continues despite oxytocin and ergometrine	Tranexamic acid
20-40 IU 1liter of intravenous fluid at 60 drops per minute, and 10 IU intramuscularly Continue oxytocin infusion (20 IU in 1liter of intravenous fluid at 40 drops per minutes) untill hemorrhage stops	• 0.2 mg intramuscularly or inravenously(slowly), or syntometerine"1ml • 15 minutes, repeat ergomertine 0.2mg intra-muscularly **After** • 0.2 mg intramuscularly or intravenously (slowly), or syntometerine"1ml • **Do not exceed** 1 mg (or five 0.2 mg doses)	**Misoprostol:** •200-800 μg subilngually •**Do not exceed** 800 μg **Prostaglandin F2** α • 0.25 mg intramuscularly • Repeat as need every 15 minutes 0.25 mg intr-amuscularly • **Do not exceed** 2mg (or eight 0.25 mg doses)	• 1 g intravenously (taking 1 minute to administer) • **If bleeding continues,** repeat 1g after 30 minutes

Fig. 135.2: Management of postpartum hemorrhage as per WHO guidelines (2009)
(Obtained with permission from the World Health Organization)

TABLE 135.2: Resuscitation of obstetric patients using blood products

Replacement	*Indication*	*Dose*	*Expected effect*	*Comment*
Packed RBCs (PRBC)	Severe anemia	1 U contains 250-325 mL	1 U increases: Hct by 3% Hb by 1%	• Use O negative cells initially if necessary· • Use a blood warmer to prevent hypothermia· • Use leukoreduced blood to prevent febrile reaction
Platelets	1. Active bleeding platelets <50,000. 2. No active bleeding + platelets <30,000*	1 U contains 35-50 mL	1 U increases total platelet count by 8,000/mm^3.	• Can be stored for up to 5 days at 20-24°C.
Fresh frozen plasma (FFP)	Active bleeding + prolonged PT/aPTT (> 1.5 × normal)	1 U contains 200-400 mL; use 1 U of FFP per 1 U of PRBC	250 mL will increase total fibrinogen by 25 mg/dL	• Can be stored up to 2 hours when thawed· • If it leads to fluid overload, use (nonactivated) prothrombin complex concentrate
Fibrinogen	Fibrinogen deficiency (<1-1.5 mg/dL)		4 g concentrate raises levels by 10 mg/dL	• May have potential viral contamination – use pasteurized concentrates
Cryoprecipitate	Hemophilia A, von Willebrand disease, fibrinogen deficiency (<1-1.5 mg/dl)	1 U contains 20-50 mL	Increases total fibrinogen by 10-15 mg/dL	• Can be stored up to 4-6 hours when thawed· • Contains fibrinogen + factors V, VIII, XIII, von Willebrand factor

Adapted with permission from [11] and [13]. U: unit, Hct: hematocrit, Hb: hemoglobin. *Platelet counts are considered as cells/cubic millimeters. Watch out for acidosis and hypothermia from transfusion of cold blood components.

diagnosis.[5] The obstetrician is immediately involved and needs to take up the patient for uterine repair. A neonatologist needs to be on board to prevent fetal anoxia and its sequelae.

Uterine inversion is a sequela of fundal pressure and excessive umbilical cord traction. The uterus turns inside out and there may be considerable bleeding. Start the basic protocol of managing obstetric hemorrhage (Fig. 135.1) and try to reposition the uterus promptly. If this fails, transfer the patient to the operating room to reposition the uterus under general anesthesia. Nitroglycerin may be tried as an adjunctive measure, initially as 400 mcg/spray sublingually, followed by 20 mcg/IV.[24] Once repositioned, stop all tocolytics and start uterotonic agents like oxytocin or prostaglandins (Fig. 135.1).

ACUTE HYPERTENSIVE DISORDERS IN OBSTETRIC CRITICAL CARE

Preeclampsia is defined as the onset of hypertension after 20 weeks of gestation, along with (1) a constellation of clinical features (edema, visual disturbances, headache, epigastric pain) and/or (2) more than 300 mg of protein in a 24-hour urine sample (>1+ on dipstick test) in a previously normotensive woman.[25,26] A blood pressure of more than 140 mm Hg systolic and/or more than 90 mm Hg diastolic, without clinical features or proteinuria in the same time frame, is known as gestational hypertension; 25% of these can go on to preeclampsia.[26] New onset clinical features or proteinuria in a woman with a) hypertension before 20 weeks b) sudden increase in proteinuria or hypertension, or c) the development of HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome is defined as superimposed preeclampsia.[26] New onset grand mal seizures or coma superimposed on preeclampsia/gestational hypertension is defined as eclampsia.[25,26] Headache, hyperreflexia, clonus and visual signs often precede eclampsia.

If uncontrolled, preeclampsia can progress to severe preeclampsia (Table 135.3A). Uncontrolled severe preeclampsia can lead to complications that are classified as maternal (hypertensive crisis, eclampsia, intracranial hemorrhage, temporary blindness, acute myocardial infarction, congestive heart failure, pulmonary edema, liver failure, renal failure, HELLP syndrome, disseminated intravascular coagulation [DIC]), placental (subchorionic hematoma, placental abruption, recurrent bleed) and fetal (preterm labor, intrauterine growth retardation, oligohydramnios, death).[25] Features of a hypertensive crisis include altered sensorium, focal

TABLE 135.3A: Diagnostic criteria for severe preeclampsia

Symptoms

- Headache
- Visual disturbances
- Epigastric/right upper quadrant pain

Signs

- Blood pressure > 160/110 mm Hg on at least 2 occasions 6 hours apart
- Pulmonary edema
- Oliguria (<400 ml/24 hours)

Laboratory tests

- Proteinuria > 5 grams/24 hours
- Elevated serum creatinine
- Evidence of HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome
- Fetal ultrasound – intrauterine growth retardation

Adapted from [26]

neurological deficits, rales, an audible S3, ascites, ecchymosis and oliguria.[25] The differential diagnoses of severe preeclampsia include placental abruption, amniotic fluid embolism and the complications of intrauterine fetal demize. The differential diagnoses of eclampsia include hypertensive encephalopathy, bleeding arteriovenous malformation, ruptured aneurysms and idiopathic seizure disorder. The absence of retinal hemorrhages and papilledema helps to differentiate eclampsia from the rare hypertensive encephalopathy. Patients with end-organ damage, complications, or a blood pressure of greater than 240/140 need ICU admission.

Management of the patient having a hypertensive emergency in pregnancy involves stabilizing the patient, preventing seizures, controlling the blood pressure and deciding the further management. Ensure airway, breathing, circulation, and place the patient on the lateral side; inform the obstetric team immediately. The maternal well-being is always given precedence; continuous fetal monitoring needs to be started as the mother is stabilizing.[27] The tests to be ordered in severe preeclampsia along with their interpretation are given in Table 135.3B. A tight fluid balance is needed that focuses on restriction (limit to 1 mg/kg/hr) in order to prevent pulmonary edema.[28] If pulmonary edema occurs, give intravenous furosemide and morphine (Furosemide: 20 to 40 mg IV over 2 minutes, followed by a repeat dose 30 minutes later if necessary, up to a maximum dose of 120 mg/hr; Morphine: 2 to 5 mg IV). Closely monitor the urine output; if oliguria is present, but the renal function is normal, diuretics are not essential.[29] Invasive hemodynamic monitoring is helpful in severe renal

TABLE 135.3B: Interpretation of diagnostic tests

Parameter	*Interpretation*
In all patients	
Complete blood count	Hemoconcentration is an indicator of severity
Peripheral smear	For evidence of hemolysis (schistocytes, burr cells)
Platelet count	Platelets <100,000/mm^3 suggests severe preeclampsia; look for HELLP syndrome
Liver function tests	ALT, AST, serum bilirubin elevated in HELLP syndrome
Serum BUN, Creatinine	Creatinine > 1.2 mg/dL + oliguria – suggest severe preeclampsia
Serum uric acid	Values > 5.6 mg/dl suggest severe preeclampsia
Urinalysis and microscopy	Muddy casts suggest acute tubular necrosis
24-hour urine collection for protein and creatinine clearance	Pregnancy-associated hypertension when associated with proteinuria (> 300 mg/24 hours) should be considered preeclampsia unless proven otherwise; high excretion (> 5 g/24 hours) indicates severe preeclampsia
Blood type and antibody screen	Keep the blood bank informed as an emergency vaginal or cesarean delivery may be needed if patient deteriorates
Obstetric ultrasound	For evidence of intrauterine growth retardation
Selective tests	
Serum LDH	Elevated in HELLP syndrome (especially when > 600 IU/L)
Coagulation profile	Elevated PT or aPTT, decreased fibrinogen indicate impending DIC
Uterine artery Doppler velocimetry	Absent or reversed end-diastolic flow indicates severe preeclampsia and possible risk to fetus
	HELLP: hemolysis, elevated liver enzymes and low platelets, DIC: disseminated intravascular coagulation, aPTT: activated partial thromboplastin time. Monitor these tests over time to identify worsening of maternal status, especially during conservative management.

Adapted with permission from Polley et al[30] failure, and refractory hypertension, oliguria and pulmonary edema[26] because central venous pressure (CVP) poorly correlates with the pulmonary arterial wedge pressure in these patients.[29]

Magnesium sulfate ($MgSO_4$) is better than phenytoin or diazepam for preventing/treating eclamptic seizures.[26] It is given through an infusion pump as a 4 to 6 grams loading dose diluted in 100 mL of isotonic fluid over 15 to 20 minutes. This is followed by a continuous infusion of 2 grams/hour. Target serum levels of Mg for prophylaxis are between 4 to 6 mEq/L. EKG changes are seen above 5 mEq/L.[29] $MgSO_4$ is safe in renal insufficiency, but is contraindicated in those with myasthenia gravis. The maintenance dose is only given if (1) Respiration is normal, (2) Oxygen saturation is adequate, (3) Urine output is greater than 20 mL/hr and (4) Patellar reflex is normal.[28] If there is respiratory depression or hyporeflexia (which suggests a Mg level > 10 mEq/L), give 1-gram calcium gluconate IV (10 mL over 10 minutes). If the seizures recur, give any of these: a 2 gram bolus of $MgSO_4$, diazepam (0.1 to 0.3 mg/kg over 60 seconds; maximum dose 30 mg), lorazepam (0.02 to 0.03 mg/kg IV up to a total of 0.1 mg/kg, maximum rate of infusion: 2 mg/min), a single dose of sodium amobarbital 250 mg IV (over 3 to 5 minutes). If seizures are still recurring, the patient may need intubation. $MgSO_4$ is continued for 24 hours following delivery or after the last seizure, whichever is later,[28] or at least 12 hours, after which it may be discontinued if (1) the patient has no headache, visual changes and epigastric pain in that interval, (2) the blood pressure has been kept below 150/100 without antihypertensive medication and (3) the urine output has been over 100 mL/hr for at least 2 hours without medication.[30]

The diastolic blood pressure should be gradually decreased—generally over 30 to 60 minutes—to between 100 to 110 mm Hg, so as to ensure adequate uteroplacental perfusion.[28] A good thumb rule is reducing it by 10 to 20 mm Hg every 10 to 20 minutes.[30] Currently, there is no preferred antihypertensive among hydralazine, labetalol or slow-release nifedipine that has proven better than the other for the management of acute hypertensive emergencies in pregnancy.[31] Some clinicians prefer using labetalol.[25] If none of these works, then nitroprusside, nitroglycerin or prazosin may be used as second line drugs. Characteristics of the most commonly used antihypertensive drugs used in severe preeclampsia are given in Table 135.4. For a more complete discussion, refer to the review article by Vadaeff et al.[25] ACE inhibitors are contraindicated in

TABLE 135.4: Commonly used antihypertensive medications in pregnancy

Drug	*Advantages*	*Disadvantages/Contraindications/Side effects*
Hydralazine IV (Dose: 5-10 mg every 15-20 minutes; Maximum dose – 30 mg)	Onset within 10-20 minutes	• Poorly tolerated compared to others· • Less effective than nifedipine • Can cause reflex tachycardia, hypotension, headaches, flushing, anxiety, vomiting, epigastric pain, fluid retention • Can cause thrombocytopenia, lupus-like syndrome, fetal distress (prolonged infusion) syndrome in neonate • Hypotensive overshoot secondary to volume depletion
Labetalol IV (Dose: 1 mg/kg continuous infusion Bolus – Start with < 20 mg, then increased as 40, 80, 80, 80 and 80 mg q15 min; maximum dose – 300 mg)	• Onset in < 5 minutes· • Reduces myocardial oxygen consumption, no reflex tachycardia nor bradycardia· • Does not influence renal function, end-organ perfusion, cardiac output or fetal heart rate· • Useful in MI, LVF, CHF, atrial fibrillation, cerebrovascular accidents, hypertensive encephalopathy	• Contraindicated in patients with asthma, preexisting myocardial disease, decompensated cardiac failure· • Can potentiate myocardial depression when given with calcium channel blockers· • Side effects include dizziness, nausea, headache, fatigue, bronchoconstriction and hyperglycemia. • Can cause hypotension, hypoglycemia, hypothermia, bradycardia in neonate
Nifedipine (SR) (10 mg capsules orally, repeat q15-30 min; maximum dose – 30 mg)	• Onset in 45-90 min • Increases cardiac index and renal flow· • No effect on end-organ perfusion and fetal heart rate	• Onset of action of SR capsules may be too slow for HT emergencies • May cause neuromuscular blockade/severe hypotension with magnesium sulfate • Side effects include tachycardia, palpitations, headaches, flushing, ankle edema

pregnancy and used only as the last resort, when other medications fail to resolve the hypertensive crisis. Diuretics are also avoided, though they may be continued if they had been started prior to pregnancy.[25] They may have value in patients with renal failure, resistant heart failure or pulmonary edema. They should be considered on a case-by-case basis, e.g. weighing the pros and cons in patients with the already established evidence of uteroplacental insufficiency or intrauterine growth retardation.

While the definitive method to abort the preeclampsia is by delivering the fetus, the physician should also consider the gestation and the maternal and fetal status. If both mother and child are stable, then the pregnancy can be delayed till term by controlling the blood pressure and using seizure prophylaxis. If the gestation has not crossed 34 weeks and the mother is in danger, preparations should be made to induce labor or for a cesarean section, which is mainly done for obstetric reasons. Intramuscular betamethasone should be administered immediately. The delivery should be well-planned and be ideally conducted under optimal circumstances, unless there is evidence of fetal distress (e.g. bradycardia or meconium stained liquor), when it should be prompt. Ergometrine is withheld even if postpartum hemorrhage occurs because it can precipitate hypertensive crisis; use oxytocin instead. Antihypertensive drugs that can be safely given postpartum are methyldopa, hydralazine, ACE inhibitors and magnesium sulfate; beta-blockers are best avoided. Hypertensive disorders still contribute to 30% of maternal mortality in India, and HELLP syndrome (Table 135.5) and pulmonary edema are the most common causes of death in these patients.[32,33]

VENOUS THROMBOEMBOLISM (VTE) IN PREGNANCY

The hypercoagulable state of pregnancy puts patients at a greater risk of deep venous thrombosis (DVT) and pulmonary embolism (PE), which can occur in any trimester of pregnancy and even up to 6 weeks after delivery.[34] An inherited thrombophilia may be unmasked in pregnancy; interestingly, thrombophilias are associated with 50% of the VTE cases in pregnancy.[34] The clinical features of VTE are same as those in nonpregnant patients; however, many of the features, such as leg swelling, dyspnea and tachycardia are normal in pregnancy. Thus, a high suspicion, but judicious objective testing helps to identify these patients. Unless it is contraindicated, treatment with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is advisable in patients who are suspected to have a VTE, at least until the results of the objective testing are available.[35]

Compression ultrasonography is the first test that should be done in pregnant patients with suspected DVT or PE.[34] However, it may miss iliac vein thrombosis, which may be picked up by magnetic resonance direct thrombus imaging (preferable over CT imaging in pregnant patients). The complete algorithm is given in Figure 135.3. A negative D-dimer test does not rule out VTE.[36] Once a VTE is detected, continue heparin. LMWH is now preferred over UFH as the standard treatment, and a twice daily regimen is preferred because of the decreased half-life of heparin in pregnancy, secondary to the increased renal excretion.[34] The dose of LMWH increases with body weight.[34,35] Factor Xa levels are recommended only in morbidly obese or thin patients, and in those with renal insufficiency. A vena caval filter is placed in (1) those whom anticoagulation is contraindicated and (2) in those whom an extensive VTE develops (a) two weeks before delivery or (b) the activated partial thromboplastin time (aPTT) is already in the therapeutic range.[37] For patients in whom heparin is contraindicated, fondaparinux (Category B drug) may be a safe alternative though there is limited knowledge of its safety.[38] Thrombolytics are reserved for those patients having an acute massive PE with hemodynamic compromise. However, if surgery/delivery has occurred within the last 10 days, it is contraindicated, although there have been exceptions to the rule.[39] Surgical/interventional methods are also available—hence, treatment should be individualized. A patient with a massive PE, at term or at a point where the fetus is in distress but has a chance of survival, may need an emergency cesarean section. All pregnant patients with a stable PE will need a temporary vena caval filter once the diagnosis is confirmed.[34] All patients with VTE need compression stockings both antepartum and postpartum.[35]

The last dose of therapeutic LMWH should be given 24 hours before the delivery while that of UFH should be given 6 hours prior to delivery. Follow it by confirming that the aPTT is in the physiological range. LMWH may be resumed 12 hours after delivery/surgery in the absence of bleeding. Warfarin is safe in the postpartum period and should be given for at least 6 weeks, ideally for at least 6 months.[34]

CARDIAC DISEASE IN PREGNANCY

The hemodynamic changes of pregnancy can unmask a hitherto undiagnosed cardiac disease in obstetric

TABLE 135.5: Liver diseases in pregnancy

Disease	*Clinical Features*	*Jaundice*	*Incidence*	*Lab Values*	*Adverse Effects*	*Treatment*	*Comments*
Hyperemesis gravidarum	Nausea, vomiting, dehydration, ketosis (uncommon), no pain usually	Rare, if present – mild	0.3-1.0%, mainly in 1st or 2nd trimester	Bilirubin < 4 mg/dl, ALT <200 IU/L (may rise to 20X normal), decreased phosphate, magnesium, potassium	Low birth weight	Hydration, antiemetics, slowly introduce solids orally; add nutrients like thiamine	• Biochemical abnormalities should normalize as vomiting resolves· • Rule out hyperthyroidism
Intrahepatic cholestasis of pregnancy	Pruritus (esp. of palms and soles) followed by generalized symptoms, no pain	Present in 20-60% of cases 1-4 weeks after pruritus	0.1-0.2%, mainly in 2nd or 3rd trimester	Bilirubin < 6 mg/dl, ALT < 300 IU/L (may rise to 20X normal), fasting serum bile acids > 10 umol/L diagnostic	Stillbirth, premature birth, bleeding, fetal mortality 3.5%	Drug of choice: UDCA; maintain bile acids <40 umol/L; add fat soluble vitamins	• Resolves after delivery; if it does not, consider the familial form that may progress to cirrhosis
Acute fatty liver of pregnancy	Upper abdominal pain, nausea, vomiting, neurologic dysfunction	Common, occurs 1-2 weeks post-onset of symptoms	4.4% of critically ill obstetric patients in an Indian ICU, commonly seen in 3rd trimester	Leukocytosis, ALT < 500 IU/L, increased bilirubin, ammonia and uric acid late in disease, renal dysfunction may be present, DIC in > 75% cases	Maternal mortality in untreated -high; with prompt treatment - <20%; SIDS in neonate	Prompt delivery of fetus should resolve jaundice (within 4 weeks) and DIC; yet may need liver transplant	• Low BMI, multiple gestations, nulliparity increase risk· Hypoglycemia suggests a poor prognosis· Neonatologist essential • Liver dysfunction resolves within 2 weeks of delivery·
Preeclampsia and eclampsia	Upper abdominal pain, edema, HTN, nausea, vomiting, neurologic dysfunction	Late, seen in 5-14% of cases	5-10%, seen in 2nd or 3rd trimester	ALT <500 IU/L (if > 500, consider infarction), proteinuria, DIC in 7% cases	Increased maternal and fetal mortality	Blood pressure control; immediate delivery may be necessary	• Subcapsular hematoma may occur • Hypertension and proteinuria may be absent in 15% cases.
HELLP syndrome (Hemolysis, elevated liver enzymes and low platelets)	Often asymptomatic, in other cases – pain, nausea, vomiting	Late, seen in 5-14% of cases	Only 5-10% of cases have preeclampsia; occurs mainly in 2nd/3rd trimester, but can also occur after delivery	ALT < 500 IU/L, platelets <10000/cu.mm, hemolysis, increased LDH (> 600 IU/L), DIC in 20-40% cases, renal dysfunction may occur; use Swansea criteria for diagnosis[60]	Increased maternal and fetal mortality; CNS dysfunction, bleeding, hepatic rupture	Supportive management; prompt delivery if: 1. > 34 weeks gestation 2. Fetal distress 3. Severe complications	• Increased PT indicates onset of DIC or severe liver injury
Hepatic hematoma	Sudden severe right upper quadrant pain, pyrexia	Generally absent; if present, due to co-morbidity	Rare, seen in 3rd trimester/puerperium	ALT >3000 IU/L, leukocytosis	Can lead to rupture, ARDS, AKI and shock	• Contained – Blood transfusion and supportive measures. • Unstable patient – May need angiographic embolization or invasive hemostatic measures	
Viral hepatitis	Fever, nausea, vomiting, pain	Common	Same as nonpregnant, any trimester	ALT > 500 IU/L, increased bilirubin, DIC rare, viral serologies positive	Hepatitis E can cause FHF and death	Supportive	

Adapted from [58] and [59]. *Other causes of right upper quadrant pain in these patients include biliary tract disease (cholecystitis or choledocholithiasis), drug-induced hepatitis and Budd-Chiari syndrome.* UDCA: ursodeoxycholic acid, ALT: alanine aminotransferase, BMI: body mass index, HTN: hypertension, LDH: lactate dehydrogenase, DIC: disseminated intravascular coagulation, PT: prothrombin time, ARDS: acute respiratory distress syndrome, AKI: acute kidney injury, FHF: fulminant hepatitis failure

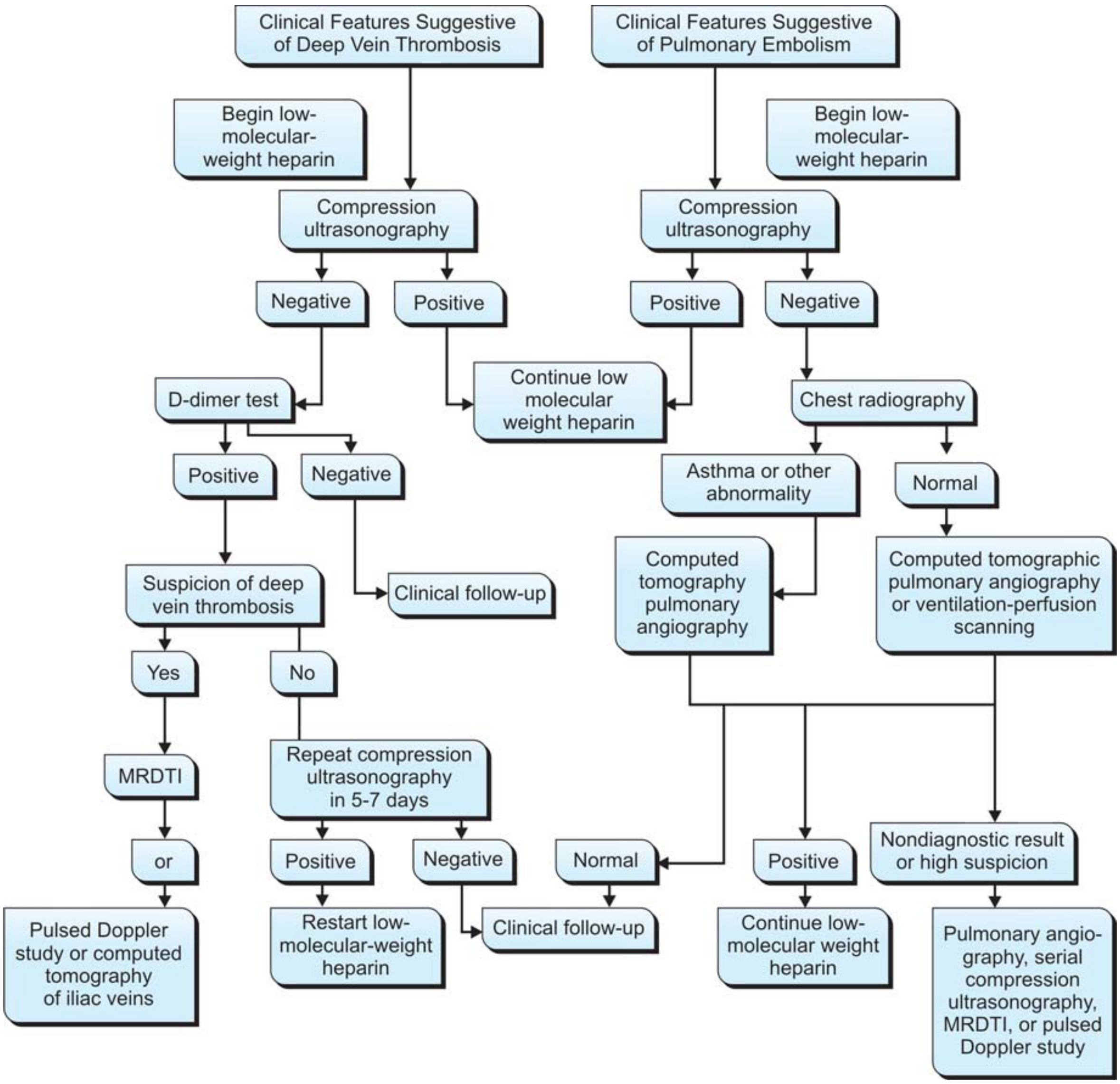

Clinical Features Suggestive of Deep Vein Thrombosis
Clinical Features Suggestive of Pulmonary Embolism
Begin low-molecular-weight heparin
Begin low-molecular-weight heparin
Compression ultrasonography
Compression ultrasonography
Negative
Positive
Positive
Negative
D-dimer test
Continue low molecular weight heparin
Chest radiography
Positive
Negative
Asthma or other abnormality
Normal
Suspicion of deep vein thrombosis
Clinical follow-up
Computed tomography pulmonary angiography
Computed tomographic pulmonary angiography or ventilation-perfusion scanning
Yes
No
MRDTI
Repeat compression ultrasonography in 5-7 days
or
Positive
Negative
Normal
Positive
Nondiagnostic result or high suspicion
Pulsed Doppler study or computed tomography of iliac veins
Restart low-molecular-weight heparin
Clinical follow-up
Continue low-molecular weight heparin
Pulmonary angio-graphy, serial compression ultrasonography, MRDTI, or pulsed Doppler study

Fig. 135.3: Diagnosis and management of venous thromboembolism (VTE) in pregnancy [Adapted with permission from (34)]

patients.[40] Some of the clinical features of cardiac disease overlap with the normal features of pregnancy. However, chest pain, severe breathlessness, orthopnea, paroxysmal nocturnal dyspnea, an irregular pulse, an S_4 heart sound, pulmonary edema or pleural effusions are pathological.[41] Obstetric patients at the highest risk of decompensation are those with NYHA Class III and IV heart failure, cyanosis, Marfan's syndrome, left heart obstruction (severe AS), Eisenmenger's syndrome, an ejection fraction of <40%, severe pulmonary hypertension (pulmonary arterial pressure > 75% of mean arterial pressure), mechanical prosthetic heart valves, and an aortic root diameter > 40 mm.[42,43]

A majority of these cases in Indian ICUs are due to rheumatic heart disease.[4] Management of these patients is similar to nonpregnant patients. The goals are to maintain normal heart rate and rhythm, and an adequate systemic vascular resistance, intravascular volume and venous return. Avoid aortocaval compression, myocardial depression by drugs, and the rise in pulmonary vascular resistance caused by pain, hypoxemia, hypercarbia and acidosis. Carefully monitor the fluid balance. If the symptoms still do not resolve, consider balloon mitral valvuloplasty.[41] Beta-blockers may be used in pregnant patients to treat arrhythmias; however, they can cause intrauterine growth retardation.

Penicillin can be used in these patients as prophylaxis for recurrences. Infective endocarditis prophylaxis is only indicated for complicated vaginal or cesarean delivery in patients with prosthetics valves, previous infective endocarditis, complex congenital heart disease, or valvulopathy in patients with cardiac transplants.[44] In patients with mechanical valves, the decision regarding anticoagulants needs to be taken along with the patient while balancing the risks of warfarin embryopathy with the less than ideal anticoagulant effects of heparin.[40] The american college of chest physicians has guidelines for anticoagulation during pregnancy.[45] Low-dose aspirin is safe and recommended in these patients, unlike in those with venous thromboembolism.[40]

Peripartum cardiomyopathy is a rare complication in pregnancy, but was found in 5.8% of the obstetric patients admitted to an American ICU.[4] It is a diagnosis of exclusion, the criteria being:[46]

1. Congestive heart failure symptoms of an unknown cause.
2. Absence of a preexisting cardiac muscle disorder.
3. Onset of symptoms during the last month of gestation until 5 months postpartum.
4. Left ventricular systolic dysfunction, identified by depressed ejection fraction.

The etiology is unknown; however, maternal age over 30 years, hypertension in pregnancy, multiparity, multiple gestations, use of beta-agonists during pregnancy and a low socioeconomic status increase the risk.[47] Management is similar to cardiac failure in nonpregnant patients. The only difference is that ACE inhibitors, if indicated, should only be started postpartum.[40] 80% of the women recover completely. In patients with refractory heart failure, a left ventricular ejection fraction of <25% and cardiac troponins raised within two weeks of onset predict a poor prognosis, and possibly the need of a transplant.[40,48] In refractory cases, delivery is necessary.

RESPIRATORY DISORDERS IN PREGNANCY

The differential diagnosis of dyspnea in pregnancy includes acute asthma, pulmonary embolism (thrombus, amniotic fluid and air), pneumonia, aspiration pneumonitis and pulmonary edema. A few of these patients may eventually need either noninvasive or invasive ventilation to sustain adequate oxygenation.

The important points in the ventilation of pregnant patients are:[49]

- Use a smaller endotracheal tube (size 6–7 mm) and nasotracheal intubation to reduce trauma to an already edematous and vascular upper airway.
- Place the patient in the left or right lateral position; change sides periodically.
- Do continuous electronic fetal monitoring to identify any signs of distress.
- Indications for neuromuscular relaxation and sedation: High levels of PEEP, hemodynamic instability (use nondepolarizing agents like atracurium, cisatracurium, vecuronium, pancuronium; cisatracurium preferred; alternatively, benzodiazepines or propofol in third trimester); when these agents or opioids are used, inform a neonatologist so that they are ready to resuscitate the fetus if necessary.

Tocolytic-induced pulmonary edema, the most common cause of pulmonary edema in pregnancy, is a noncardiogenic side effect that occurs either immediately after starting high doses of beta-agonists, within 24 hours of discontinuation or within 12 hours postpartum,[50] especially in mothers with multiple gestations, concurrent infection or those who are receiving steroid therapy.[51] Fluid retention in the days preceding the onset can alert the clinician to this complication.[49] It is a Type 1 (hypoxic, hypo/normocapneic) respiratory failure, promptly responds to oxygen, diuretics and discontinuation of medication, and is fortunately associated with very low maternal and fetal mortality.[50]

AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism is a rare complication that causes rapid deterioration of the mother's hemodynamic status and in a majority of cases, leads to her death.[52] Most of the cases occur during labor or within 30 minutes of delivery. However, it may occur earlier due to uterine manipulation during trauma or abortion.[53] It is characterized by sudden onset hypotension and cardiorespiratory arrest along with fetal distress (if fetus is still present *in utero*). Soon, the patient develops cyanosis, neurodysfunction and starts bleeding uncontrollably.[52] The physician needs to rule out uterine rupture, sepsis and hemorrhage that present similarly.[53] Amniotic fluid embolism is especially suspected when the results of the coagulation tests are abnormal for the first time within 30 minutes of delivery. The pathogenesis is believed to be due to the activation of inflammatory and coagulation cascades when the amniotic fluid gains access to the systemic circulation, leading to a

- Cricoid pressure to be applied in bag and mask ventilation, and intubation
- Hands to be placed higher on the sternum in chest compressions
- Endotracheal tube diameter to be 0.5–1 mm smaller than that in non-pregnant women
- Do not administer any medication by any IV access placed in the lower extremity
- Disconnect fetal and uterine monitors prior to defibrillation
- Method of delivery: Hysterotomy indicated after 24 weeks, and between 20–24 weeks if there is a likelihood of saving the mother by the procedure.
- Hysterotomy to be ideally done within 5 minutes.

Fig. 135.4: Modification in the guidelines for cardiopulmonary resuscitation in pregnant women

phenomenon that has been compared to anaphylaxis.[54] However, unlike anaphylaxis, initially there is pulmonary vasospasm followed by left heart failure, which eventually leads to the pulmonary edema and shock.

Management is supportive, starting with cardiopulmonary resuscitation[55] (Fig. 135.4) followed by stabilizing the patient's ventilation, circulation, and preventing the postpartum complications associated with coagulopathy, especially postpartum hemorrhage. If the fetus has not been delivered, emergency cesarean section should be considered.[52] Nearly three out of five mothers die, often within five days. Out of the survivors, nearly half of the mothers have permanent neurodeficit.[53,54]

A differential diagnosis of amniotic fluid embolism is air embolism, which presents after either delivery or invasive procedures. While the clinical features are similar, a mill-wheel murmur over the chest can alert the physician to this diagnosis. Management should be prompt, involving placing the patient in left lateral position and administering 100% oxygen to shrink the volume of air by driving the nitrogen out of it.[56] The physician should remain alert for pulmonary edema that may develop a few hours later, if the patient survives.

LIVER DYSFUNCTION IN PREGNANCY

Jaundice is the presenting feature in around one-fifth of obstetric ICU admissions, and hepatic dysfunction is seen in nearly 40% of critically ill obstetric patients.[4] Liver function tests need to be interpreted considering the changes associated with pregnancy—however, any elevation of aminotransferases and bilirubin during pregnancy is always pathological (Table 135.6).[57,58] The distinguishing features of the different causes of liver dysfunction are given in Table 135.5.[58-60] It is important to distinguish acute viral hepatitis from pregnancy-associated acute liver disease (PAALD), as the management of the former is often supportive. Generally, hypertension, acute-onset ascites, encephalopathy and oliguria, high serum creatinine and thrombocytopenia favor PAALD over viral hepatitis (which is associated with extremely high (>10X) transaminases).[61]

TABLE 135.6: Pregnancy and alterations in liver function tests

Parameter	*Changes in pregnancy*
Serum ALT, AST	Within normal range; can rise after delivery
Serum LDH	Within normal range
Alkaline phosphatase	Increases to 2-4X normal (bone and placental)
Serum GGT	Normal to low
Serum bilirubin	Normal to low
Serum bile acids	Increase by 200-300% of non-pregnant values
Prothrombin time, APTT	Within normal range
Serum fibrinogen	Increases by 50% from 2nd trimester of pregnancy
Serum albumin	Decreases by 10-60%
Serum uric acid	Decreases
Serum cholesterol	Increases often up to 2X
Serum alpha-fetoprotein	Increases

Adapted from [57] and [59]. ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, GGT: gamma glutamyltransferase, APTT: activated partial thromboplastin time

RENAL DYSFUNCTION IN PREGNANCY

Renal dysfunction is seen in 35 to 50% of critically ill obstetric patients.[4] Pregnancy-related acute kidney injury (PR-AKI), while ill-defined, contributes up to a fifth of all AKI cases.[62] While patients with chronic mild renal dysfunction (estimated GFR > 60 ml/min/1.73m^2) remain stable with minimal effect on either pregnancy or renal function, those with moderate-severe renal failure are prone to worsening of renal function and complications of pregnancy.[63] The hemodynamic changes in pregnancy affect renal function, and thus the normal values tend to change with the trimester.[63] In this context, a proteinuria of < 300 mg/24 hours is considered normal, as is a respiratory alkalosis (PCO_2 of up to 10 mm Hg below baseline) and a compensatory metabolic acidosis (HCO_3 = 18-20 mm Hg).[62] However, what are considered as upper normal values of BUN and creatinine in nonpregnant patients, are often pathological in pregnancy due to the physiological hemodilution. Generally, a serum creatinine of

> 0.8 mg/dL in these patients should alert the physician to the diagnosis of renal failure.[64]

The classification of renal failure into prerenal, renal and postrenal AKI and the initial workup is similar to nonpregnant patients. Apart from the usual causes, specific etiologies of PR-AKI can be grouped into hypertensive and thrombotic microangiopathies (preeclampsia/HELLP syndrome, acute fatty liver of pregnancy, amniotic fluid embolism, TTP/HUS, postpartum idiopathic AKI), infection (pyelonephritis, sepsis), volume depletion (obstetric hemorrhage, hyperemesis gravidarum) and obstruction (gravid uterus, stone).[62] The most common cause of AKI in pregnancy is preeclampsia; however, this is usually the case only along with another insult like hemorrhage, or HELLP.[64] The role of biopsy in PR-AKI is mainly to find an alternative diagnosis to preeclampsia, in order to avoid the delivery and iatrogenic prematurity, if unnecessary.[62] Hence, the physician should consider the gestational period and the risk of complications, such as perirenal hematoma and gross hematuria (which are higher than in nonpregnant patients) when deciding whether to biopsy.

Management is aimed at treating the underlying cause, preventing complications and supporting the renal function until recovery.[62] While the etiological factors are being corrected, accurate fluid management is essential to ensure adequate renal perfusion. Concurrent medications (e.g. magnesium sulfate) need to be renally dosed. While there is no role of dopamine currently in PR-AKI, judicious use of diuretics is restricted to the cases of volume overload, and that too only when utero-placental perfusion can be frequently assessed.[62] Furosemide and mannitol (Class B) are preferred over thiazides (Class C).[64] Management of complications, such as hyperkalemia, metabolic acidosis and anemia is similar; however, erythropoietin can worsen hypertension[65] and may also require higher dosing.[62] The indications for renal replacement therapy are similar to nonpregnant patients, and early-onset and continuous therapy is considered beneficial (though a randomized control trial is missing, and the exact threshold is undetermined). Increasing the number of dialysis hours per week (over the threshold intervention of 20 hours/week) in order to keep the predialysis threshold of BUN < 60–100 mg/dl is associated with an improvement in fetal birth weight and trends towards improved survival.[62] The physician should prevent sudden fluctuations in hemodynamic status, increase supplementation of vitamins and folate that are removed with dialysis and monitor for preterm labor.

Hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) can occur anytime during pregnancy or postpartum, and can mimic preeclampsia/HELLP syndrome with AKI.[62] Fever, purpura and neurological symptoms point the diagnosis towards TTP, as compared to HUS, which predominantly presents as hemolytic anemia and renal failure. vWF (von Willebrand Factor) multimers can help to differentiate the condition from preeclampsia, because coagulation studies are normal in both disorders. AKI occurs in two-thirds of these patients, and many of them have persistent renal insufficiency, hypertension and often long-term neurologic dysfunction. Fetal consequences include intrauterine growth retardation, fetal distress and death. Management is supportive along with plasmapheresis as the first-line of management, with steroids useful in only 25% of the cases. Unlike preeclampsia, delivery is not beneficial. This helps to differentiate the cause of AKI postpartum in those deteriorating patients who were initially labeled as "AKI secondary to pre-eclampsia".[66] When a patient with similar clinical features has no clear-cut diagnosis, he/she is labeled as "postpartum AKI." The pathogenesis of the condition is similar to other thrombotic microangiopathies, and the management is similar to that of HUS/TTP.[62]

INFECTION IN PREGNANCY

Up to 20% of all maternal deaths can be due to infection. Sepsis is the most common infectious cause of admission in a critically ill obstetric patient.[33] While common causes include pelvic, respiratory and urinary tract infections, patients in the developing countries face an additional threat from viral hepatitis, malaria, leptospirosis, dengue, military tuberculosis and tetanus.[33] A description of different infections specific to pregnancy is given in Table 135.7. Other infections, which are also seen in nonpregnant women, are covered in other chapters.[67-70]

A cesarean section is the most common risk factor for maternal sepsis.[67] The initial source of infection is often polymicrobial, but the predominant organism involved is *Escherichia coli*. The diagnosis and treatment in pregnancy is similar to nonpregnant patients, in line with the Surviving Sepsis guidelines, which have been covered in detail in previous chapters. However, there are certain salient features regarding the management of sepsis in pregnancy.

Diagnosis

- The initial presentation may be nonspecific, and a high index of suspicion is needed. Fever and

TABLE 135.7: Infectious complications in pregnancy

Disease	*Clinical Features*	*Management*	*Comments*
Chorioamnionitis (MC organisms: *E. coli*, Group B *Streptococcus)*	Fever > 100.4F, leukocytosis, tachycardia (maternal/fetal), uterine tenderness, foul vaginal discharge	• Diagnosis primarily clinical; do a sepsis screen • Induce delivery if patient not yet in labor • Start ampicillin 2 g IV q6h + Gentamicin 1.5 mg/kg IV q8h (check renal function) • Clindamycin (900 mg) at time of cord clamping/cesarean section • Acetaminophen for pyrexia	• Be aware of preterm/prolonged labor in all cases • Bacteremia in 5-10% • Fetus may develop neurologic damage despite antibiotic use
Endomyometritis (Organisms- anaerobes, streptococci, gonococci, Chlamydia, Mycoplasma, Gardnerella)	Often presents 24 hours after delivery with similar features as chorioamnionitis + subinvoluted, tender uterus and cervical motion tenderness with or without lochia	• Do endocervical + blood cultures with routine sepsis screen; while false positives may occur, definitely be alert for Group A streptococci • Assume polymicrobial infection (Clindamycin 900 mg IV q8h + gentamicin 5 mg/kg q24h) • Continue for 48h until patient afebrile and has negative blood cultures • If infection spreads to the parametrium and is uncontrolled, hysterectomy may be needed	• Risk factors: Operative interventions, PPH, retained POC, chorioamnionitis • Spiking fever despite antibiotics: consider pelvic abscess; persistent low grade fever: pelvic thrombophlebitis or noninfectious causes • Can spread locally and later generalize → septic shock
Septic abortion (polymicrobial)	Fever, lower abdominal pain and vaginal bleeding in any trimester	• Start empiric therapy [Penicillin 5 MU IV q6h + gentamicin 2 mg/kg IV loading dose (adjust appropriately) + clindamycin 900 mg IV q8h] • Do an upright abdominal X-ray to rule out perforation, foreign bodies and gas in tissues • Uterus may need evacuation – send contents for gram stain and culture • Crepitus ± perforation → surgical exploration	• Cresol, phenol used as abortifacients lead to faster multiorgan dysfunction • Watch out for Clostridial infection, especially those without immunization may suffer from tetanus
Septic thrombophlebitis	Persistent fever, and non-colicky, constant lower-abdominal and flank pain ± radiation; rope-like mass palpable on exam	• Diagnosis confirmed with CT or MRI • Treat with antibiotics • Add anticoagulation (heparin for 5-7 days) with target aPTT of 1.5-2.5 × normal • If thrombus extends into iliac veins or leads to pulmonary embolus β oral anticoagulation	• Common in those who have undergone cesarean section
Necrotizing fasciitis (polymicrobial; MC organisms - *S. aureus*, Group A streptococci	Initially asymptomatic. Swelling, erythema, discoloration, brown discharge. Pain out of proportion to physical findings	• Antimicrobial regimen described for septic abortion + urgent, wide surgical debridement	• Complicates both vaginal and cesarean deliveries- Can rapidly progress to septic shock • Without surgical intervention, mortality is extremely high

MC: most common, PPH: postpartum hemorrhage, POC: products of conception, aPTT: activated partial thromboplastin time. Other common infections in pregnancy are acute pyelonephritis, acute pneumonia, viral hepatitis and malaria. The management of these infections has been covered in detail in other chapters of this book.

leukocytosis or bands on a peripheral smear in a pregnant patient should prompt a search for infection. Incidentally, fever may be absent.
- The localization of infection, when not obvious, should start from genital tract. A thorough clinical examination, followed by ultrasound or MRI is useful.
- The septic screen should include specimens from the cervix, urine and placenta if possible, especially if the blood cultures are negative and the focus is unknown.
- A decrease in blood pressure in the left lateral position, an increase in capillary refill time, change in baseline variability in fetal heart rate and/or late decelerations on the electronic fetal monitor are all signs of impending severe sepsis.

Resuscitation

- The patient should be kept in the left/right lateral position during resuscitation.
- The observed mortality rate in pregnant septic patients is significantly lower as compared to their nonpregnant counterparts. Hence, prompt resuscitation of the mother can often stabilize both the mother and the fetus (which may be in distress). Operative interventions are considered as the last resort.[67]

Breathing

- Unresolving maternal or fetal hypoxia may require mechanical ventilation.
- If permissive hypercapnia is used, ensure that there is no fetal acidosis.

Circulation

The central venous pressure is a poor indicator of the fluid balance and cardiac function in pregnancy. Hence, a pulmonary artery catheter may be necessary in a subset of these patients who are at an increased risk of fluid overload.

Monitoring

- Pregnant patients are at an increased risk of multiorgan dysfunction. The distributive shock of sepsis superimposed on the lower vascular tone predisposes them to acute kidney injury. The increased permeability and lower oncotic pressure predisposes them to pulmonary edema. Their hypercoagulability predisposes them to DIC. Hence, they should be closely monitored.
- The mode of delivery depends on the maternal and fetal condition. If delivery is essential between 24 and 34 weeks of gestation, maternal corticosteroids should be given to promote fetal lung maturity.

Prognosis

The observed mortality in pregnant septic patients is approximately 3%. Fetal survival is good, in spite of severe sepsis in the mother.[67]

In summary, while the management of critically ill obstetric patients is a challenge, the intensivist can help to improve maternal and fetal survival through the following principles:
- Giving precedence to the well-being of the mother over that of the fetus.
- Correctly identifying the conditions that will improve with interventions, such as the induction of delivery and/or operative intervention (e.g. severe preeclampsia), as compared to those that can be managed supportively (e.g. acute viral hepatitis).
- Ensuring a multidisciplinary coordination right from the start between the intensivist, obstetrician, anesthesiologist, neonatologist and subspecialist (as required).

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Cardiac Emergencies in the Intensive Care Unit: Cardiac Arrhythmias

Mohamed S Rahman, M Eyman Mortada

INTRODUCTION

Patients in the intensive care unit (ICU) are prone to severe and dramatic swings in fluid and electrolyte balance, cardiac ischemia, hypoxia, catecholamine excess and exposure to cardiotoxic drugs. These situations are a crucible for cardiac arrhythmias. In the current era, sustained arrhythmia in the general ICU is around 8% for supraventricular and ventricular arrhythmias; and 2% for conduction abnormalities.[1] The presence of arrhythmias in the ICU is associated with increased mortality.[2]

Although the most common arrhythmias in ICU patients are supraventricular tachycardias, the ominous specter of ventricular arrhythmia is justifiably the most alarming. From a management perspective, arrhythmias in the ICU can be classified as bradyarrhythmias (heart rate <60), tachyarrhythmias (heart rate >100) and ectopic beats.

PREMATURE VENTRICULAR COMPLEXES (PVCS) (FIG. 136.1)

Premature ectopic QRS complexes arising from the ventricular myocardium – are usually the result of hyper-catecholaminergic states and are relatively benign. They are usually asymptomatic, but occasionally can cause palpitations or neck/chest discomfort. Isolated PVCs do not merit further workup or intervention. However, "multifocal" or polymorphic PVCs, couplets, bigeminy, trigeminy and quadrigeminy may produce more dramatic symptoms. If hemodynamically unstable PVCs persist after the correction of electrolytes and treatment of ischemia, the drug of choice for suppression is intravenous (IV) lidocaine, however, if it fails, intravenous procainamide can be used acutely. Amiodarone and Class Ic drugs are useful for long-term oral maintenance. However, Class Ic drugs (flecainide and moricizine) should not be used after myocardial infarction increase the mortality rate.[3]

ACCELERATED IDIOVENTRICULAR RHYTHM

Accelerated idioventricular rhythm (AIVR) (Fig. 136.2) is usually transient and due to the acceleration of ventricular ectopic focus (automaticity). Accelerated idioventricular rhythms is often seen in the setting of myocardial revascularization, postresuscitation, and occasionally, with digitalis toxicity. This is a benign rhythm and should not be suppressed, as the AIVR is often a back-up rhythm. However, if AIVR is too rapid and producing symptoms or hemodynamic instability, or if it degenerates into ventricular tachycardia (VT) or ventricular fibrillation (VF), it may deserve treatment. Accelerating the sinus rhythm with atropine or pacing may be adequate to suppress the AIVR.

Accelerated idioventricular rhythm needs to be differentiated from sinus rhythm with widening of QRS due to electrolyte imbalance. In hyperkalemia (Figs 136.3A and B), initially peaked tall T waves occur, followed by progressive slowing in conduction through the myocardium with prolongation of the PR interval and the widening of QRS duration. Ultimately, the QRS widens into a "sine wave" and, lastly, a flat line. In hypokalemia, ST depression and decreased amplitude of T wave, as well

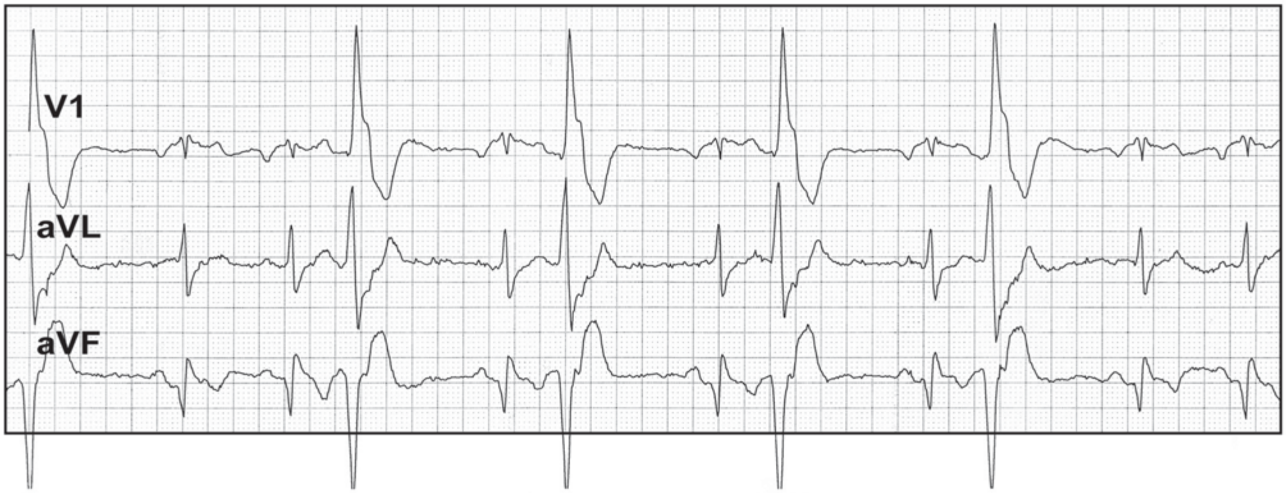


Fig. 136.1: Premature ventricular complexes (PVCs). PVCs occur initially after every two sinus beats (trigeminy), followed by bigeminy. Note the alternating sinus beats and wide (>120 ms) bizarre QRS complexes, which are followed by a compensatory pause. This patient has severe cardiomyopathy and a history of ventricular tachycardia

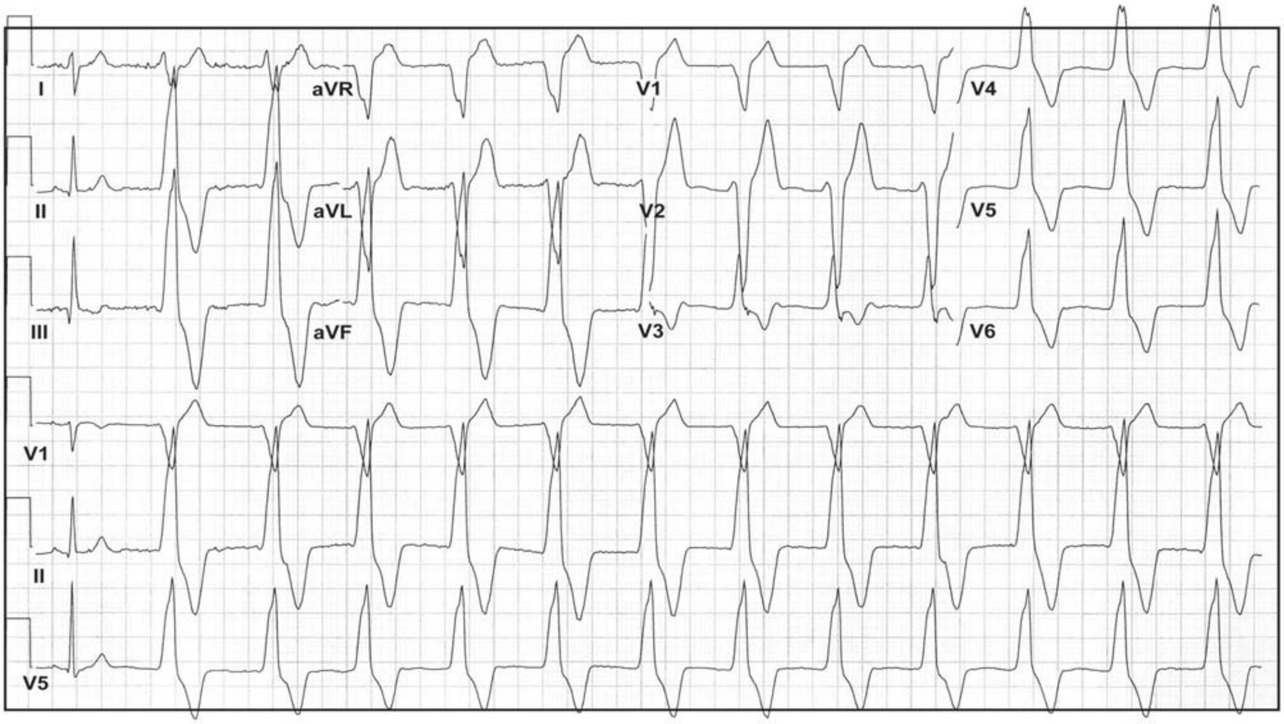
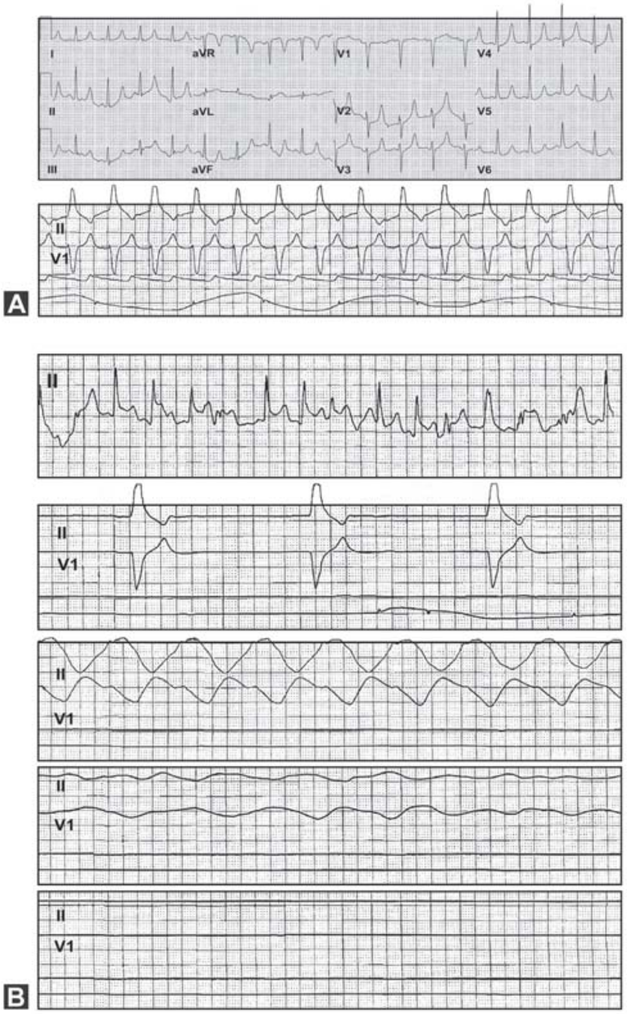


Fig. 136.2: Accelerated idioventricular rhythm (AIVR). 12-lead electrocardiogram (ECG) of AIVR, which is a wide QRS complex ventricular rhythm at a rate of 60-100 bpm. In this ECG, it is associated with atrioventricular (AV) dissociation



Figs 136.3A and B: Hyperkalemia. Panel A: 12-lead ECG with peaked T waves characteristic of hyperkalemia. Panel B: In the same patient, note the progression of changes on ECG with peaked T waves, followed by prolongation of PR interval and widening of the QRS complexes and ST-T changes resembling acute myocardial infarction, further degeneration to sine wave, and ending in asystole during profound hyperkalemia and severe acidosis due to acute renal failure. Acute hyperkalemia should be addressed by emergent hemodialysis

as U wave in V4-6, may progress to wider QRS and markedly depressed ST with T-wave inversion.

WIDE COMPLEX TACHYCARDIA

A wide complex (QRS >120 ms) tachycardia (WCT) (heart rate >100 beats/min) can be broadly classified as polymorphic when the QRS complex appearance varies from beat to beat and monomorphic when the beat-to-beat QRS complex appearance is identical (Table 136.1). It is crucial to exclude artifact.

Artifact

When examining the rhythm strip, it is essential to evaluate all available leads. Artifact (Figs 136.4A and B) might be present in some leads and not others; hence, the presence of normal rhythm in one lead will exclude WCT. If not, careful review of noisy artifact can reveal regular notches at the same rate as the preceding or continuous rhythm of the patient. Other clues may include an arterial pulse wave tracing that corresponds to the underlying rhythm.

Polymorphic WCT

Polymorphic WCT is almost always ventricular in origin when artifact is excluded — polymorphic ventricular tachycardia (PMVT). Torsades de pointes (TdP) is PMVT due to prolonged QT (Figs 136.5A and B). Atrial fibrillation (AF) in the presence of an accessory pathway may mimic PMVT (Fig. 136.6).

There are five major causes of PMVT:

1. The most important cause in the ICU is myocardial ischemia/infarction (MI);
2. Electrolyte abnormalities (e.g. hypokalemia, hypomagnesemia);
3. Profound bradycardia due to sick sinus node, atrioventricular (AV) nodal block or from medications, such as digoxin, calcium channel blockers or beta blockers;
4. Prolonged QT interval due to medication,[4] electrolyte abnormalities or channelopathies (e.g. long QT syndrome);
5. Idiopathic PMVT.

It is prudent to take steps to avoid TdP/PMVT in the ICU, and recommendations to achieve this are outlined in Table 136.2.

Polymorphic ventricular tachycardia is a rapid, hemodynamically unstable rhythm, which needs electrical cardioversion when persistent. Additional measures include withdrawal of any offending medications, IV magnesium (even when serum magnesium level is "normal"), urgent angiography and angioplasty if myocardial ischemia is suspected or cannot be excluded, temporary pacing or medications to alleviate bradycardia and correction of electrolyte abnormalities. For acute suppression of PMVT, IV lidocaine and oral mexilitine can be used, especially in patients with myocardial ischemia or long QT interval.[6]

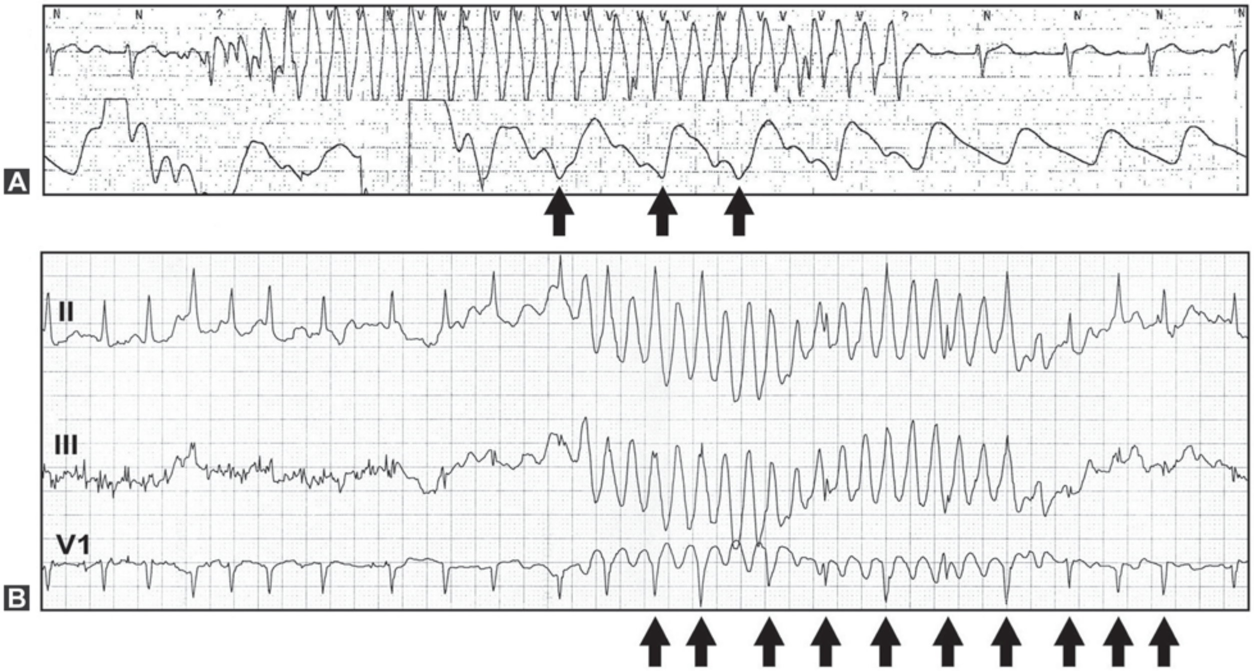
It is crucial to recognize the presence of an accessory pathway (AP) with atrial fibrillation, which produces WCT with irregularity of the QRS morphology and intervals. In this scenario, AV-nodal blocker agents are contraindicated. If they are given, the conduction over

TABLE 136.1: Classification and definition of different ventricular arrhythmias by clinical presentation, ECG features and underlying disease conditions

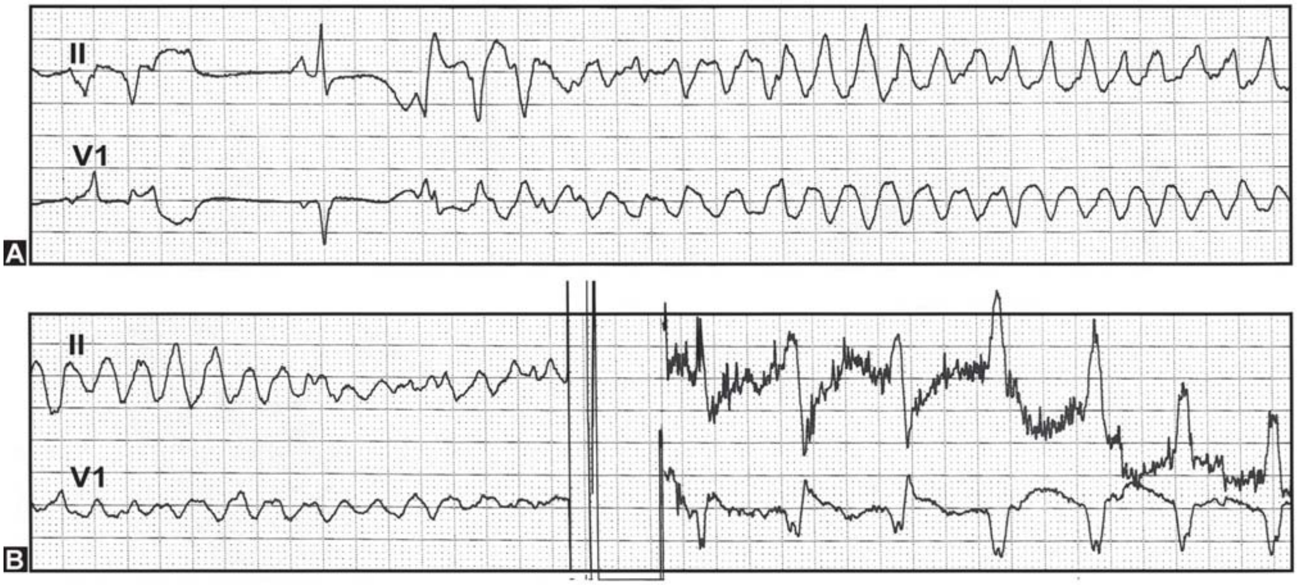
Classification by Clinical Presentation		
Hemodynamically stable	Asymptomatic	The absence of symptoms that could result from an arrhythmia.
	Minimal symptoms	Patient reports palpitations felt in either the chest, throat or neck as described by the following: • Heartbeat sensations that feel like pounding or racing • An unpleasant awareness of heartbeat • Feeling skipped beats or a pause
Hemodynamically unstable	Presyncope	Patient reports presyncope as described by the following: • Dizziness • Lightheadedness • Feeling faint • Graying out
	Syncope	Sudden loss of consciousness with the loss of postural tone, not related to anesthesia, with spontaneous recovery as reported by the patient or observer. Patient may experience syncope when supine.
	Sudden cardiac death	Death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within an hour of the onset of symptoms.
	Sudden cardiac arrest	Death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within an hour of the onset of symptoms in whom medical intervention (e.g. defibrillation) reverses the event.
Classification by Electrocardiography		
Non-sustained VT		Three or more beats in duration, terminating spontaneously in less than 30 seconds. VT is a cardiac arrhythmia of three or more consecutive complexes in duration emanating from the ventricles at a rate greater than 100 bpm (cycle length less than 600 ms).
	Monomorphic	Nonsustained VT with a single QRS morphology.
	Polymorphic	Nonsustained VT with a changing QRS morphology at cycle length between 600 and 180 ms.
Sustained VT		VT greater than 30 s in duration and/or requiring termination due to hemodynamic compromise in less than 30 seconds.
	Monomorphic	Sustained VT with a stable single QRS morphology.
	Polymorphic	Sustained VT with a changing or multiform QRS morphology at cycle length between 600 and 180 ms.
Bundle branch re-entrant		VT due to reentry involving the His-Purkinje system, usually with LBBB morphology, this usually occurs in the setting of cardiomyopathy.
Bidirectional VT		VT with a beat-to-beat alternans in the QRS frontal plane axis, often associated with digitalis toxicity.
Torsades de Pointes		Characterized by VT associated with a long QT or QTc and electrocardiography characterized by twisting of the peaks of the QRS complexes around the isoelectric line during the arrhythmia: • "Typical", initiated following "short-long-shot" coupling intervals • Short coupled variant initiated by normal-short coupling
Ventricular flutter		A regular (cycle variability 30 ms or less) ventricular arrhythmia approximately 300 bpm (cycle length 200 ms) with a monomorphic appearance; no isoelectric interval between successive QRS complexes.
Ventricular fibrillation		Rapid, usually more than 300 bpm/200 ms (cycle length 180 ms or less), grossly irregular ventricular rhythm with marked variability in QRS cycle length, morphology and amplitude.
Classification by Disease Entity		
Chronic coronary heart disease		
Heart failure		
Congenital heart disease		
Neurological disorders		
Structurally normal hearts		
Sudden infant death syndrome		
Cardiomyopathies		
Dilated cardiomyopathy		
Hypertrophic cardiomyopathy		
Arrhythmogenic right ventricular cardiomyopathy		

Abbreviations: LBBB = left bundle branch block; VT = ventricular tachycardia.

(From Zipes et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol. 2006; 48:e247-e346. Reproduced with permission from Elsevier)



Figs 136.4A and B: Artifact. It can be difficult to differentiate artifact from real arrhythmia. Clues include regular pulse wave curves on arterial line tracing during the "tachycardia," as in Panel A. Panel B: Artifact is often noted in one lead while other leads may reveal the underlying rhythm. In the third lead, note the irregular but clear QRS complexes shown by the arrows and corresponding sharp notches in the bizarre artifactual tracings resembling ventricular tachycardia in the upper two leads



Figs 136.5A and B: Torsades de pointes (TdP). Panel A: An ECG tracing of TdP with prolonged QT interval. Notice typical beat-to-beat change in QRS configuration and axis where there is a gradual transition of QRS complex from negative to positive complex relative to baseline. Panel B: Following direct current shock, spontaneous rhythm is restored

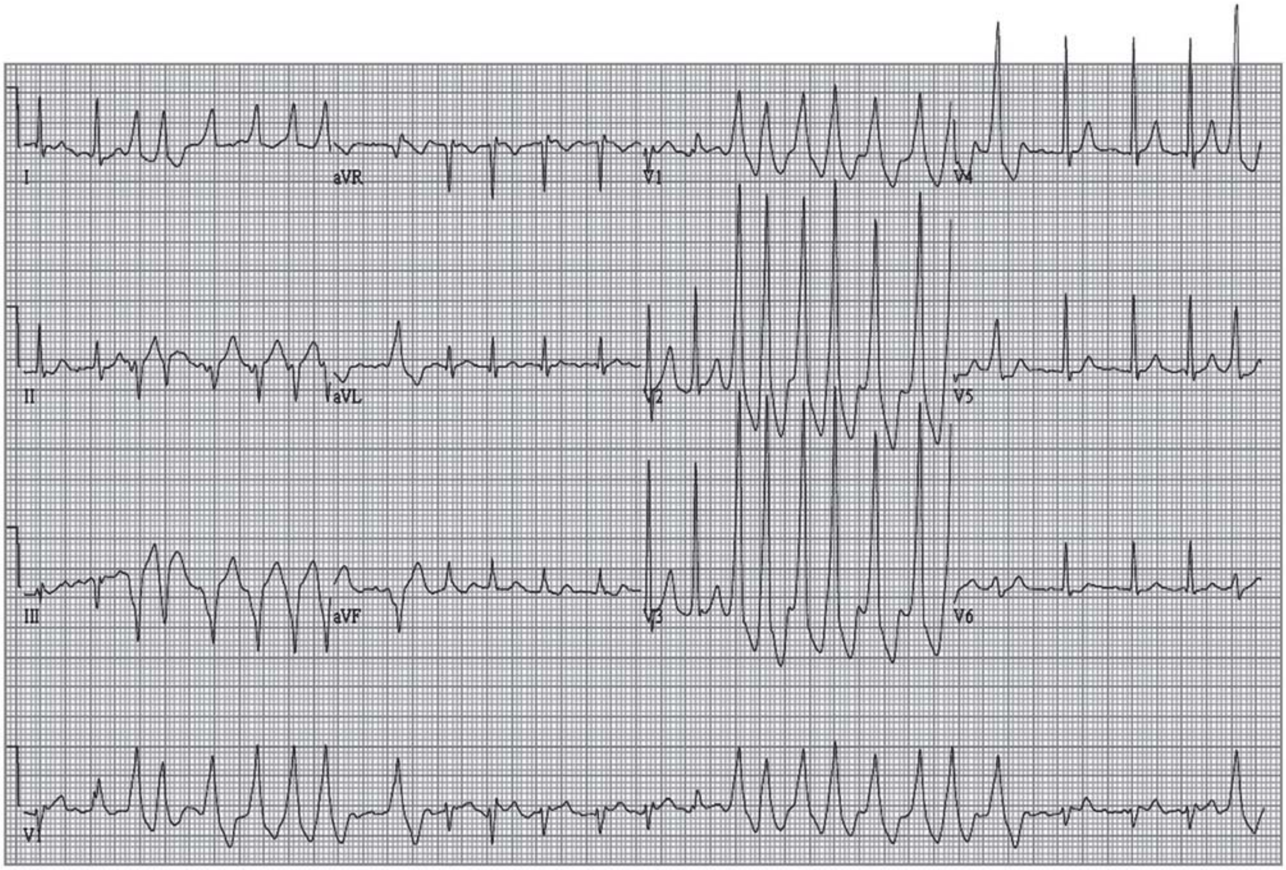


Fig. 136.6: Atrial fibrillation with Wolff-Parkinson-White syndrome. Irregularly irregular wide complex tachycardia. Impulses from the atria are conducted to the ventricles via either the atrioventricular (AV) node and accessory pathway, producing a broad fusion complex, or just the AV node, producing a narrow complex (without a delta wave), or just the accessory pathway, producing a very broad "pure" delta wave. People who develop this rhythm and have very short R-R intervals are at higher risk for ventricular fibrillation.

the AP will be accelerated and ventricular fibrillation may be provoked. The drugs of choice are procainamide or amiodarone (suppressing AV node and AP).

Monomorphic WCT

Monomorphic WCT can be due to VT, pre-excited tachycardia [antidromic atrioventricular re-entry tachycardia (AVRT) or supraventricular tachycardia (SVT) with bystander AP], SVT with aberrant conduction, SVT with preexisting bundle branch block and, rarely, pacemaker-mediated tachycardia (PMT) in which the pacemaker tracks either a sensed atrial tachyarrhythmia or a retrograde atrial activity in an endless loop. Pacemaker-mediated tachycardia is recognized by observing the pacing spike at the initiation of the QRS and by interrogating the pacemaker and can be abolished by special reprogram maneuvers.

It is essential to differentiate VT, which is a dangerous arrhythmia, from SVT in WCT. Patients with structural heart disease have more than a 95% chance of having VT, especially those with prior myocardial infarction (98%). Electrocardiogram (ECG) features, suggestive of VT as a cause for a WCT, include:

- Atrioventricular dissociation;
- QRS > 140 ms with right bundle branch block or >160 ms with left bundle branch block;
- Positive QRS concordance;
- Extreme left-axis deviation (-90° to 180°) "north-west axis"
- Left bundle right-axis configuration [right ventricular outflow tract (RVOT) VT];
- Different QRS during tachycardia than baseline.[6]

Sustained Monomorphic Ventricular Tachycardia

Among adults with in-hospital cardiac arrest, survival was worse when ventricular arrhythmia was the first documented rhythm (Figs 136.7A and B), compared to when asystole or pulseless electrical activity (PEA) was

TABLE 136.2: Approach to ventricular tachycardias in the adult ICU patient*

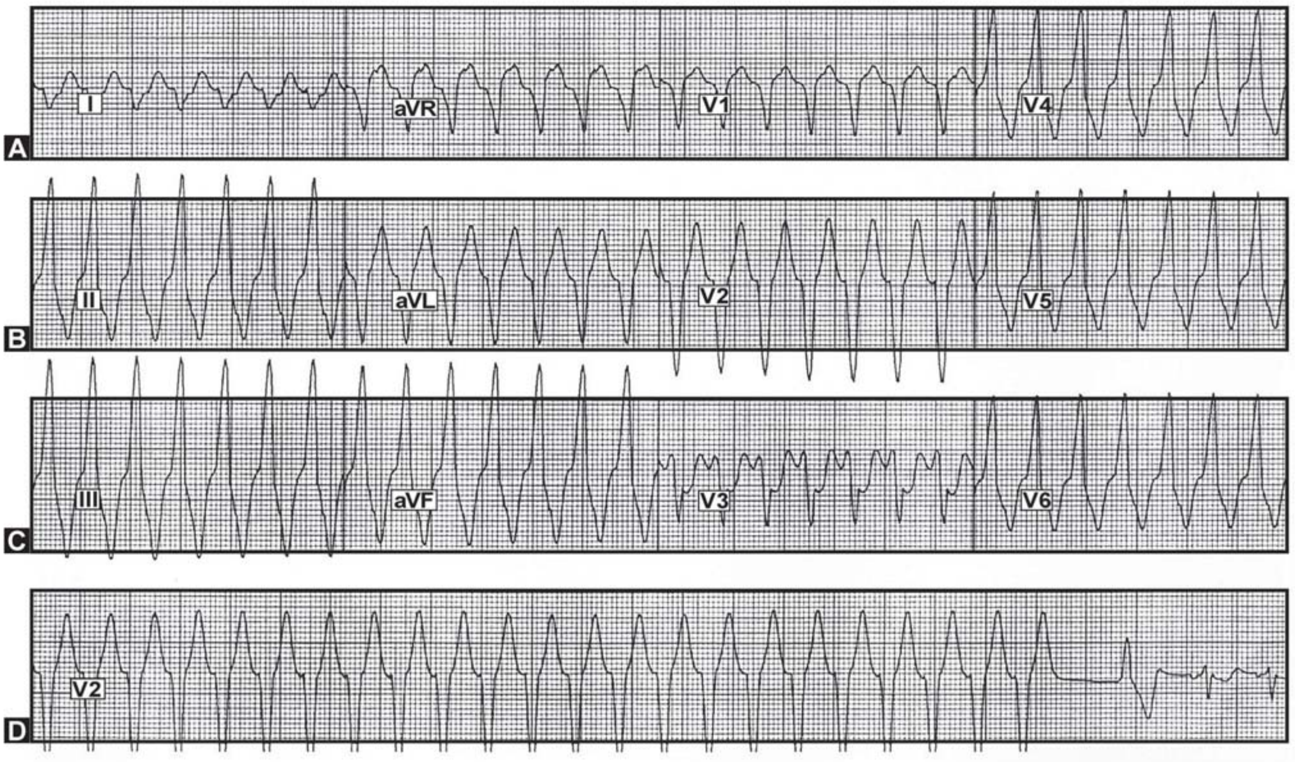
Condition	*Treatment*	
No pulse – pulseless ventricular tachycardia	Synchronized cardioversion	
Unstable ventricular tachycardia	Synchronized cardioversion	
Stable ventricular tachycardia	Assess QRS complex morphology	
Stable Monomorphic VT		
Normal cardiac function	**Medications: First line** Procainamide (min 20-30 mg to max total 17 mg/kg) Sotalol **Medications: Second line** Amiodarone (150 mg IV bolus over 10 min) Lidocaine (0.5-0.75 mg/kg IV push) **Synchronized cardioversion**	
Reduced LVEF	**Medications** Amiodarone (150 mg IV bolus over 10 min) Lidocaine (0.5-0.75 mg/kg IV push) **Synchronized cardioversion** **EP Study** **ICD**	
Stable Polymorphic VT		
Normal baseline QT interval	**Correct electrolytes** **Rule out myocardial ischemia** **Correct profound bradycardia** **Medications** Beta blocker Lidocaine (0.5-0.75 mg/kg IV push) Procainamide (20-30 mg/min to max total 17 mg/kg) Amiodarone (150 mg IV bolus over 10 min) Sotalol	
Synchronized cardioversion		
Prolonged baseline QT interval (torsades de pointes)	Acquired QT prolongation	**Stop offending agent** **Correct electrolyte disturbance** Potassium repletion to 4.5-5 mmol/L **Medications** Magnesium sulfate **Cardiac pacing**
	Congenital QT prolongation	**Beta blockers** **Pacing** **ICD**

*The first priority is hemodynamic stability. Stable VT can be addressed based on QRS morphology as outlined.

Abbreviations: EP = Electrophysiology; ICD = Implantable cardioverter defibrillator; ICU = Intensive care unit; IV = Intravenous; LVEF = Left ventricular ejection fraction; VT = Ventricular tachycardia.

the first documented rhythm.[7,8] Survival after in-hospital cardiac arrest is almost exclusively dependent on the speed of defibrillation with an approximately 10% decrease in survival for every 1-minute delay in defibrillation.[9] Regardless of cause, the treatment of unstable WCT is immediate and effective electrical cardioversion.

In hemodynamically stable sustained monomorphic ventricular tachycardia (MMVT), antiarrhythmic medications can be used for cardioversion as outlined in Table 136.2. Further, an electrophysiology consultation for possible implantable cardioverter defibrillator (ICD) placement or an electrophysiology study (EPS) with ablation [e.g. idiopathic left VT, RVOT VT (left bundle +



Figs 136.7A to D: Monomorphic ventricular tachycardia (MMVT). 12-lead electrocardiogram of MMVT. QRS complex is wide (200 ms), with right axis (+120°) and marked slurring of 'S' wave on V2 and V3. This rhythm lasted more than 30 seconds with consecutive ventricular beats at a heart rate of more than 100 bpm. At the end of the tracing, note a fusion complex followed by sinus beats

right axis)], and bundle branch reentry VT should be considered.

Nonsustained VT

Nonsustained VT (NSVT) (Figs 136.8A and B) is a marker for increased risk of sudden cardiac arrest (SCA) in patients with prior MI and reduced left ventricular ejection fraction (LVEF).[10,11] Implantable cardioverter defibrillator (ICD) is indicated in patients with NSVT, LVEF < 40%, and inducible VT on EPS (mortality reduces from 50 to 24% over 5 years).[12,13]

However, patients with preserved LVEF (>55%) do not represent increased risk of SCA. Correcting electrolyte abnormalities and ruling out cardiac ischemia is sufficient. Beta blocker therapy is reasonable in symptomatic NSVT. There is no need to use antiarrhythmics, which may conversely increase mortality.[3,14]

Ventricular Fibrillation and SCA

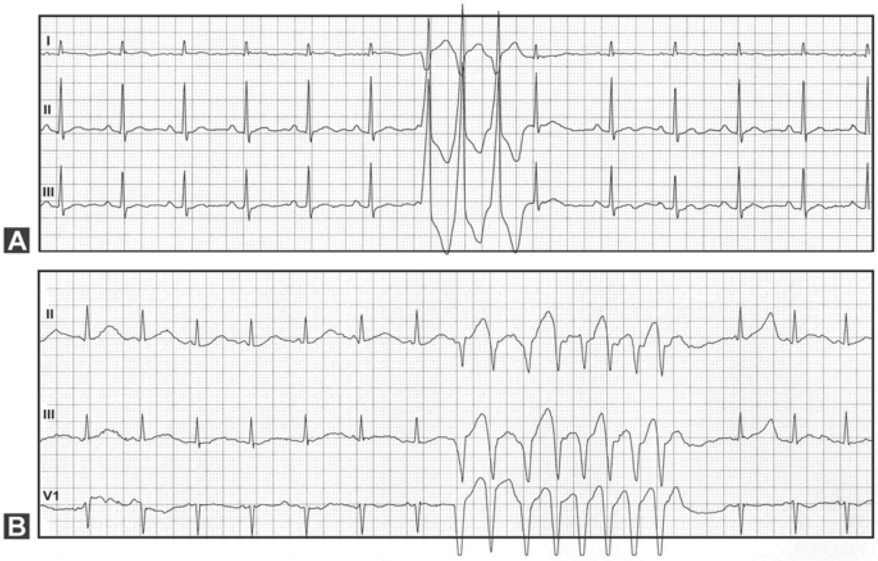
Ventricular fibrillation is a rapid, disorganized ventricular depolarization accompanied by loss of pumping action of the heart (Figs 136.9A to C). VT, both monomorphic and polymorphic, can degenerate into VF.

Acute management of sudden cardiac arrest is outlined in the advanced cardiac life support guidelines (Fig. 136.10). Postresuscitation deaths are highest in the first 24 hours; therefore, postresuscitation care, with IV antiarrhythmics and work-up for possible etiologies, is critical.[15,16] Reperfusion injury is associated with damaging biochemical reactions, which are suppressed by mild therapeutic hypothermia (MTH). Thus, the International Liaison of Committee on Resuscitation (ILCOR) recommends all unconscious VF adult patients with return of circulation after SCA should be cooled to 32 to 34° C for 12 to 24 hours.[16,17]

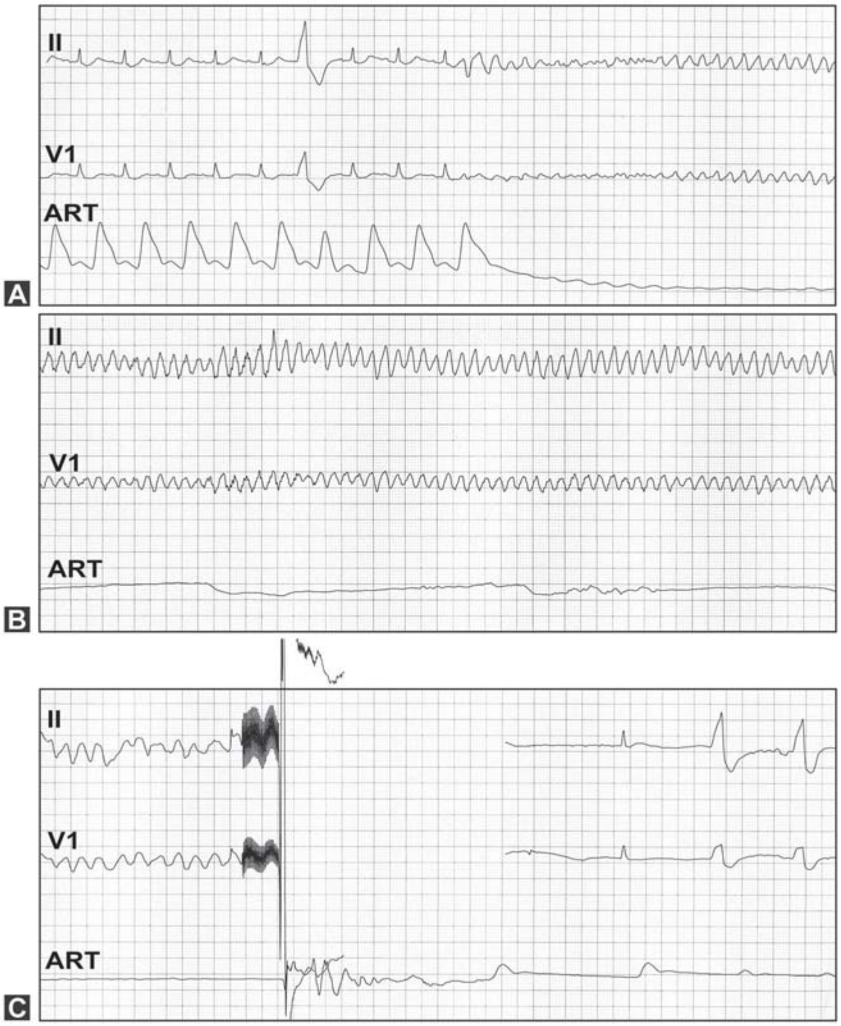
SUPRAVENTRICULAR TACHYCARDIA

Supraventricular tachycardia (>100 beats per minute) typically conducts to all Purkinje fibers at the same time, inscribing a narrow QRS. However, it can present with a WCT as described earlier.

Supraventricular tachycardias are the most frequently encountered cardiac rhythm disturbances.[18,19] While SVT



Figs 136.8A and B: Nonsustained ventricular tachycardia (NSVT). Panel A: An electrocardiogram ECG of NSVT. It is defined as three or more consecutive ventricular beats with spontaneous termination in less than 30 seconds at a heart rate of more than 100 bpm. Note in Panel B the initial few beats demonstrate slight irregularity, but quickly settle into a regular rhythm



Figs 136.9A to C: Ventricular fibrillation (VF). Panel A: Electrocardiogram of VF. Note the abrupt onset of irregularly irregular wide complex tachycardia with fibrillatory waves. Panel B: The arterial line pulse wave tracing shows the fall in blood pressure and absence of pulse wave. Panel C: Also shown is the defibrillation, followed by resumption of QRS complexes and return of arterial pulse waveform

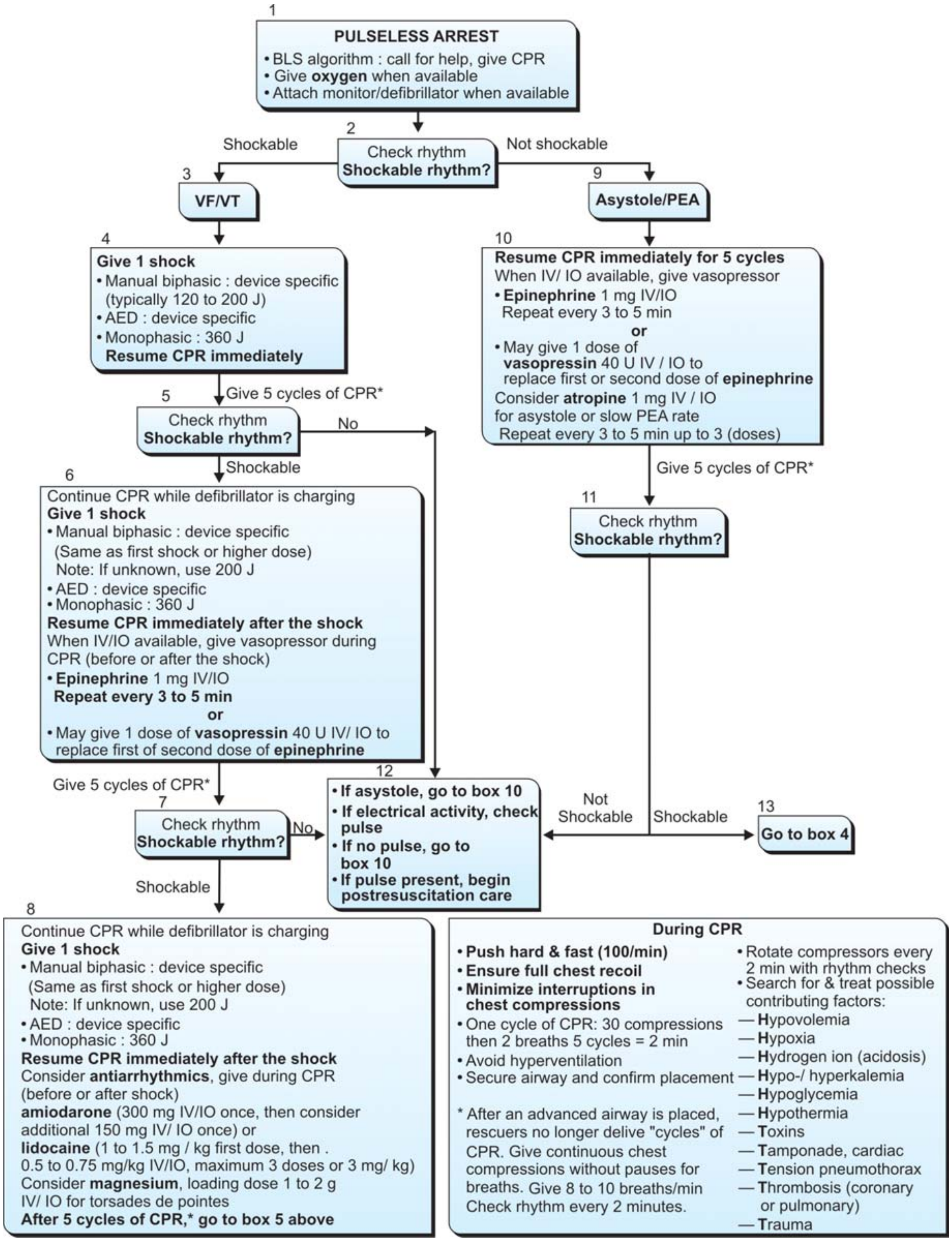

1
PULSELESS ARREST
• BLS algorithm : call for help, give CPR
• Give oxygen when available
• Attach monitor/defibrillator when available
2
Check rhythm
Shockable rhythm?
Shockable
Not shockable
3
VF/VT
9
Asystole/PEA
4
Give 1 shock
• Manual biphasic : device specific (typically 120 to 200 J)
• AED : device specific
• Monophasic : 360 J
Resume CPR immediately
Give 5 cycles of CPR*
5
Check rhythm
Shockable rhythm?
No
Shockable
6
Continue CPR while defibrillator is charging
Give 1 shock
• Manual biphasic : device specific (Same as first shock or higher dose) Note: If unknown, use 200 J
• AED : device specific
• Monophasic : 360 J
Resume CPR immediately after the shock
When IV/IO available, give vasopressor during CPR (before or after the shock)
• Epinephrine 1 mg IV/IO Repeat every 3 to 5 min
or
• May give 1 dose of vasopressin 40 U IV/ IO to replace first of second dose of epinephrine
Give 5 cycles of CPR*
7
Check rhythm
Shockable rhythm?
No
Shockable
8
Continue CPR while defibrillator is charging
Give 1 shock
• Manual biphasic : device specific (Same as first shock or higher dose) Note: If unknown, use 200 J
• AED : device specific
• Monophasic : 360 J
Resume CPR immediately after the shock
Consider antiarrhythmics, give during CPR (before or after shock)
amiodarone (300 mg IV/IO once, then consider additional 150 mg IV/ IO once) or
lidocaine (1 to 1.5 mg / kg first dose, then . 0.5 to 0.75 mg/kg IV/IO, maximum 3 doses or 3 mg/ kg)
Consider magnesium, loading dose 1 to 2 g IV/ IO for torsades de pointes
After 5 cycles of CPR,* go to box 5 above
10
Resume CPR immediately for 5 cycles
When IV/ IO available, give vasopressor
• Epinephrine 1 mg IV/IO Repeat every 3 to 5 min
or
• May give 1 dose of vasopressin 40 U IV / IO to replace first or second dose of epinephrine
Consider atropine 1 mg IV / IO for asystole or slow PEA rate Repeat every 3 to 5 min up to 3 (doses)
Give 5 cycles of CPR*
11
Check rhythm
Shockable rhythm?
Not Shockable
Shockable
12
• If asystole, go to box 10
• If electrical activity, check pulse
• If no pulse, go to box 10
• If pulse present, begin postresuscitation care
13
Go to box 4
During CPR
• Push hard & fast (100/min)
• Ensure full chest recoil
• Minimize interruptions in chest compressions
• One cycle of CPR: 30 compressions then 2 breaths 5 cycles = 2 min
• Avoid hyperventilation
• Secure airway and confirm placement
* After an advanced airway is placed, rescuers no longer delive "cycles" of CPR. Give continuous chest compressions without pauses for breaths. Give 8 to 10 breaths/min Check rhythm every 2 minutes.
• Rotate compressors every 2 min with rhythm checks
• Search for & treat possible contributing factors:
— Hypovolemia
— Hypoxia
— Hydrogen ion (acidosis)
— Hypo-/ hyperkalemia
— Hypoglycemia
— Hypothermia
— Toxins
— Tamponade, cardiac
— Tension pneumothorax
— Thrombosis (coronary or pulmonary)
— Trauma

Fig. 136.10: Advanced cardiac life support (ACLS) algorithm for approach and management of pulseless ventricular tachycardia or ventricular fibrillation. AED = Automated external defibrillator; BSL = Basic life support; CPR = Cardiopulmonary resuscitation; IV/IO = Intravenous/intraosseous infusion; PEA = Pulseless electrical activity; VF/VT = Ventricular fibrillation/ventricular tachycardia (From Part 7.2: Management of Cardiac Arrest. Circulation. 2005;112;IV-58-IV-66. Reproduced with permission from American Heart Association.)

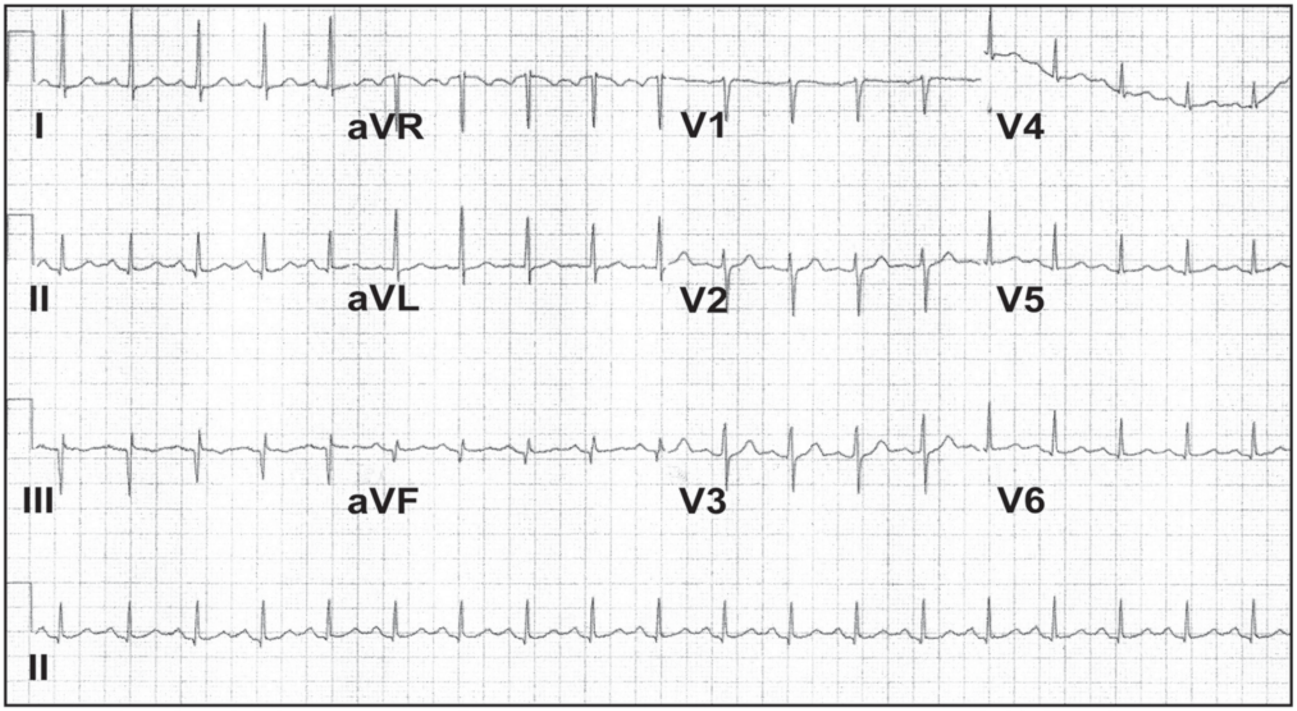


Fig. 136.11: Sinus tachycardia (ST). 12-lead electrocardiogram of ST with regular narrow QRS complexes and a 'P' wave preceding each QRS complex with rate greater than 100 bpm. The 'P' wave has the same morphology of the sinus 'P' (upright "+" in leads II, III and aVF, and converted "-" in lead aVR), and the 'PR' interval is constant

can be spontaneous, triggers include hypoxemia, hypovolemia, hyperthermia, hyperkalemia or hypokalemia, cardiac tamponade, tension pneumothorax, toxins, medications and drugs (caffeine, tobacco, alcohol, pseudoephedrine), pulmonary thromboembolism and, finally, the ubiquitous pain or stress. Supraventricular tachycardia includes the following:

Sinus Tachycardia

Sinus tachycardia (ST) is the most common SVT in the ICU. The rates are typically 100 to 160 bpm (lower than the usual paroxysmal supraventricular tachycardia rate) (Fig. 136.11). Sinus tachycardia is usually physiological (e.g. pain, fever, hypotension, hypoxia, drug-induced). Hence, management is alleviation of the cause. Rarely, ST needs to be slowed down by medication (e.g. beta blocker, calcium channel blocker or digoxin), such as in myocardial ischemia.

Atrial Fibrillation

After sinus tachycardia, the most common arrhythmia in the ICU is atrial fibrillation (AF) (Figs 136.12A and B), which is especially common after cardiac and thoracic surgery. It is usually associated with an irregular ventricular response, except in complete heart block, an accelerated junctional or idioventricular rhythm, or a ventricular-paced rhythm with AV block.

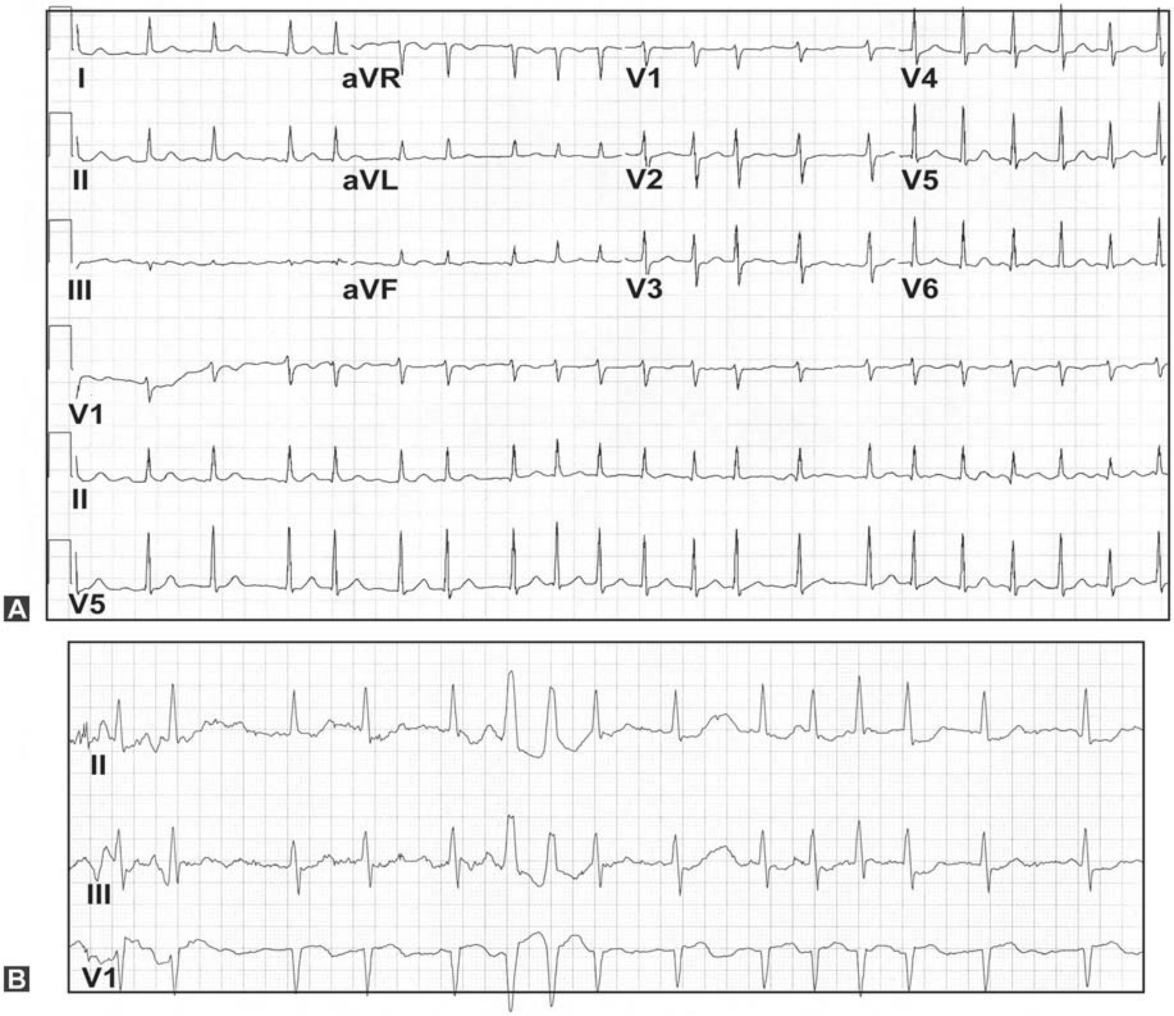
Symptoms in patients with atrial fibrillation range from minimal or no symptoms to palpitations, dizziness, syncope, chest discomfort or angina, worsening heart failure or even acute pulmonary edema. Management of atrial fibrillation in the ICU includes thromboembolic prevention and rhythm management.

Thromboembolic Prevention

Patients with AF have increased risk of thromboembolic events; therefore, anticoagulation is warranted, especially in the presence of:

1. Valvular disease (e.g. mitral stenosis or prosthetic heart valve).
2. Prior thromboembolism or persistent atrial thrombus.
3. Thyrotoxicosis.
4. High-risk patients with CHADS2 score $\geq$ 2 (cardiomyopathy = 1, hypertension = 1, age $\leq$ 75 years old = 1, age 65-74 = 0.5, diabetes mellitus = 1, stroke = 2, coronary artery disease = 0.5, female = 0.5).
5. Planned direct cardioversion and continue for at least 4 to 6 weeks post conversion.

Anticoagulation therapy with intravenous unfractionated or subcutaneous low-molecular weight heparin



Figs 136.12A and B: Atrial fibrillation (AF). Panel A: Electrocardiogram (ECG) of AF with irregularly irregular narrow complex tachycardia with an undulating baseline with fibrillatory ‘P’ waves that vary in size, shape and timing called ‘f’ waves. Panel B: ECG of AF with short-long sequence preceding an aberrantly conducted beat (Ashman phenomenon)

therapy should be initiated along with warfarin until international normalized ratio (INR) is therapeutic. Target INR level is 2.0 to 3.0 (2.5-3.5 in valvular disease or presence of thrombus).

Antiplatelet therapy should be used in patients at low risk for thromboembolic events (CHADS score $\leq$1) or if anticoagulation is contraindicated (e.g. bleeding or post surgery).

Rhythm Management (Fig. 136.13)

Rate-control medication doses and comments are demonstrated in Table 136.3. Rhythm control algorithm and medication doses and comments are illustrated in Figure 136.14 and Table 136.4. It is important to recognize digoxin toxicity-induced arrhythmia (0.8-4% in the U.S.). Life-threatening arrhythmias due to delayed afterdepolarization or bradycardias due to excessive vagal tone usually occur at levels > 2.0 ng/mL. The classic arrhythmias include bidirectional ventricular tachycardia, AV junctional rhythms and atrial tachycardia (faster than AFL with isoelectric baseline between the ‘P’ waves) with AV block. Treatment consists of discontinuing digoxin, atropine for bradycardia and potassium replacement. Digoxin-specific Fab fragments (Digibind) is recommended in patients with life-threatening arrhythmias, unstable severe bradycardia, plasma potassium > 5 mEq/L, plasma

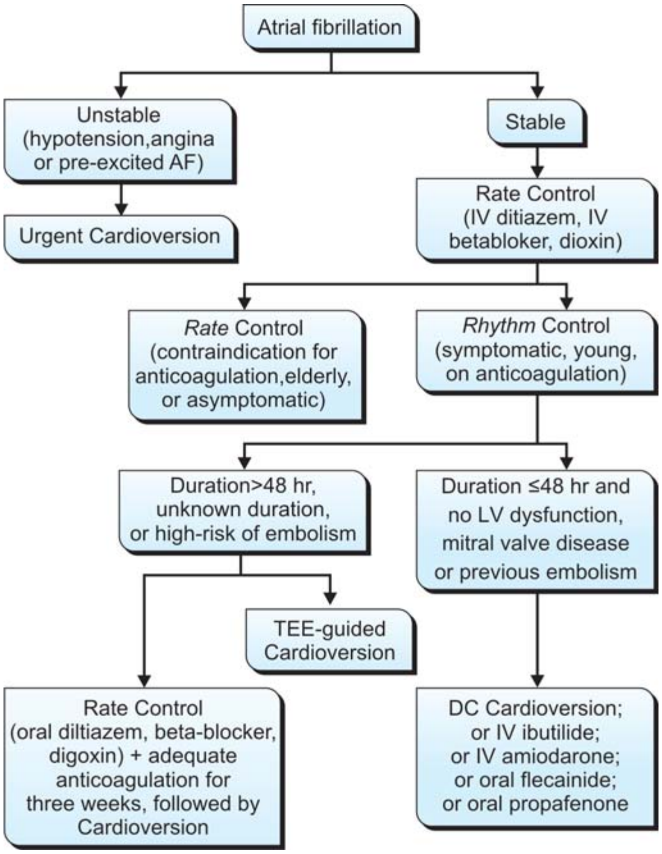

Atrial fibrillation
Unstable (hypotension,angina or pre-excited AF)
Stable
Urgent Cardioversion
Rate Control (IV ditiazem, IV betabloker, dioxin)
Rate Control (contraindication for anticoagulation,elderly, or asymptomatic)
Rhythm Control (symptomatic, young, on anticoagulation)
Duration>48 hr, unknown duration, or high-risk of embolism
Duration ≤48 hr and no LV dysfunction, mitral valve disease or previous embolism
TEE-guided Cardioversion
Rate Control (oral diltiazem, beta-blocker, digoxin) + adequate anticoagulation for three weeks, followed by Cardioversion
DC Cardioversion; or IV ibutilide; or IV amiodarone; or oral flecainide; or oral propafenone

Fig. 136.13: An approach to the rhythm management of atrial fibrillation in the ICU. AF = atrial fibrillation; IV = intravenous; LV = left ventricle; TEE = transesophageal echocardiogram

digoxin >10 ng/mL, ingestion of > 10 mg of digoxin in adults and > 4 mg in children and any digoxin toxic rhythm in the setting of an elevated digoxin level.[20]

Atrial Flutter

Atrial flutter (AFL) is characterized by organized 'P' waves with same morphology and axis at a rate of 250 to 350 bpm with intermittent AV conduction (2:1, 3:1 or 4:1 AV block). Typically, the ventricular rate is around 150 bpm with a 2:1 AV block (Fig. 136.15). Management of AFL is similar to AF in thromboembolic event prevention and rhythm management. Isthmus-dependent atrial flutter is easily treated by radiofrequency ablation, which is curative.

Multifocal Atrial Tachycardia

Multifocal atrial tachycardia (MAT) (Fig. 136.16) typically is seen in patients with enlarged atria, chronic lung disease, congestive heart failure, electrolyte abnormalities and acid-base disturbance. Management includes alleviation of the cause and consideration of rate control with calcium channel blockers, beta blockers or digoxin. It is essential to differentiate it from AF since there is no need for anticoagulation therapy in MAT.

Other Types of SVTs

The other three types of SVTs [atrioventricular nodal reentry tachycardia (AVNRT), atrioventricular reentry tachycardia (AVRT) due to an AP (Wolff-Parkinson-White) and unifocal/ectopic atrial tachycardia (AT)] have almost similar electrocardiograms. All have narrow QRS tachycardia with 'P' wave either right after the QRS, "short RP tachycardia" (common AVNRT, orthodromic AVRT, or AT with first-degree AV block) (Fig. 136.17) or right before the QRS, "long RP tachycardia" (uncommon AVNRT, or AT). Typically there is sudden onset and sudden offset of the tachycardia with heart rate usually ranging between 160 and 200 bpm.

After obtaining a 12-lead ECG, blocking the AV node may help determine the type of SVT. Persistent 'P' waves in the absence of a QRS complex confirms the diagnosis of AT. However, blocking the AV node could terminate the SVT; then the only diagnostic tool would be an EP study. The AV node can be blocked by Valsalva maneuvers, carotid massage (only in young patients without carotid bruit) or AV blocking agents (e.g. adenosine, beta blockers, calcium channel blockers or digoxin).

Supraventricular tachycardia with hemodynamic instability needs immediate DC cardioversion (50J for SVT/AFL; 200J for AF). Hemodynamically, stable SVT can be treated by vagal maneuvers, or with one of the following medications:

- Intravenous adenosine (6 mg followed in 2 min with another 6 mg and in 2 more min with 12 mg).
- Diltiazem (0.25-0.35 mg/kg loading dose followed by infusion 5-15 mg/hour) – caution with hypotension.
- Beta blockers (metoprolol titrate 0.5-1 mg, esmolol 0.5 mg/kg/min for 1 min followed by 0.05-0.2 mg/kg/min) – caution with hypotension.
- Intravenous digoxin (1 mg over 24 hours in increments of 0.25-0.5 mg, followed by 0.125-0.25 mg daily).
- Intravenous amiodarone (loading dose of 150 mg over 10 min, may repeat if failed to control rate; followed by infusion 30 mg/hour) – especially in AF with presence of AP.

The best long-term management for AVNRT and AVRT is EPS and radiofrequency ablation.

TABLE 136.3: Commonly used medications for controlling ventricular rate in atrial fibrillation

Drug	*Control of Acute Episode*	*Control of Sustained Atrial Fibrillation*	*Comments*
Calcium channel blockers			
Diltiazem	20-mg bolus followed, if necessary, by 25 mg given 15 min later. Maintenance infusion of 5-15 mg/hr.	Oral controlled-release formulation, 180-300 mg daily.	Long-term control may be better with the addition of digoxin.
Verapamil	5-10 mg IV over 2-3 min, repeated once, 30 min later. Maintenance infusion rate is not reliably documented.	Slow-release formulation, 120-240 mg once or twice daily.	Causes elevation in digoxin level. May be more negatively inotropic than diltiazem.
Beta blockers†			
Esmolol	0.5 mg/kg of body weight IV, repeated if necessary. Follow with infusion at 0.05 mg/kg/min, increasing as needed to 0.2 mg/kg/min.	Not available in oral forms.	Hypotension may be troublesome but responds to drug discontinuation.
Metoprolol	5-mg bolus IV, repeated twice at intervals of 2 min. No data on maintenance infusion.	50-400 mg daily in divided doses.	Useful if there is concomitant coronary disease.
Propranolol	1-5 mg IV, given over 10 min.	30-360 mg in divided doses or in long-acting form.	Noncardioselective: use cautiously in patients with a history of bronchospasm.
Digoxin	1.0-1.5 mg IV or orally over 24 hr in doses of 0.25-0.5 mg.	0.125-0.5 mg daily.	Renally excreted. Slow onset even if given IV with less effective control than other agents, although may be synergistic with them. Poor efficacy for exertional heart rate control.

†The beta blockers listed are representative of agents in this category. Other intravenous or oral beta blockers may be equally acceptable. (From Falk RH. Atrial fibrillation. N Engl J Med 2001;344:1067-78. Copyright © Massachusetts Medical Society. All rights reserved.)

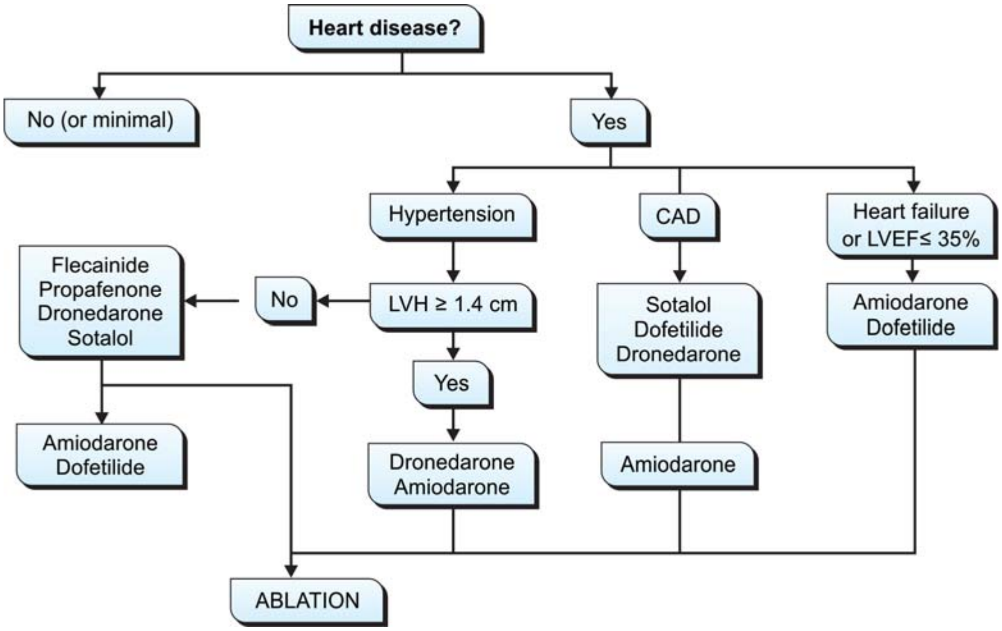

Heart disease?
No (or minimal)
Yes
Hypertension
CAD
Heart failure or LVEF≤ 35%
Flecainide Propafenone Dronedarone Sotalol
No
LVH ≥ 1.4 cm
Sotalol Dofetilide Dronedarone
Amiodarone Dofetilide
Yes
Amiodarone Dofetilide
Dronedarone Amiodarone
Amiodarone
ABLATION

Fig. 136.14: Algorithm for antiarrhythmic choices and indication of ablation to maintain sinus rhythm in patients with atrial fibrillation. CAD = coronary artery disease; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy

TABLE 136.4:.Medications used for conversion of atrial fibrillation and maintenance of sinus rhythm

Drug Name	*Conversion Dose*	*Oral Maintenance Dose*	*Comments*
Ibutilide	1 mg IV over 10 min if weight >60 kg. (For weight <60 kg, 0.01 mg/kg over 10 min. May repeat after 10 min of initial infusion.)	Not for maintenance.	Contraindicated in patients with hypokalemia, QT prolongation or history of torsades de pointes. Always use magnesium IV 2 gm before ibutilide.
Dofetilide	0.5 mg twice daily (adjust for renal disease).	0.5 mg twice daily.	Hospitalize for initiation.
Flecainide	300 mg oral. 2 mg/kg IV.	50-150 mg twice daily.	Only for paroxysmal AF with structurally normal heart
Propafenone	600 mg oral. 2 mg/kg IV.	150-300 mg twice daily.	Only for paroxysmal AF with structurally normal heart.
Amiodarone	1200 mg IV in 24 hr.	600 mg daily for 2 weeks, then 200-400 mg daily.	IV amiodarone moderately effective for cardioversion.
Dronedarone	400 mg twice daily oral.	400 mg twice daily.	Less effective than amiodarone for conversion. Lower risk of amiodarone-related side effects.
Sotalol	Low success rate. Not recommended for cardioversion.	120-160 mg twice daily.	Used primarily for maintenance of sinus rhythm. Hospitalize for initiation and monitor QT for prolongation.
Disopyramide	200 mg oral every 4 hr to max of 800 mg.	100-150 mg 4 times daily (200-300 mg controlled release formulation twice daily).	Negative inotropic effect. Can be used in hypertrophic cardiomyopathy.
Quinidine Sulfate	200 mg oral followed 2 hr later by 400 mg.	200-400 mg 4 times daily (gluconate 324-648 mg 3 times daily).	Long-term therapy associated with increased risk of death.

AF = atrial fibrillation; IV = intravenous. (From Falk RH. Atrial fibrillation. N Engl J Med 2001;344:1067-78. Copyright © Massachusetts Medical Society. All rights reserved.)

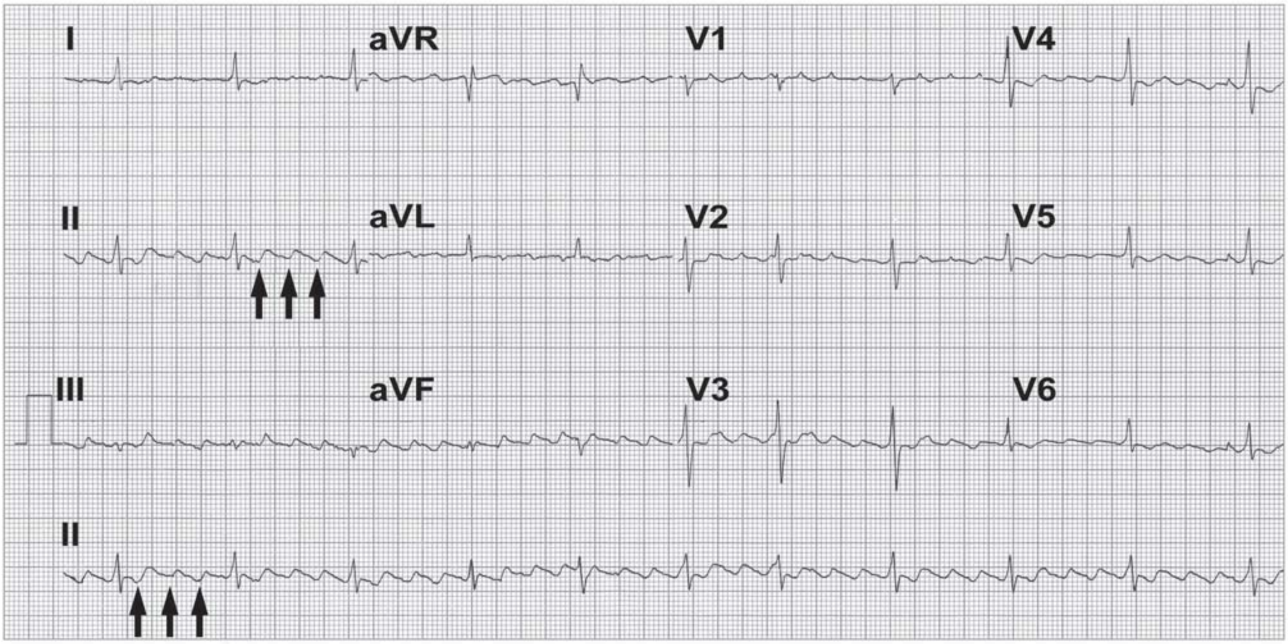


Fig. 136.15: Atrial flutter (AFL). 12-lead electrocardiogram of a typical clockwise, isthmus-dependant AFL, which has a saw-tooth pattern ‘P’ waves morphology that is negative in the inferior leads (II, III and aVF). Note the absence of an isoelectric interval between the flutter waves, and the presence of an AV block with only every third beat being conducted with a corresponding QRS complex

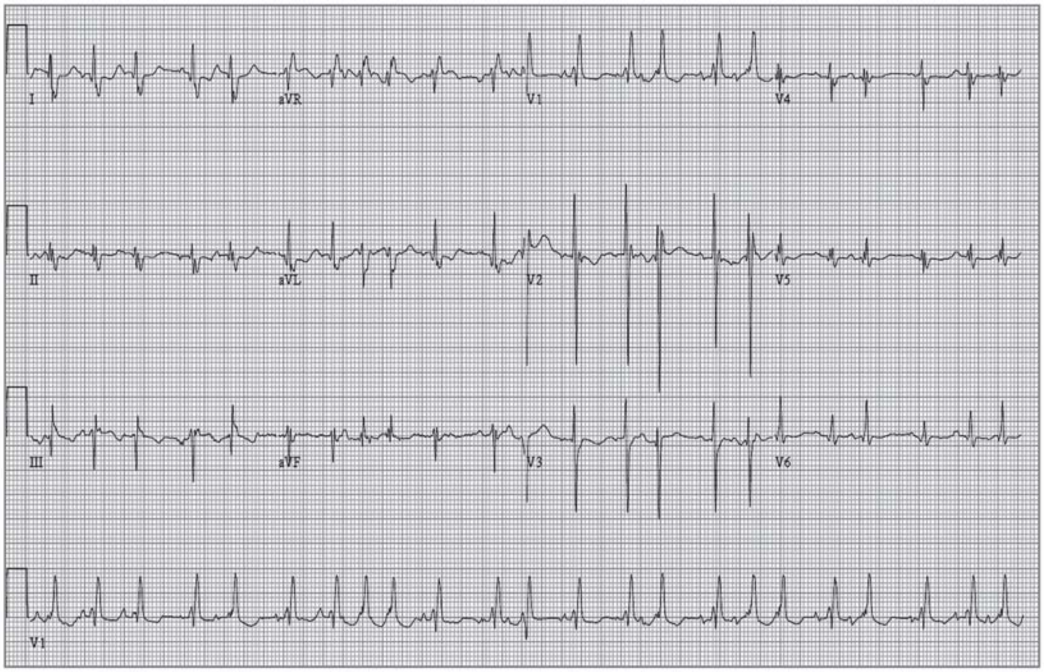

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

Fig. 136.16: Multifocal atrial tachycardia (MAT). An electrocardiogram of MAT with ≥ 3 distinct ‘P’ wave morphologies each followed by a QRS with slight variation in the ‘PR’ interval. MAT results in heart rates of 130-180 bpm

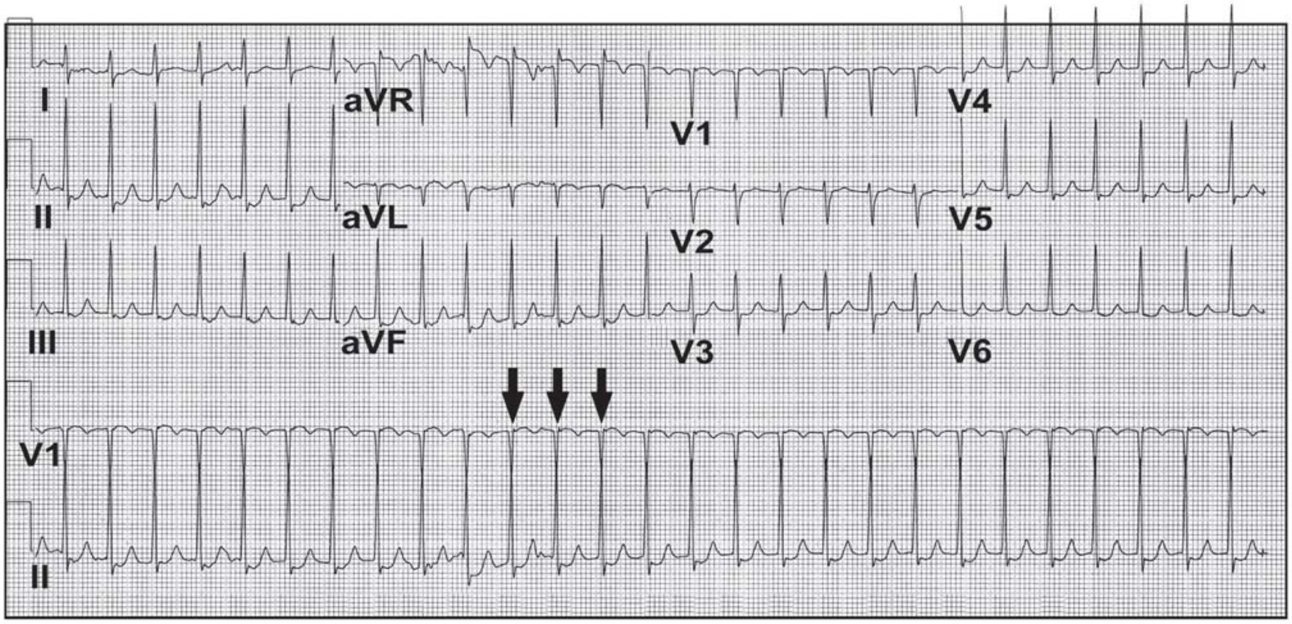

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II

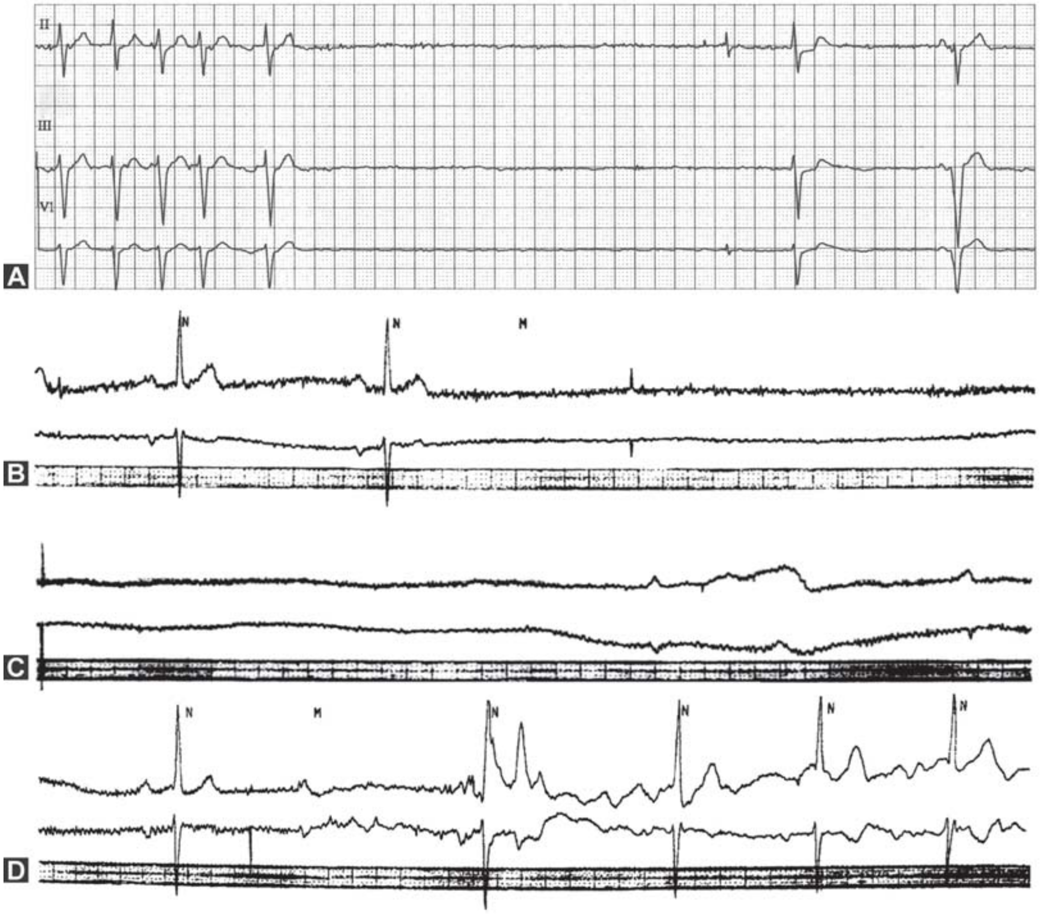
Fig. 136.17: Supraventricular tachycardia (SVT). 12-lead ECG of SVT. Note the r’, a slight notch at the end of the QRS complex, best seen in lead V1, which represents the retrograde ‘P’ wave occurring at the end of the QRS complex, suggestive of short ‘RP’ SVT

BRADYCARDIA (HEART RATE <60 BPM)

Bradycardia is due to:

1. Sinus node dysfunction (sinus bradycardia or sinus pause);
2. AV node dysfunction (first-, second- and third-degree AV block). Most bradycardias in ICU patients are induced by vagally mediated causes such as intubation, suctioning, increased intracranial pressure, urination, defecation, vomiting, or retching. Other extrinsic causes might include:
   - Drugs (beta blockers, calcium channel blockers, digoxin, antiarrhythmics)
   - Acute MI (inferior acute MI-related AV blocks, often transient; anterior acute MI-related AV blocks, often irreversible)
   - Electrolytes imbalance (K, Mg, Ca)
   - Hypothyroidism
   - Hypothermia
   - Sepsis
   - Specific infection (e.g., endocarditis, rheumatic fever, Lyme, Chagas)
   - Valvular disease (especially post valvular surgery)
   - Collagen disorder
   - Hypoxia (sleep apnea)
   - Advanced age (calcification)

Management includes eliminating the cause and possible pacing. Because transcutaneous pacing may be uncomfortable, it is intended to be temporary. Refer to cardiologist for transvenous pacing (TVP) in patients who require ongoing pacing. It is necessary to monitor the TVP once a day to ensure appropriate pacing



Figs 136.18A to D: Sinus pause. Panel A: Sinus pause is seen with sudden and prolonged cessation of atrial activity. No 'P' waves and no QRS complexes are seen. Junctional rhythm or ventricular escape rhythm usually takes over until the sinus recovers or pacemaker-induced atrial activity takes over the role of dominant pacemaker of the heart. Note that the preceding rhythm is atrial fibrillation with a long pause of 5 seconds followed by resumption of sinus beats. This is called "postconversion" pause. If longer than 5 seconds, it is an indication for permanent pacemaker. Panels B, C and D: Note the prolonged sinus pause, which occurred spontaneously in a patient with underlying sinus rhythm and spontaneous recovery. Some atrial activity ('P' waves) is noted in Panel C with no conduction to the ventricles. This occurred spontaneously in an ICU patient

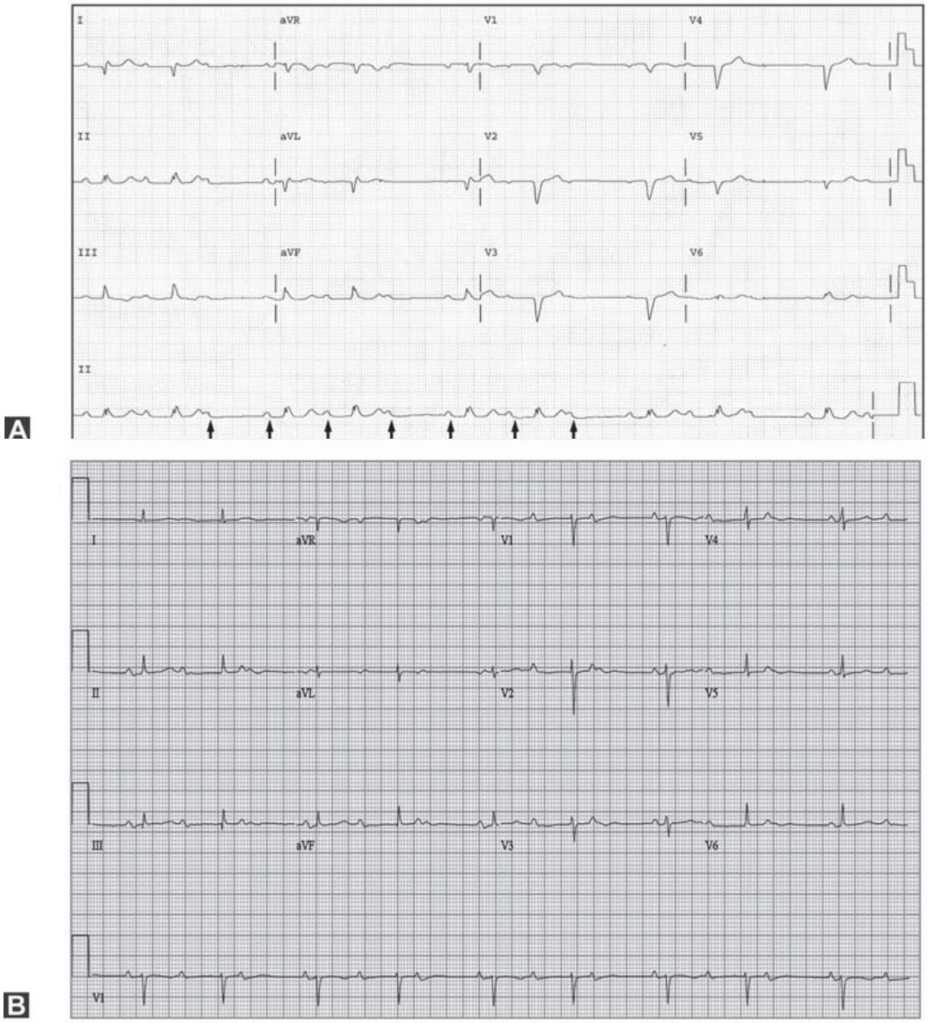
thresholds and sensing functions. Postcardiac surgery patients may have bradycardia due to local edema in the region of the AV node. Temporary pacing for 5 to 7 days is the first course of action; if no recovery, then permanent pacemaker implantation.

Sinus Node Dysfunction

If sinus node dysfunction (Figs 136.18A to D) persists after removing the cause and the patient is symptomatic, then medical management is warranted, which includes: immediate IV atropine (0.6 mg, max 3 mg), IV dopamine (2-5 mcg/kg/min), IV isopreterenol (0.5-10 mcg/min) (caution in ischemic heart disease), or IV glucagon (3-10 mg bolus followed by 2-5 mg/h infusion, in beta blocker overdose-induced bradycardia). Pacemaker (temporary or permanent) is indicated if symptomatic bradycardia and sinus pauses (>3 second while awake, >6 seconds while sleeping) are unrespon-sive to management.

First-degree AV Block

Defined as normal 'P' wave with increased 'PR' interval (>200 ms), first-degree block is usually in the AV node and needs no treatment. Pacemaker is indicated only if the patient is symptomatic with PR > 300 ms.



Figs 136.19A to B: Second-degree heart block Mobitz I (Wenckebach) and Mobitz II. Panel A: Second-degree Mobitz Type I AV block (Wenckebach) is characterized by a normal 'P' wave with constant 'P-to-P' interval; prolonging PR interval until one QRS fails to conduct, then PR interval shortens again. Panel B: ECG of second-degree Mobitz type II AV block, defined as normal 'P' wave with constant 'P-to-P' and PR intervals with sudden drop of one or two QRS complexes

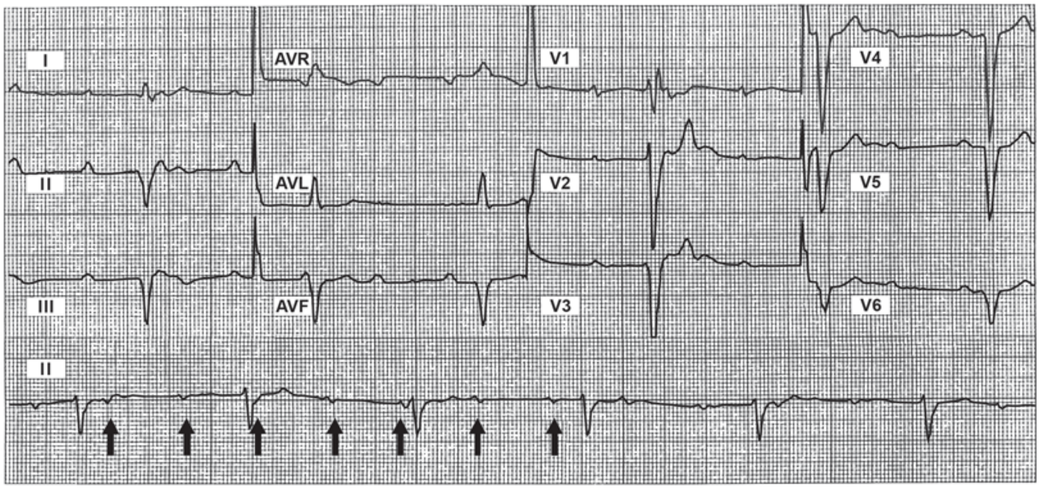


Fig. 136.20: Complete heart block or third-degree heart block. 12-lead electrocardiogram showing third-degree AV block with normal 'P' waves, constant PP intervals, constant PR intervals, and AV dissociation where the QRS complexes are less than 'P' waves

Second-degree AV Block, Type I (Mobitz I, "Wenckebach")

Location of second-degree, Type I block (Fig. 136.19A) is mostly in the AV node and needs no treatment other than removing any possible cause. Pacemaker is indicated only if the patient is symptomatic and failed other medical actions, especially if it is accompanied by fascicular block.

Second-degree AV Block, Type II (Mobitz II)

Second-degree, Type II block (Fig. 136.19B) can be unpredictable and lead to abrupt AV block with ventricular asystole due to the location of block (either intra- or infra-Hisian). If it persists after removing any possible cause, pacemaker should be considered.

Third-degree AV Block

Location of third-degree block (Fig. 136.20) is almost always below the His bundle. Thus, pacemaker is indicated in these patients. If a reversible cause is present (e.g. MI, Lyme disease, electrolyte imbalance, etc.), a temporary pacemaker should be placed until the condition resolves.

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Cardiac Emergencies in the Intensive Care Unit: Cardiogenic Shock and Acute Coronary Syndrome

M Fuad Jan, Suhail Allaqaband

INTRODUCTION

Cardiogenic Shock (CS) is characterized by hypoperfusion of the extremities and vital organs and is defined by the following hemodynamic hallmarks:

1. Persistent hypotension (systolic blood pressure [SBP] < 80 to 90 mm Hg or mean arterial pressure 30 mmHg lower than baseline);
2. Severely reduced cardiac index (<1.8 L/min/m^2 without support or <2.0–2.2 L/min/m^2 with support)
3. Adequate or elevated ventricular filling pressure (e.g. Left Ventricular [LV] end-diastolic pressure >18 mmHg or Right Ventricular [RV] end-diastolic pressure >10-15 mmHg), a diagnosis usually made with the help of Pulmonary Artery (PA) catheterization.

ETIOPATHOGENESIS

Cardiogenic shock classically occurs in the setting of Acute Myocardial Infarction (AMI) associated with left ventricular dysfunction. Approximately 5 to 8% of patients hospitalized with ST-Elevation Myocardial Infarction (STEMI) and 2.5% of patients with non-STEMI (NSTEMI) have cardiogenic shock. Mortality due to CS is approximately 50% in the modern era.[1] The pathophysiology of CS involves a vicious cycle characterized by progressive myocardial dysfunction (Fig. 137.1). However, severe impairment of contractility is not necessary for CS, and conversely, LV Ejection Fraction (LVEF) may be only moderately depressed in CS,[1] while approximately half of all CS patients have small or normal LV size,[2,3] representing a failure of the adaptive mechanism of acute dilation to maintain stroke volume in the early phase of MI. Whereas LV failure or dysfunction resulting from acute ischemia is the predominant underlying theme in CS, RV dysfunction may also cause or contribute to CS. Shock due to isolated RV dysfunction carries nearly as high a mortality as LV shock. Predominant RV shock characterized by disproportionate elevation of right-heart filling pressures (RV end-diastolic pressure often >20 mmHg) and low-output hypotension despite preserved LV systolic function occurs in 5% of cases of CS complicating MI.[4]

Since MI with LV failure is the most common cause of CS, it is critical to exclude complicating factors that may cause shock in MI patients. Among these are the mechanical complications of ventricular septal rupture, contained free wall rupture and papillary muscle rupture. Mechanical complications must always be strongly suspected in patients with CS complicating nonanterior MI, particularly a first MI, and echocardiography remains the benchmark of cardiac imaging for the diagnosis of these usually fatal complications. Hemorrhage, infection and/or bowel ischemia may contribute to shock in the setting of MI and a high index of suspicion is required to make these diagnoses in MI patients, since survival may depend on their timely recognition and treatment.[1]

During the initial management strategy, it is also important to consider other causes of acute LV or RV dysfunction that may lead to CS. Acute myopericarditis, takotsubo (stress-induced) cardiomyopathy and hypertrophic cardiomyopathy can all present with ST elevation, elevated cardiac biomarkers and shock in the absence of significant coronary artery disease. Stress-

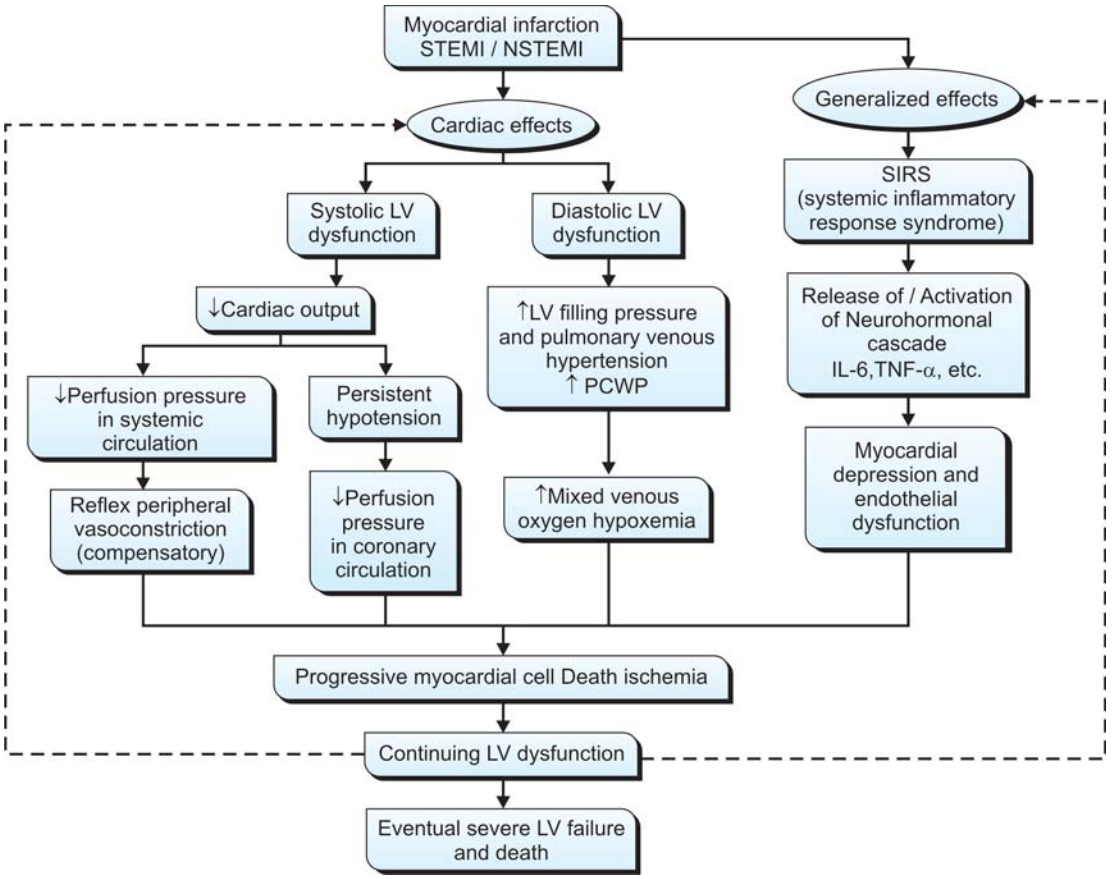
Myocardial infarction
STEMI / NSTEMI
Generalized effects
Cardiac effects
SIRS
(systemic inflammatory
response syndrome)
Systolic LV
dysfunction
Diastolic LV
dysfunction
↓Cardiac output
↑LV filling pressure
and pulmonary venous
hypertension
↑ PCWP
Release of / Activation
of Neurohormonal
cascade
IL-6,TNF-α, etc.
↓Perfusion pressure
in systemic
circulation
Persistent
hypotension
Reflex peripheral
vasoconstriction
(compensatory)
↓Perfusion
pressure
in coronary
circulation
↑Mixed venous
oxygen hypoxemia
Myocardial
depression and
endothelial
dysfunction
Progressive myocardial cell Death ischemia
Continuing LV dysfunction
Eventual severe LV failure
and death

Fig. 137.1: The classic pathophysiology of cardiogenic shock with progressive left ventricular dysfunction. Essentially, myocardial ischemia and infarction results in both systolic and diastolic dysfunction along with activation of the neurohormonal cascade. Left ventricular pump failure is a self-propagating cycle with continually worsening hemodynamics and eventually LV failure and death. NSTEMI = Non-ST-Elevation Myocardial Infarction; STEMI = ST-Elevation Myocardial Infarction; PCWP = Pulmonary Capillary Wedge Pressure; IL-6 = Interleukin-6; TNF-α = Tumor Necrosis Factor-Alpha

induced cardiomyopathy, a syndrome of acute LV failure after emotional or respiratory distress, can be complicated by CS in up to 4.2% of cases,[5] while acute valvular regurgitation, secondary to infective endocarditis or chordal rupture due to trauma or degenerative disease, may also cause CS. Aortic dissection may also lead to CS via severe aortic insufficiency or MI. Acute stress in the setting of aortic or mitral stenosis can also cause shock. Cardiac tamponade or massive pulmonary embolism can present as cardiogenic shock without associated pulmonary congestion.

Although the vast majority of patients with CS have a high Systemic Vascular Resistance (SVR) triggered by the compensatory release of catecholamines, vasopressin and angiotensin II in response to hypoperfusion, this reflex mechanism is not always fully effective as demonstrated by variable SVR, with median SVR during CS in the normal range despite vasopressor therapy. This is documented in the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial results.[6] In some patients, SVR may be low, similar to septic shock. In fact, sepsis was suspected in 18% of the SHOCK trial cohort, 74% of whom developed positive bacterial cultures.[6] SVR was lower in these patients and low SVR preceded the clinical diagnosis of infection and culture positivity by days. This is consistent with the observation that MI can cause Systemic Inflammatory Response Syndrome (SIRS) and the inappropriate vasodilatation that is a part of SIRS can result in impaired perfusion of the intestinal tract, enabling transmigration of bacteria and sepsis.

It is also important to note that approximately three-fourths of patients with CS complicating MI develop shock after hospital presentation,[7,8] and several classes of medications used to treat MI have been associated with

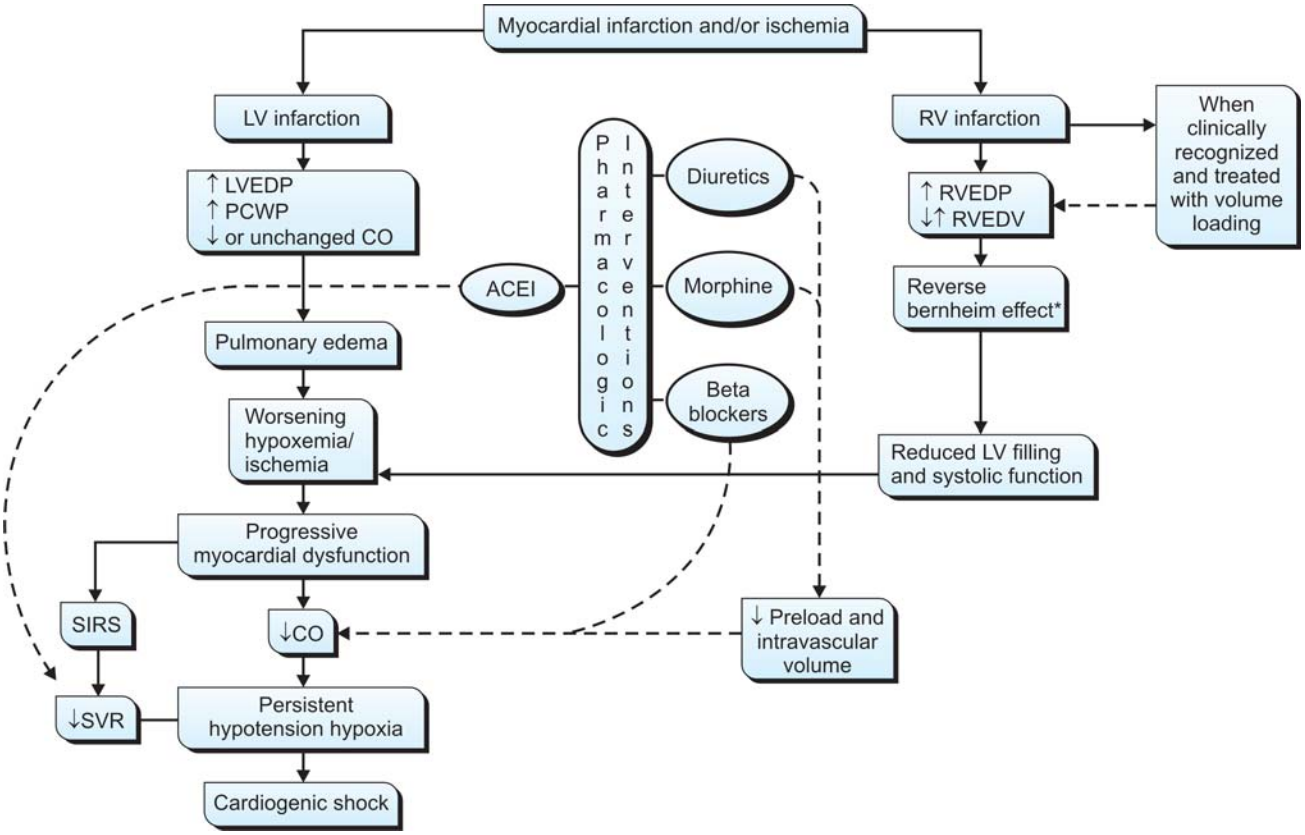
Myocardial infarction and/or ischemia
LV infarction
↑ LVEDP
↑ PCWP
↓ or unchanged CO
ACEI
Pulmonary edema
Worsening hypoxemia/ ischemia
Progressive myocardial dysfunction
SIRS
↓CO
↓SVR
Persistent hypotension hypoxia
Cardiogenic shock
Pharmacologic Interventions
Diuretics
Morphine
Beta blockers
RV infarction
When clinically recognized and treated with volume loading
↑ RVEDP
↓↑ RVEDV
Reverse bernheim effect*
Reduced LV filling and systolic function
↓ Preload and intravascular volume

Fig. 137.2: Cardiogenic shock occurs in a significant number of patients after admission to hospital, and pharmacologic intervention is a contributory factor in many. Several classes of medication are associated, as shown, and although each is associated with only a small excess risk, the large number of patients treated with these medications can translate into a substantial number of events. Deleterious effect of volume expansion when used in excess for RV configuration is shown. LVEDP = Left Ventricular End Diastolic Pressure; PCWP = Pulmonary Capillary Wedge Pressure, CO = Cardiac Output; SIRS = Systemic Inflammatory Response Syndrome, RVEDP = Right Ventricular End Diastolic Pressure, RVEDV = Right Ventricular End Diastolic Volume. *Reverse Bernheim effect describes a condition where volume or pressure overload of RV causes a shift of the interventricular septum, which causes impairment of LV filling and contraction

shock, including beta-blockers, angiotensin-converting enzyme inhibitors, diuretics and morphine. As depicted in Figure 137.2, MI may lead to pulmonary edema even without a decrease in cardiac output (the earliest effect of ischemia is often a decrease in LV compliance or acute diastolic dysfunction) and redistribution of intravascular volume into the lungs may lead to an acute decrease in circulating plasma volume in those without prior heart failure. Thus, when high-dose diuretics are administered, plasma volume declines further.[1]

CLINICAL PRESENTATION AND DIAGNOSIS

Cardiogenic shock in AMI usually occurs in the context of risk factors, such as old age, anterior MI, hypertension, diabetes mellitus, multivessel coronary artery disease, prior MI or angina, prior diagnosis of heart failure, STEMI and left bundle branch block.[9] Clinical presentation is usually dramatic, with hypoperfusion manifesting clinically as cool extremities, decreased urine output and/or alteration in mental status. More often, however, CS evolves over several hours, or may develop during hospitalization as mentioned earlier. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) trial, CS developed during hospital admission in 89% of cases with cardiogenic shock,[10] while median delay from onset of AMI to CS in the SHOCK trial and the SHOCK trial registry was 5.6 and 7 hours, respectively.[6,7]

Chest Roentgenogram (CXR), Electrocardiogram (ECG) and cardiac biomarkers are usually the initial investigations undertaken. The CXR can provide valuable clues about the presence of infection, pulmonary edema or aortic dissection, while a normal ECG makes CS due to myocardial infarction highly unlikely. Hemodynamic criteria (see CS definition) suggestive of cardiogenic shock include the presence of sustained hypotension with a decreased urine output (<0.5 ml/kg/min), increased pulmonary capillary wedge pressure, increased right atrial pressure (>20 mm Hg), decreased cardiac output and increased systemic vascular resistance (>2100 dynes/cm^2).

Many of the hemodynamic criteria of CS are obtained by Right Heart Catheterization (RHC). Although routine use of RHC has been associated with increased mortality in a well-known and quoted study,[11] data from GUSTO-I[12] and the SHOCK registry[13] suggest that it is not harmful, and possibly beneficial, in terms of outcome. The mortality rate was lower in patients who underwent RHC than in those who did not (45.2 vs. 63.4%) in the GUSTO-I population. In the SHOCK registry, no increase was reported in the in-hospital mortality among patients undergoing right heart catheterization. The current American and European guidelines recommend RHC for patients who have STEMI, or who have progressive heart failure, cardiogenic shock, or mechanical complications, despite the paucity of evidence proving its efficacy.[14,15] It should be stressed, however, that there are no data regarding the optimal hemodynamic values to be targeted in cardiogenic shock patients.

Doppler echocardiography continues to be an excellent modality for hemodynamic assessment and evaluation of myocardial and valvular function and also mechanical complications related to CS. It is a routine assessment tool in patients with suspected myocardial infarction and cardiogenic shock, and can be readily performed by the patient's bedside. For example, in the SHOCK trial,[3] 175 echocardiograms were performed within 24 hours of randomization (64%), while in the Euro-Heart-Survey, 68% of cardiogenic shock patients underwent an echocardiographic evaluation.[16] Due to the ease and speed of availability, it is not surprising that this noninvasive method has supplanted RHC use in many patients with suspected cardiogenic shock.

TREATMENT

Treatment usually involves general supportive measures and pharmacological and mechanical interventions. Aspirin and intravenous Unfractionated Heparin (UFH) is routinely administered as recommended for MI. Clopidogrel is sometimes deferred until after emergency coronary angiography, because on the basis of angiographic findings, coronary artery bypass grafting (CABG) may need to be performed immediately. However, all patients who undergo percutaneous coronary intervention (PCI) receive a loading dose of 300 to 600 mg clopidogrel. Negative inotropes and vasodilators (including nitroglycerin) are avoided, while arterial oxygenation and near-normal pH are maintained in order to minimize ischemia. A low threshold for mechanical ventilation via mask or endotracheal tube is maintained.

Although, there has been a decline in PA catheter (Swan-Ganz) use due to controversy sparked by a prospective observational study suggesting that PA catheters were associated with poor outcomes,[11] Swan-Ganz catheterization continues to be important in establishing the relationship between filling pressures and cardiac output in the individual patient, and therefore supplementing clinical assessment of responses with this data.[1] Individualized PA catheter use is recommended for severely hypotensive MI patients.[14]

Pharmacotherapy

Pharmacotherapy in CS includes inotropic and vasopressor support. Inotropes are central in treatment because the initiating event in CS is contractile failure. Unfortunately, inotropes increase myocardial ATP consumption, and the short-term hemodynamic improvement afforded by them may occur at the cost of increased oxygen demand in a failing heart. On the other hand, higher doses of vasopressors are also associated with poor survival in CS, representing both more severe underlying hemodynamic derangement and direct toxic effects.[17] However, inotropic and vasopressor support is always required to maintain coronary and systemic perfusion until (and often after) an intra-aortic balloon pump (IABP) is placed or until shock resolves. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend norepinephrine for more severe hypotension because of its high potency,[14] and although both dopamine and norepinephrine have inotropic properties, dobutamine is also often needed.

Mechanical Support

IABP

Intra-aortic balloon counterpulsation remains the most widely used circulatory assist device in CS, and with advanced technology, including smaller diameter catheters, sheathless insertion techniques and enhanced automation, greater efficacy and safety has been achieved. Use of an IABP (Table 137.1) improves

TABLE 137.1: Effects of intra-aortic balloon pump in cardiogenic shock

Left Ventricular (LV) Myocardium	1.	↓ Volume
	2.	↓ wall tension
	3.	↓ systolic pressure
	4.	↓ LV end-diastolic pressure
Aorta	1.	↓ systolic pressure
	2.	↓ diastolic pressure
Coronary Blood Flow	1.	Increased*

*Balloon inflation causes "volume displacement" of blood within the aorta, both proximally and distally, leading to an increase in coronary blood flow and enhanced systemic blood flow by augmentation of the intrinsic "Windkessel effect," whereby potential energy stored in the aortic root during systole is converted to kinetic energy with the elastic recoil of the aortic root.

coronary and peripheral perfusion via diastolic balloon inflation that augments coronary perfusion and via systolic balloon deflation with an acute decrease in afterload that improves LV performance. It also increases collateral blood flow, improves subendocardial oxygenation and decreases myocardial oxygen consumption.

Intra-aortic balloon pump support should be instituted as quickly as possible – if a skilled operator is available and insertion can be performed quickly. In the large National Registry of Myocardial Infarction, IABP use was independently associated with survival at centers with higher rates of IABP use, whether PCI, fibrinolytic therapy or no reperfusion had been used[18]; although no completed trials to date demonstrate its benefit. Complications associated with IABP in the largest series so far demonstrate overall and major complication rates of 7.2 and 2.8%, respectively[19] and risk factors for complications identified include, female sex, small body size and peripheral vascular disease.

Left Ventricular Assist Device (LVAD) use has also been attempted in CS, but is limited by the need for a surgical procedure. However, recently, percutaneous LVADs have been introduced into practice and can be used to rapidly establish mechanical circulatory support in the catheterization laboratory. The Impella Recover® LP 2.5 system (ABIOMED Inc., Danvers, MA) is one such percutaneous LVAD implanted through a 13 French sheath in the common femoral artery and inserted through the aortic valve into the left ventricle, providing axial flow to the ascending aorta at a maximum flow rate of 2.5 L/min. In a prospective, randomized study of 26 patients[20] with CS (n = 13 IABP, n = 12 Impella LP 2.5), the Cardiac Index (CI), after 30 min of support, was significantly increased in patients with the Impella LP 2.5 compared with patients with IABP (Impella: change in CI = 0.49 ± 0.46 $l/min/m^2$, IABP: change in CI = 0.11 ± 0.31 $l/min/m^2$; $p = 0.02$). However, overall 30-day mortality was 46% in both groups. Thus, a percutaneously placed LVAD is feasible and safe to use and may provide superior hemodynamic support compared with standard treatment using an IABP. In our institution, we have also successfully used the Impella device and IABP simultaneously in patients with refractory and profound cardiogenic shock.[21]

Of the implantable Mechanical Circulatory Support (MCS) systems, the percutaneous ventricular assist device TandemHeart® pVAD™ system (Cardiac Assist, Inc., Pittsburgh, PA) has also been used to support patients in cardiogenic shock until cardiac recovery occurs or as a bridge to definitive therapy.[22] The device is a left atrial-to-femoral artery bypass system comprising a transseptal cannula, arterial cannulae and a centrifugal blood pump. The pump can deliver flow rates up to 4.0 L/min at a maximum speed of 7,500 revolutions per minute.

Revascularization

The survival benefit of early revascularization in CS was convincingly established in the randomized SHOCK trial, which found a 13% absolute increase in one-year survival in patients assigned to early revascularization (number needed to treat is <8 patients to save one life).[23,24] Numerous registry studies have also confirmed the survival benefit of early revascularization (surgical or PCI) in both the young and the elderly, including the incomplete randomized Swiss Multicenter Study of Angioplasty for Shock,[25] and it is observed that earlier the revascularization, the better the survival benefit seen, for as long as 48 hours after MI and 18 hours after shock onset. PCI with stenting and use of glycoprotein IIb/IIIa inhibitors is independently associated with improved outcomes in CS patients.[26,27] Among patients with CS undergoing PCI, age and time from symptom onset to PCI and post-PCI Thrombolysis In Myocardial Infarction (TIMI) flow grade are independent predictors of mortality.[24,26] Figure 137.3 relates the ACC/AHA guidelines for revascularization in patients with cardiogenic shock, with early revascularization recommended for patients <75 years (Class I) and for suitable candidates ≥ 75 years (Class IIa).

In contrast to PCI, thrombolytic therapy in CS is probably futile and this is supported by data from the SHOCK registry,[28] where patients receiving thrombolysis

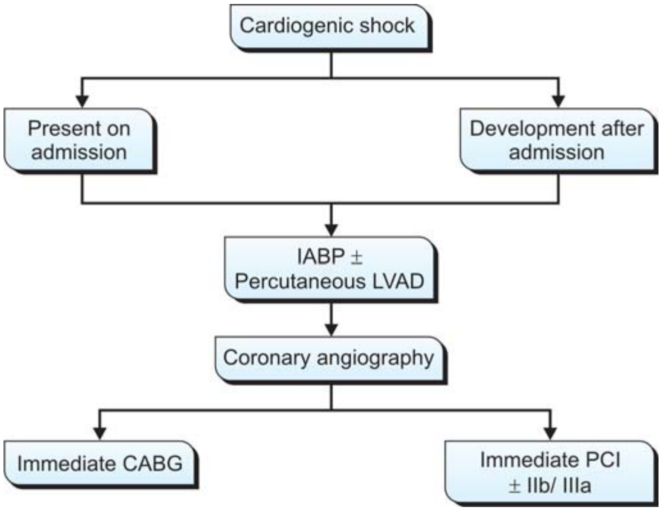
Cardiogenic shock
Present on admission
Development after admission
IABP ±
Percutaneous LVAD
Coronary angiography
Immediate CABG
Immediate PCI
± IIb/ IIIa

Fig. 137.3: Revascularization strategies in cardiogenic shock. CABG = Coronary Artery Bypass Graft; IABP = Intra-aortic Balloon Pump; LAVD = Left ventricular Assist Device; PCI = Percutaneous Coronary Intervention

had similar mortality compared to thrombolytic-eligible patients who did not receive thrombolysis (61 vs. 71%; p = 0.334).

In summary, rapid evaluation and early initiation of the definitive therapy for CS (revascularization) affords a reasonable chance for full recovery as demonstrated by the SHOCK trial,[24] where the three- and six-year survival rates in patients with CS were respectively 41.4 and 32.3%, i.e. persistent treatment benefit. An early invasive revascularization approach is associated with benefit at every level of risk, with potential for full recovery and improved quality of life.

ACUTE CORONARY SYNDROME

Definition and Classification

Acute Coronary Syndrome (ACS) is an operational term that refers to a constellation of clinical symptoms and signs that are compatible with acute myocardial ischemia. It is often due to rupture of atherosclerotic plaques that contain large necrotic cores and although substantially large, are often positively remodeled (Glagov effect) and may not always compromise luminal integrity. Such plaques (also called vulnerable plaques) are covered by a thin, intact fibrous cap (cap thickness < 65 micrometers), which is inflamed with macrophages. Although plaque rupture and intraluminal obstruction are the most common mechanisms underlying ACS, in the CASPAR study,[29] nearly 25% of patients with ACS undergoing coronary angiography did not have a culprit lesion, thereby suggesting that coronary artery endothelial dysfunction, in addition to vessel morphology, can play a critical role in ACS.

Clinically, plaque rupture results in thrombus formation with complete vessel occlusion (fibrin-rich clot) in acute STEMI, or a nonoccluding thrombus (platelet-rich clot) in unstable angina or non-STEMI (also referred to as non-ST-segment elevation acute coronary syndrome [NSTE ACS]).[30] The Joint Task Force of the European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association and the World Health Federation defines acute MI as a clinical event consequent to the death of cardiac myocytes (myocardial necrosis) that is caused by ischemia. In the spectrum of ACS, NSTEACS is defined by electro-cardiographic ST-segment depression, prominent T-wave inversion, and/or positive biomarkers of necrosis (e.g. troponin) in the absence of ST-segment elevation in an appropriate clinical setting (chest discomfort or angina equivalent) (Fig. 137.4).

In 2007, the Joint Task Force also introduced a clinical classification of MI[31] according to the proximate cause of the myocardial ischemia with implications for differing treatment approaches (Table 137.2).

Challenges for implementing the new definition and classification include the interpretation of raised troponin levels in the context of other plausible differential diagnoses (Table 137.3). In this regard, the clinician must be aware of the pitfalls of interpreting elevated troponin levels solely as ACS without assessing the entire clinical context.

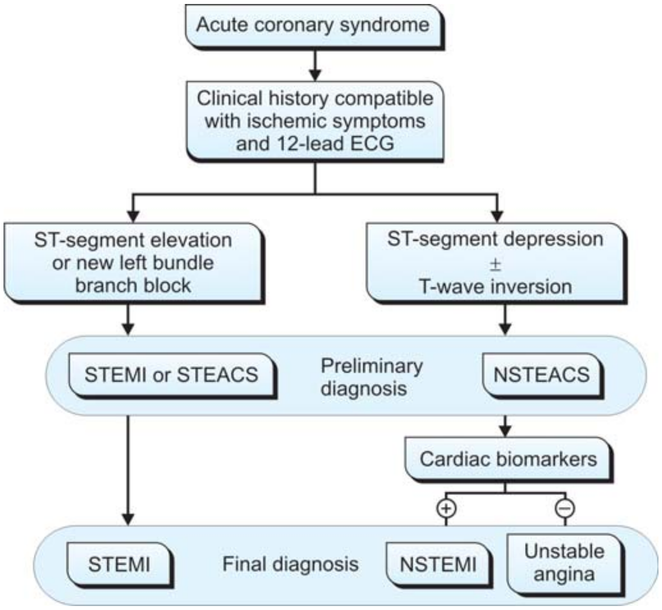
Acute coronary syndrome
Clinical history compatible with ischemic symptoms and 12-lead ECG
ST-segment elevation or new left bundle branch block
ST-segment depression
±
T-wave inversion
STEMI or STEACS
Preliminary diagnosis
NSTEACS
Cardiac biomarkers
+
−
STEMI
Final diagnosis
NSTEMI
Unstable angina

Fig. 137.4: Spectrum of acute coronary syndrome. ECG = Electro-cardiogram; NSTEACS = Non-STEACS; NSTEMI = Non-STEMI; STEACS = ST-Segment Elevation Acute Coronary Syndrome; STEMI = ST-Segment Elevation Mycocardial Infarction

TABLE 137.2: Types of myocardial infarction

Type 1	Myocardial Infarction consequent to a pathologic process in the wall of the coronary artery (e.g. plaque erosion/rupture, fissuring or dissection).
Type 2	Myocardial Infarction consequent to increased oxygen demand or decreased supply (e.g. coronary artery spasm, coronary artery embolus, anemia, arrhythmias, hypertension or hypotension).
Type 3	Sudden unexpected cardiac death before blood samples for biomarkers could be drawn or before their appearance in the blood.
Type 4a	Myocardial infarction associated with percutaneous coronary intervention.
Type 4b	Myocardial infarction associated with stent thrombosis.
Type 5	Myocardial infarction associated with coronary artery bypass graft surgery.

TABLE 137.3: Differential diagnosis of elevated troponin levels: Putative causes of a type 2 myocardial infarction

Cardiac	*Noncardiac or miscellaneous*
1. Heart failure (acute or chronic)	1. Pulmonary embolism
2. Aortic stenosis or regurgitation	2. Renal failure
3. Hypertrophic obstructive cardiomyopathy	3. Pulmonary hypertension
4. Aortic dissection	4. Severe COPD (emphysema or asthma)
5. Takotsubo cardiomyopathy	5. Sepsis (including septic shock) or SIRS*
6. Cardiac contusion or chest wall trauma	6. Intracranial hemorrhage including subarachnoid hemorrhage
7. Direct current cardioversion/defibrillation	7. Strenuous exercise or extreme exertion
8. Infiltrative diseases of myocardium (e.g. amyloidosis, sarcoidosis, hemochromatosis, scleroderma)	8. Hypovolemia and hypotension without sepsis*
9. Atrioventricular ablation	9. Pheochromocytoma
10. Cardiac surgery other than CABG	10. Severe burns (affected BSA >30%)
11. Tachyarrhythmia, bradyarrhythmia, heart block	11. Kawasaki disease
12. Rhabdomyolysis with cardiac myocyte necrosis	12. Snake venom
13. Myopericarditis	13. Accelerated hypertension
14. Transplant vasculopathy	14. Critically ill patients with respiratory failure*
15. Chemotherapy (adriamycin, 5-FU, daunorubicin, etc.)	
16. Systemic vasculitis	
17. Rheumatoid arthritis	
18. Rheumatic fever	
19. Left ventricular hypertrophy	
20. Sympathomimetic drugs/overdose	

Alternative causes of an elevated troponin in the absence of a thrombotic acute coronary syndrome. Many of these elevations arise from a combination of demand ischemia (supply-demand mismatch), ventricular wall stretch, decreased perfusion pressure, direct myocardial damage, or imbalance of the autonomic nervous system.

*Most frequent causes in the ICU.

Abbreviations: 5-FU = 5-fluorouracil; BSA = Body Surface Area; CABG = Coronary Artery Bypass Graft; COPD = Chronic Obstructive Pulmonary Disease; SIRS = Systemic Inflammatory Response Syndrome.

MANAGEMENT OF ACS

Early recognition of ACS symptoms is critical for timely management (Fig. 137.5). An ECG and an abbreviated history and physical examination should be obtained rapidly in patients suspected to have ACS and patients should be stratified based on their risk early on in the course of their illness (Table 137.4). All patients in the ICU consulted for chest discomfort or other symptoms suggestive of ACS (Table 137.5) should be promptly evaluated and treated, usually on the basis of a predetermined, institutional ACS protocol, which should include several different possibilities (Fig. 137.6). An ECG should be obtained and interpreted immediately by the consulting or ICU resident. For cases in which the initial diagnosis and treatment plan are unclear to the initial evaluating physician, immediate cardiology consultation is advisable.

Acute Phase Pharmacotherapy

Contemporary management of ACS involves a complex array of antithrombotics, including dual oral antiplatelet

TABLE 137.4: Risk assessment tools in acute coronary syndrome

TIMI Risk Score[1]*	*GRACE Risk Model[2]*	*FRISC Score[3]*
1. Age ≥ 65 years	1. Age	1. Age ≥ 65 years
2. Three risk factors for CAD	2. Heart rate (bpm)	2. Male sex
3. Prior coronary stenosis of 50% or more	3. Systolic blood pressure (mmHg)	3. History of MI
4. ST-segment deviation on ECG presentation	4. Creatinine (mg/dL)	4. Diabetes mellitus
5. At least two anginal events in past 24 hours	5. Killip Class	5. ST-segment depression
6. Use of aspirin in prior 7 days	6. Cardiac arrest at admission	6. Elevated troponin-T concentration (≥0.03 µg/L)
7. Elevated serum cardiac biomarkers	7. Elevated cardiac markers	7. Elevated C-reactive protein concentration (≥10 mg/L)
	8. ST-segment deviation	
	9. Congestive heart failure	
	10. In-hospital PCI	
	11. In-hospital CABG	
	12. Past history of MI	
	13. ST-segment depression	

*In the TIMI Risk model, one point is given to each variable.

Abbreviations: CABG = Coronary Artery Bypass Graft; CAD = Coronary Artery Disease; ECG = Electrocardiogram; FRISC = Fracture and Immobilization Score; GRACE = Global Registry of Acute Coronary Events; PCI = Percutaneous Coronary Intervention; TIMI = Thrombolysis in Myocardial Infarction.

[1] *Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000; 284:835-42.*

[2] *Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004; 291(22):2727-33.*

[3] *Hirsch A, Windhausen F, Tijssen JG, et al. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin-T (the ICTUS trial): a follow-up study. Lancet. 2007; 369(9564): 827-35.*

TABLE 137.5: Symptoms and signs of acute coronary syndrome

Symptoms	*Signs*
Clinical Features	
1. Circadian periodicity with peak incidence of events between 6 AM and noon	1. Clenched fist held against sternum (Levine sign)
2. Chest discomfort described as a heavy weight, squeezing, choking or heavy pain; can be associated with a general feeling of malaise or exhaustion	2. Bradycardia or sinus tachycardia
3. Nausea and vomiting due to the activation of vagal reflexes; occasionally, patients may complain of diarrhea or a violent urge to defecate	3. Fever up to 101–102ºF (rectal)
4. Other symptoms may include dizziness, palpitations, cold perspiration, and cough productive of pink frothy sputum (e.g. in pulmonary edema)	4. Tachypnea; Cheyne-Stokes respiration in elderly patients with cardiogenic shock or heart failure
	5. Elevated JVP in pulmonary edema and right ventricular infarction
	6. Rales in patients with left ventricular failure; in such patients diffuse wheezing may occur*
	7. Soft or muffled first heart sound (S1) to a universally present fourth heart sound (S4)[†]
	8. Systolic murmur[§]
	9. Pericardial friction rub[#]

Table listing some of the important features on history and physical examination in patients with ACS.

*In 1967, Killip proposed a prognostic classification on the basis of presence and severity of rales in patients with STEMI: Class I patients have no rales or third heart-sound (S3); Class II patients have rales at <50% of lung fields ± S3; Class III patients have rales in >50% of each lung field; Class IV patients are in cardiogenic shock.

[†] A third heart sound (S3) in patients with ACS usually reflects severe left ventricular dysfunction with elevated filling pressures.

[§] Transient or persistent systolic murmur is usually secondary to papillary muscle dysfunction.

[#] This is usually heard in patients with STEMI sustaining large transmural infarctions.

Abbreviations: ACS = Acute Coronary Syndrome; JVP = Jugular Venous Pressure; STEMI = ST-segment Elevation Mycordial Infarction.

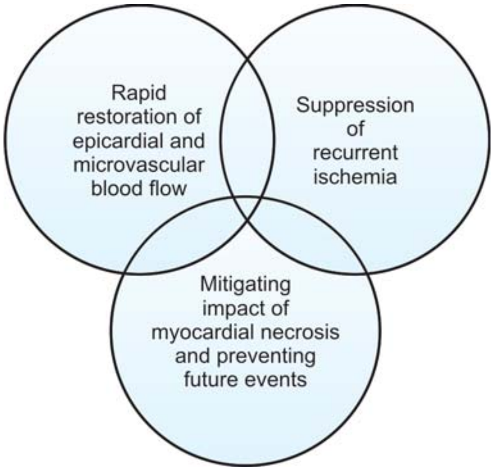
Rapid restoration of epicardial and microvascular blood flow
Suppression of recurrent ischemia
Mitigating impact of myocardial necrosis and preventing future events

Fig. 137.5: Framework of management strategies in acute coronary syndrome (ACS)

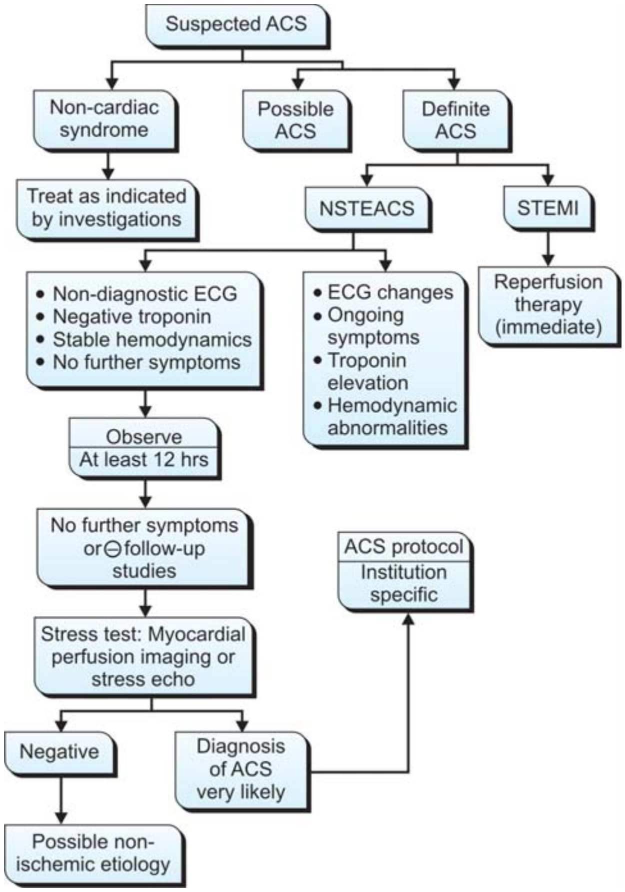
Suspected ACS
Non-cardiac syndrome
Possible ACS
Definite ACS
Treat as indicated by investigations
NSTEACS
STEMI
• Non-diagnostic ECG
• Negative troponin
• Stable hemodynamics
• No further symptoms
• ECG changes
• Ongoing symptoms
• Troponin elevation
• Hemodynamic abnormalities
Reperfusion therapy (immediate)
Observe
At least 12 hrs
No further symptoms or ⊖ follow-up studies
ACS protocol
Institution specific
Stress test: Myocardial perfusion imaging or stress echo
Negative
Diagnosis of ACS very likely
Possible non-ischemic etiology

Fig. 137.6: Algorithm for initial evaluation, risk stratification and management for a patient with suspected ACS. ACS = Acute Coronary Syndrome; ECG = Electrocardiogram; NSTEACS = Non-ST-Segment Elevation Acute Coronary Syndrome; STEMI = ST-Segment Elevation Myocardial Infarction

therapy (aspirin plus a thienopyridine) and an anticoagulant. The clinical challenge is the optimal combination of these therapies for effective suppression of ischemic events, while avoiding bleeding events.

Antiplatelet Therapies

Since early fibrinolytic studies,[32] aspirin (150 to 325 mg) has been the mainstay treatment for patients undergoing either pharmacological or catheter-based reperfusion. All patients with ACS and without contraindications benefit from 150 to 300 mg of aspirin.[33, 34]

The thienopyridine clopidogrel, which irreversibly blocks the Adenosine Diphosphate (ADP) receptor P2Y12 on platelets, has also become an essential component of therapy in patients with ACS because it helps significantly improve outcome. When comparing clopidogrel 300 mg loading and 75 mg daily dosage with placebo on a background of aspirin in NSTEACS patients, a 20% Relative Risk Reduction (RRR) in cardiovascular death, nonfatal MI and stroke was observed (clopidogrel 9.3% vs. placebo 11.4%; relative risk [RR] 0.80, 95 confidence interval [CI] 0.72-0.90, $p < 0.001$).[35] A higher loading dose of clopidogrel (600 mg) has also been shown to achieve more rapid platelet inhibition,[36] and in the recently presented CURRENT-OASIS-7 trial (European Society of Cardiology 2009 meeting, Barcelona, Spain) comparing two different regimens of clopidogrel (loading/maintenance dose regimens of 300/75 mg vs. 600/150 [1 week] to 75 mg) and aspirin (75–100 mg vs. 300–325 mg), there was a significant (15%) reduction in cardiovascular death, MI and stroke in the higher-dosed clopidogrel group.

Prasugrel — a newer thienopyridine that irreversibly binds to P2Y12 — has a more rapid onset of action and a stronger inhibitory effect than clopidogrel.[37] In comparison with clopidogrel, prasugrel shows lower variability in platelet response and no measurable vulnerability to genetic variation in CYP isoenzymes. In a randomized controlled trial[38] of moderate-to high-risk ACS patients, the primary efficacy endpoint occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (Hazard Ratio [HR] for prasugrel vs. clopidogrel, 0.81; 95% CI, 0.73-0.90; $p < 0.001$), with the authors concluding that in ACS patients with scheduled PCI, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding and probable avoidance in patients with any history of stroke/transient ischemic attack (TIA), body weight <60 kg or age >75 years.

Ticagrelor, an orally active drug that binds "reversibly" to P2Y12, was recently reported in the

PLATO study, where it was compared to clopidogrel.[39] Ticagrelor was associated with a 16% RRR with regard to the primary endpoint — a composite of death from cardiovascular causes, MI, and stroke — but no significant increase in the overall risk of major bleeding.

Glycoprotein IIb/IIIa Inhibitors

Three Glycoprotein (GP) IIb/IIIa inhibitors are currently available for use – tirofiban, eptifibatide and abciximab. The former two are used in patients who may or may not undergo immediate PCI, while abciximab is administered only when patients with ACS are being considered for early PCI. In patients undergoing primary PCI for ACS, abciximab is associated with a reduction in the composite endpoint of death, recurrent MI and target vessel revascularization.[40-42] On the other hand, tirofiban and eptifibatide have not been extensively studied, although mechanistic studies have suggested improved vessel patency.[43, 44]

In a meta-analysis of NSTEACS patients initiated early after admission, GP IIb/IIIa inhibitors reduced death and MI by 9% at 30 days ($p = 0.015$), whereas major bleeding occurred in 2.4% of patients vs. 1.4% of patients receiving placebo ($p < 0.0001$).[45] The analysis also suggested that treatment effect was greater (18% reduction in death and MI) in patients who had elevated troponin levels (9.3 vs. 11.3%, $p < 0.001$) and that GP IIb/IIIa inhibitors, when used in patients who did not undergo revascularization, were of questionable benefit. Based on current evidence, the best practice is to initiate clopidogrel in addition to aspirin and anticoagulant therapy, e.g. UFH, before diagnostic angiography for lower-risk troponin-negative NSTEACS patients, while both GP IIb/IIIa and clopidogrel should be added before angiography for high-risk troponin-positive NSTEACS patients.[30]

As for STEMI patients, evidence for the use of GP IIb/IIIa inhibitors has evolved from 4 recent trials – BRAVE 3, ON TIME 2, HORIZONS-AMI and MULTI-STRATEGY.[46-49] The results of these studies suggest that in the setting of dual antiplatelet therapy with UFH or bivalirudin as the anticoagulant, adjunctive use of a GP IIb/IIIa antagonist can be useful at the time of primary PCI (PPCI) but not as routine therapy. These agents might provide more benefit in selective use, for example, in patients with a large thrombus burden or those who have not received adequate thienopyridine loading.[50]

Antithrombotic Therapies

Despite limited data, UFH continues to be the most common antithrombotic agent in the management of ACS. The use of adjunctive UFH with streptokinase has been controversial, although a meta-analysis showed a reduction in mortality in comparison with placebo.[51] In a meta-analysis of six randomized studies of NSTEACS patients, UFH added to aspirin was associated with a nonsignificant reduction in death or MI (Odds Ratio [OR] 0.67, 95% CI 0.44-1.02; $p = 0.06$).[52]

Limitations of UFH include required monitoring of activated partial thromboplastin time, a variable therapeutic response dependent on age, weight and renal function. In comparison to UFH, Low-Molecular-Weight Heparins (LMWH) have anti-Xa and anti-IIa activity and high bioavailability, provide more consistent anticoagulation (thereby avoiding the need for monitoring), and are associated with lower risk for heparin-induced thrombocytopenia. At least nine randomized trials have compared LMWH directly with UFH (2 involving dalteparin, 1 with nadroparin and 6 with enoxaparin),[53-61] and 5 of 6 trials of enoxaparin have found end point estimates for death or nonfatal MI favoring enoxaparin over UFH with a pooled OR of 0.91 (95% CI 0.83-0.99).[30]

Among 20,479 patients with STEMI receiving fibrinolysis, enoxaparin administered for 4 to 7 days compared with UFH for 48 hours, reduced the risk of death and nonfatal MI at 30 days (9.9 vs. 12%, RR 0.83, $p < 0.001$), with an increase in the risk of major bleeding (2.1 vs. 1.4%, RR 1.53, $p < 0.001$).[62] In NSTEACS, a meta-analysis of trials comparing enoxaparin to UFH reported an overall 9% reduction in death and MI at 30 days, with a greater effect of 20% seen in trials using more conservative management and when time to PCI was greater.[63] In studies where most patients had early angiography, an increase in the risk of major bleeding was also evident in patients receiving enoxaparin in comparison with UFH, with similar rates of death or MI at 30 days and 6 months.[61]

Direct Thrombin Inhibitors

Of the direct thrombin inhibitors (lepirudin, argatroban and bivalirudin), only bivalirudin is US FDA-approved for use in ACS. In an early study of STEMI patients, bivalirudin, a short-acting direct thrombin inhibitor used as an adjunct to streptokinase, was not associated with further reduction in 30-day mortality.[64] However, in the case of PPCI, use of bivalirudin reduced major bleeding in comparison with UFH in combination with a GP IIb/IIIa inhibitor from 8.3 to 4.9% ($p < 0.001$), as well as 30-day cardiac mortality (1.8% vs. 2.9%; $p = 0.03$), total mortality (2.1 vs. 3.1%, $p=0.047$) and net adverse clinical events at both 30 days (9.2% vs. 12.1%; RR 0.76; 95% CI 0.63-0.92; $p < 0.005$; NNT = 34) and 1 year (15.7 vs. 18.3%, HR 0.84; 95% CI 0.71-0.98; $p=0.3$). These results suggest that this agent might be the antithrombotic agent of choice in PPCI.[48] For moderate- and high-risk NSTEACS, bivalirudin showed similar ischemic benefit to UFH or enoxaparin with a GP IIb/IIIa antagonist but with a 47% reduction in the risk of major bleeding (3.0 vs. 5.6%; $p < 0.001$)[65,66] and is an appropriate choice for these patients.

Factor Xa Inhibition

Fondaparinux, a synthetic factor Xa inhibitor, has been found to reduce 30-day death or MI in patients receiving fibrinolysis (10.9 vs. 13.6%; $p < 0.05$) and in those not receiving fibrinolysis (12.2 vs. 15.1%; $p < 0.01$) compared with UFH or placebo.[67] However, in patients undergoing primary PCI, there was no benefit with fondaparinux vs. enoxaparin at nine days for the composite endpoint of death, MI, or refractory ischemia (5.8% fondaparinux vs. 5.7% enoxaparin) and catheter-associated thrombus was reported 3 times more frequently (0.9 vs. 0.3%); [68] however, a 48% reduction in major bleeding (4.1 to 2.2%) was reported ($p<0.0001$). At 30 days and 6 months, however, fondaparinux was associated with a significant reduction in deaths (295 vs. 352, $p < 0.02$ and 574 vs. 638, $p < 0.05$, respectively). Fondaparinux was also associated with significant reductions in death, MI and stroke ($p < 0.007$) at 6 months and catheter-related thrombus was observed to be mitigated by the addition of UFH. Thus, fondaparinux is an appropriate choice in STEMI patients treated with or without fibrinolysis and in patients with NSTEACS, but should not be used with PPCI, pending additional clinical trial information.

In summary, all ACS patients should receive aspirin and clopidogrel/prasugrel and one antithrombin agent (unfractionated heparin, enoxaparin, bivalirudin, or fondaparinux, but not a combination). When there is increased bleeding risk and an invasive PCI strategy is planned, use of bivalirudin is supported. Although evidence also supports additive benefits of GP IIb/IIIa inhibition, such therapy should be deferred until angiographic assessment is complete. Glycoprotein IIb/IIIa inhibition, commenced in the catheterization laboratory rather than soon after admission, has been shown to reduce major bleeding (4.9 vs. 6.1%, $p < 0.01$) with a nonsignificant increase in ischemic events (7.9 vs. 7.1%, $p = 0.13$).[69]

Reperfusion for STEMI (Fibrinolysis vs. PCI)

Expeditious restoration of flow in the obstructed Infarct-Related Artery (IRA) after symptom onset in STEMI is the key determinant of short- and long-term outcomes, regardless of whether reperfusion is achieved by fibrinolysis or PCI (Table 137.6).

Although availability of an interventional cardiologist is a key determinant of whether PCI is the preferred approach, the literature suggests that this approach is superior to fibrinolysis for facilities that can offer PCI.[70] When a composite endpoint of death, nonfatal recurrent MI and/or stroke is analyzed, superiority of PPCI is based principally on evidence that it reduces the rate of nonfatal recurrent MI (Fig. 137.7).[71, 72]

Fibrinolysis

Fibrinolysis can be achieved either by using nonfibrin-specific agents (streptokinase and urokinase) via intravenous infusions or by infusions of fibrin-specific agents (tissue-type plasminogen activator [tPA])[73] that offer a mortality advantage over streptokinase. Bolus-only fibrin-specific agents (refeplase[rPA], tenecteplase [TNK-tPA])[74,75] are also available and these may achieve greater vessel patency in comparison to streptokinase with similar mortality benefit as tPA. Bolus-only agents are also associated with less systemic bleeding than tPA (TNK-tPA).[75]

The earlier the fibrinolysis, the greater the preservation of left ventricular function and reduction in mortality.[76-78] In the ICU setting, where fibrinolysis is readily available, the decision to administer a fibrinolytic is dictated by the availability of an interventional cardiologist, since not all centers are able to provide

TABLE 137.6: Reperfusion strategies for ST-elevation myocardial infarction

I. Fibrinolysis
    a. Intravenous nonfibrin-specific agents, e.g. streptokinase
    b. Intravenous fibrin-specific agents, e.g. tissue-type plasminogen activator (tPA)
    c. Bolus only fibrin-specific agents, e.g. reteplase (rPA), tenecteplase (TNK-tPA)
II. Catheter-based Reperfusion
    a. Primary percutaneous coronary intervention (PCI)
    b. Rescue PCI
    c. Facilitated PCI
    d. Routine PCI after fibrinolysis

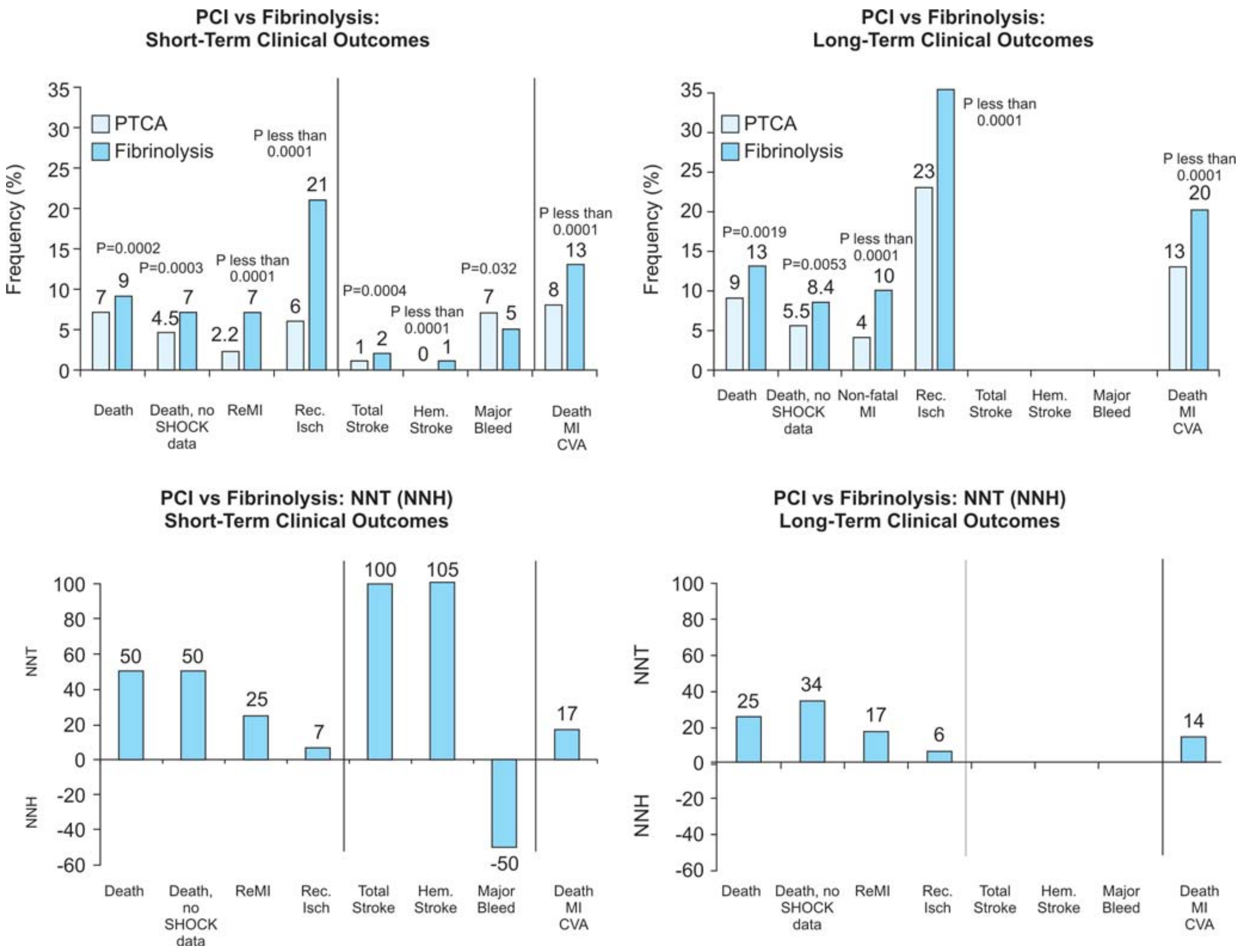

Fig. 137.7: Percutaneous coronary intervention (PCI) vs. fibrinolysis for STEMI. Short-term (4 to 6 weeks; top left) and long-term (top right) outcomes for various endpoints shown are plotted for STEMI patients randomized to PCI or fibrinolysis for reperfusion in 23 trials (n = 7739). Given the frequency of events for each endpoint in the two treatment groups, the Number Needed to Treat (NNT) or Number Needed to Harm (NNH) is shown for the short-term (bottom left) and long-term (bottom right) outcomes. The magnitude of treatment differences for death, nonfatal reinfarction and stroke varies depending on whether PCI is compared with streptokinase or a fibrin-specific lytic agent. For example, when primary PCI is compared with alteplase and the SHOCK trial is excluded, the mortality rate is 5.5 vs. 6.7% (odds ratio 0.81, 95% confidence interval 0.64-1.03, p = 0.081)

PTCA = Percutaneous Transluminal Coronary Angioplasty; ReMI = Recurrent MI; Rec. Isch = Recurrent Ischemia; Hem. Stroke = Hemorrhagic Stroke; CVA = Cerebrovascular Accident.

(From Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomized trials. Lancet. 2003; 361:13-20. Reproduced with permission from Elsevier.)

24-hour coverage of a catheterization laboratory. Catheterization laboratory staff may also not be readily available during off hours and weekends. While clinical decision-making is under way regarding the use of a fibrinolytic, it augurs well to pay consideration to the contraindications of fibrinolysis (Table 137.7).

Catheter-Based Reperfusion Strategy

Primary PCI has been compared with fibrinolysis in several randomized clinical trials,[79-99] and in the SHOCK trial,[100] which compared medical stabilization to immediate revascularization for cardiogenic shock. This wealth of information has demonstrated that PCI-treated patients experience lower short-term mortality (7 vs. 9%, $p = 0.002$), less nonfatal reinfarction (3 vs. 7% $p < 0.0001$) and less stroke (1 vs. 2%, $p = 0.0004$) than those treated by fibrinolysis.[71,72] This benefit of PCI over fibrinolysis is evident when patients are treated early after symptom onset and increases with greater delay in presentation.[101] The benefit of PCI over fibrinolysis remains dependent

TABLE 137.7: Contraindications to the use of fibrinolysis in STEMI

Absolute	*Relative (Cautious Use)*
1. Any prior ICH	1. Uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)
2. Suspected aortic dissection	2. Recent internal bleeding (within 4 weeks)
3. Active bleeding (excluding menstruation)	3. Active peptic ulcer disease
4. Ischemic stroke in past 3 months	4. Pregnancy
5. Known primary or metastatic brain tumor	5. Major surgery within past 3 weeks
6. Known cerebral AVM	6. Prolonged CPR (>10 min)
7. Significant head or facial trauma in past 3 months	7. Ischemic stroke >3 months ago

The above conditions are viewed as an advisory for clinical decision making and are not all-inclusive.
For streptokinase/anistreplase, prior exposure >5 days ago or prior allergic reaction to these agents are also relative contraindications.
Abbreviations: AVM = Arteriovenous Malformation; CPR = Cardiopulmonary Resuscitation; DBP = Diastolic Blood Pressure; ICH = Intracerebral Hemorrhage; SBP = Systolic Blood Pressure.

on timely implementation, and it has been shown that after adjustment for baseline characteristics, time from symptom onset to balloon inflation is significantly correlated with one-year mortality in patients undergoing PPCI for STEMI (relative risk = 1.08 for each 30-minute delay from symptom onset to balloon inflation; p = 0.04).[102.103] Thus, if the expected medical contact-to-balloon time exceeds the expected medical contact-to-needle time by more than 60 minutes, fibrinolytic treatment with a fibrin-specific agent should be considered unless it is contraindicated.[14] This is particularly important when symptom duration is less than 3 hours, but is less important with longer symptom duration when less ischemic myocardium can be salvaged. There is a complex interplay between the patient's age, infarct location and initial delay in presentation and the tolerable delay for achieving the benefit of PPCI over fibrinolysis. This is less important in the hospital setting (e.g. ICU), although symptoms and signs may be masked for several reasons. In general, the improved outcome of PPCI over fibrinolysis is lost earlier in patients younger than 65 years of age and in those presenting within 120 minutes of symptom onset.[104]

Rescue PCI

In patients with failed fibrinolysis, defined as ongoing chest pain and/or failure of ST-segment resolution by more than 50% at 90 minutes after fibrinolysis, rescue PCI (PCI within 12 hours of failed fibrinolysis) can achieve desirable results. In a meta-analysis of 8 trials, rescue PCI was associated with lower rates of death, heart failure and reinfarction at 6 months (29.2 vs. 41%, 11.8 absolute reduction, 95% CI 5-18, p < 0.001) than a conservative strategy of PCI only for recurrent ischemia after fibrinolysis, although rescue PCI was associated with a 3% (95% CI 0-5, p = 0.02) absolute increase in risk of stroke.[105] Percutaneous Coronary Intervention for reinfarction after fibrinolysis is also better than re-administration of fibrinolytics.[106]

Facilitated PCI

Defined as routine emergent PCI after fibrinolysis, facilitated PCI has not been associated with benefits. The ASSENT-4 PCI study[107] of 1,667 STEMI patients reported an increase in composite death, heart failure and shock compared with PPCI alone (18.6 vs. 13.4%, p = 0.005). Similarly, the FINESSE trial showed no benefit of facilitated PCI following half-dose rPA and abciximab compared with PPCI in 2,452 STEMI patients.[108]

Routine PCI after Fibrinolysis (RPAF)

Defined as early PCI within 24 hours, RPAF could potentially consolidate the benefits of successful fibrinolysis. A meta-analysis of three trials comparing routine PCI with stenting after fibrinolysis to ischemia-guided stenting after fibrinolysis showed a reduction in death of 3.8 vs. 6.7%, (OR 0.56; 95% CI 0.29-1.05, p = 0.07) and a significant reduction in death and MI at 6 months (7.4 vs. 13.2%, p < 0.01). [109] A pharmacoinvasive strategy of immediate fibrinolysis and early revascularization would be practical in many parts of the developing world, where 24-hour access to a catheterization laboratory is not possible.

Reperfusion for NSTEACS

Several studies have explored Routine Invasive Strategy (RIS) versus a Conservative Ischemia-Driven, or "cooling off", Strategy (CIDS) in NSTEACS (Fig. 137.8).[110-115] Two meta-analysis have analyzed this data.[116,117] The first, by

Mehta et al. (n = 9,212), demonstrated a greater rate of in-hospital death or MI with RIS (conservative 3.8 vs. invasive 5.2%; OR 1.36; 95% CI 1.12-1.66, p = 0.002) but a lower rate of these events after hospital discharge (conservative 11.0% vs. invasive 7.4%; OR 0.64; 95% CI 0.56-0.75, p < 0.001). A more recent meta-analysis of studies incorporating randomized controlled trials with higher rates of GP IIb/IIIa inhibitor and clopidogrel use noted a 17% relative reduction in late mortality (OR 0.83, 95% CI 0.72-0.96, p = 0.012) with RIS compared to CIDS. The majority of studies in the past 15 years on this topic have, in general, shown better outcomes with an invasive strategy over medical management, and current debate has now shifted to comparing a strategy of early, routine use of angiography with the less costly alternative of a Selective Deferred Use Strategy (SDUS).[118] Disadvantages of SDUS include the potential for the deterioration of LV function while awaiting coronary angiography and longer delays in or discharge without angiography in the highest-risk patients, such as those with heart failure or renal dysfunction.[119-123]

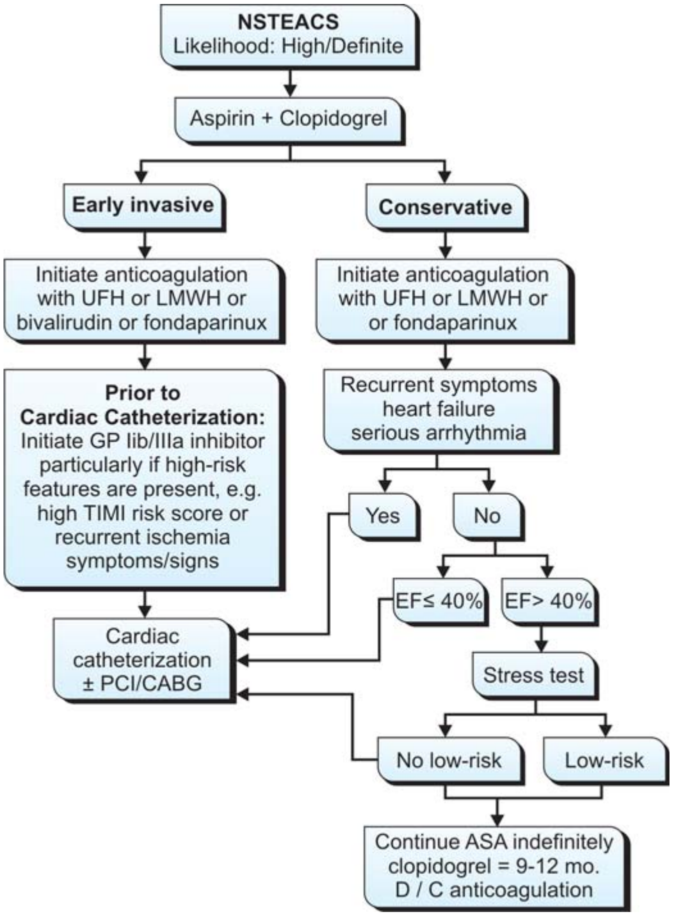
NSTEACS
Likelihood: High/Definite
Aspirin + Clopidogrel
Early invasive
Conservative
Initiate anticoagulation with UFH or LMWH or bivalirudin or fondaparinux
Initiate anticoagulation with UFH or LMWH or or fondaparinux
Prior to Cardiac Catheterization: Initiate GP IIb/IIIa inhibitor particularly if high-risk features are present, e.g. high TIMI risk score or recurrent ischemia symptoms/signs
Recurrent symptoms heart failure serious arrhythmia
Yes
No
EF≤ 40%
EF> 40%
Cardiac catheterization ± PCI/CABG
Stress test
No low-risk
Low-risk
Continue ASA indefinitely clopidogrel = 9-12 mo. D / C anticoagulation

Fig. 137.8: Algorithm for early invasive versus conservative ischemic-driven strategy in patients with NSTEACS. ASA = aspirin; CABG = Coronary Artery Bypass Graft; EF = Ejection Fraction; GP = Glycoprotein; LMWH = Low-Molecular-Weight Heparin; NSTEACS = Non-ST-Segment Elevation Acute Coronary Syndrome; PCI = Percutaneous Coronary Intervation; UFH = Unfractionated Heparin

In general, clinical evidence suggests that early provision of an invasive strategy (within 48 to 72 hours of presentation) is important in achieving lower rates of death or MI in NSTEACS.[124-126] The objective is to provide a strategy with the most potential to yield the best clinical outcome and improved long-term prognosis. Patients with NSTEACS often can be divided into different risk groups on the basis of initial clinical presentation. The TIMI PURSUIT and GRACE scores (Table 137.4) are useful clinical tools for assigning risk to NSTEACS patients, and risk stratification identifies patients who are most likely to benefit from subsequent revascularization. Where clinically appropriate, after considering comorbid conditions, early invasive management of ACS should be implemented as early as possible.

Other Therapies

Oxygen is routinely used in all patients with ACS for at least 24 to 48 hours because of the potential for hypoxemia. Analgesia is important in ACS, since inadequate pain control leads to heightened sympathetic activity, and is usually accomplished with a combination of morphine, nitrates and beta-adrenergic receptor blockers. Morphine, for example, not only is analgesic but also reduces anxiety and helps alleviate autonomic activity, besides achieving a medical phlebotomy in patients with pulmonary edema. Though no randomized trials exist for their use, nitrates are routinely used when managing ACS patients from a pathophysiological standpoint by causing coronary vasodilation and decreasing ventricular preload. There are, however, contraindications in those with inferior wall MI, right ventricular infarction, sustained hypotension (SBP <90 mmHg), and severe bradycardia (<50 bpm), and in patients who have received a phosphodiesterase inhibitor for erectile dysfunction within the last 24 hours (48 hours for tadalafil).

Based on overwhelming evidence,[127] beta-blockers in ACS are recommended routinely and are believed to help in pain relief, reduce infarct size and life-threatening arrhythmias. However, they should be avoided in patients with heart failure (rales greater than 10 cm from the diaphragm), hypotension, severe bradycardia and heart block. Angiotensin-Converting Enzyme (ACE) inhibitors or angiotensin II receptor blockers are indicated in patients with heart failure, anterior infarction, or a history of previous infarction and exert some of their effects in reducing LV remodeling. [128-130] Early initiation of statin

TABLE 137.8: Bird's-eye view of contemporary ACS management

Diagnosis

1. Immediate assessment by physician
2. 12-lead electrocardiogram interpreted within 10 minutes
3. Measurement of serum troponin concentration

Risk Stratification

1. TIMI Score
2. GRACE Score
3. PURSUIT Score

Initial Management

1. Continuous cardiac rhythm monitoring
2. Oxygen therapy
3. Antiplatelet therapy (e.g. aspirin, clopidogrel, prasugrel and/or intravenous glycoprotein IIb/IIIa receptor antagonist)
4. Anticoagulant therapy with enoxaparin, unfractionated heparin or fondaparinux
5. Immediate intravenous and oral β-blockade, if clinical scenario permits
6. Percutaneous coronary intervention, including treatment with a glycoprotein IIb/IIIa receptor antagonist or direct thrombin inhibitor and intracoronary stent implantation
7. Thrombolytic therapy with a fibrin-specific agent
8. Development of local protocols for rapid treatment of patients
9. Rescue percutaneous coronary interventions

Other Interventions

1. Risk stratification using clinical scores and assessment of cardiac function
2. Early pharmacologic intervention with statins, ACE inhibitors, angiotensin receptor blockers and/or aldosterone receptor antagonists

Treatment of Hypoxia and Cardiogenic Shock

1. Noninvasive positive airway pressure ventilation
2. Intravascular volume loading
3. Inotropic therapy
4. Intra-aortic balloon counter pulsation
5. Coronary revascularization
6. Corrective surgery for mechanical complications of acute myocardial infarction

therapy to lower low-density-lipoprotein cholesterol (LDL-C) level to below 100 mg/dl (and preferably to <70 mg/dl) is the preferred approach in ACS, although a meta-analysis of 12 clinical trials with 13,024 patients enrolled soon after ACS found no significant reduction in death, recurrent MI and stroke at 30 days compared with placebo, low-dose statins, or usual care.[131] However, two recent studies utilizing intravascular ultrasound showed that aggressive statin therapy regressed coronary artery disease following ACS,[132] particularly when an Low-Density-Lipoprotein Cholestrol (LDL-C) <70 mg/dl was achieved.[133] These findings support the notion of using even more intensive lipid-lowering therapies post ACS, a notion currently being evaluated in the IMPROVE-IT trial,[134] which is designed to achieve an LDL-C of 50 to 55 mg/dl with the combination of ezetimibe and simvastatin. Although this endpoint approaches the level of LDL-C in newborns, analysis from the PROVE IT-TIMI 22 trial demonstrated continued benefit of intensive lipid lowering among patients with baseline LDL-C values as low as 66 mg/dl.[135,136]

CONCLUSION

Therapeutic options for ACS patients have improved substantially over the past two decades, and our increased understanding of the pathophysiology underlying ACS has also meant a shift in our focus. Biotechnological innovation, such as gene-modulating strategies that favorably affect inflammation, remodeling, oxidative stress and angiogenesis, are being tested in animals and might further change the current framework (Table 137.8) of optimum treatment for patients. However, the largest gains are likely to come from improvements in the effectiveness of our ability to apply these therapies.

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Pulmonary Hypertension in the Intensive Care Unit

Neil Ninan, Amber Monson, Arthur Sung

INTRODUCTION

Pulmonary Hypertension (PH) is a rare but debilitating disease that affects individuals of all ages and walks of life. As recently as 15 years ago, a patient diagnosed with PH was given an average survival rate of 2.8 years.[1] Recent advances in treatment options have allowed patients to improve quality and quantity of life. Early diagnosis is essential to slow disease progression.

Pulmonary hypertension is defined as an increase of pressure in the pulmonary arteries where the mean pulmonary artery pressure (mPAP) is $\geq$25 mm Hg. Pulmonary Arterial Hypertension (PAH) has the additional criteria of the pulmonary capillary wedge pressure $\leq$15 mm Hg (Table 138.1). Initial screening for PH is through echocardiography with final diagnosis confirmed through right heart catheterization. Pulmonary hypertension is now considered to have five major classifications with subgroups among each[2,3] (Table 138.2).

TABLE 138.1: Classification of pulmonary hypertension by mean pulmonary arterial pressure (mPAP) into mild, moderate or severe disease

Pulmonary hypertension mPAP $>$25 mm Hg
Pulmonary arterial hypertension wedge $<$15 mm Hg

Mild	25 mm Hg $<$ mPAP $>$ 35 mm Hg
Moderate	35 mm Hg $<$ mPAP $>$ 55 mm Hg
Severe	55 mm Hg $<$ mPAP

Note: Patients with severe right ventricle or atrial dilatation and enlargement may present with lower mPAP due to right sided heart failure.

TABLE 138.2: Classification of pulmonary hypertension according to etiology. The first World Health Organization (WHO) Conference on PH was held in 1973 then again in 1998, 2003. guidelines were most recently assessed at Dana Point in 2008

1. Pulmonary arterial hypertension
    a. Idiopathic
    b. Heritable
    c. Drug/toxin induced
    d. Associated with
        i. Connective tissue disease
        ii. HIV
        iii. Portal hypertension
        iv. Congenital heart disease
        v. Schistosomiasis
        vi. Chronic hemolytic anemia
    e. Pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis
2. Pulmonary hypertension due to left sided heart disease
3. Pulmonary hypertension due to lung disease and chronic hypoxemia
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension of other mechanisms.

Adapted from: The guidelines for the diagnosis and treatment of pulmonary hypertension. Galie et al. European Respiratory Journal. 34:1219-63.

The Intensive Care Unit (ICU) presents a challenging environment for physicians and nurses caring for patients with pulmonary vascular diseases. In the intensive care unit, functional classification and diagnostic testing for etiologies of pulmonary arterial hypertension becomes difficult to perform. Patients are often sedated and mechanically ventilated, thus more thorough investigations similar to outpatient settings are not feasible. In general, clinical groups can be divided into three general categories:

1. Pulmonary venous hypertension
2. Acute onset chronic pulmonary arterial hypertension
3. Newly diagnosed pulmonary arterial hypertension (de novo).

Pulmonary venous hypertension accounts for the majority or two-thirds of the cause of right heart failure.[4] Underlying etiologies include congestive heart failure secondary to systolic and diastolic dysfunction, valvular abnormalities including aortic stenosis, mitral stenosis and mitral regurgitation.[5] Management entails standard of care therapy including preload and afterload reduction and inotropic therapy. In general, invasive hemodynamic monitoring is not required if the diagnosis is clinically compatible. In the remaining of the cases, patients with pulmonary artery hypertension require a different diagnostic and therapeutic approach to improve outcomes.

Pulmonary arterial hypertension is under-diagnosed in the ICU setting as patients are being treated for acute conditions. Quite often, PH is regarded as a secondary diagnosis and clinicians do not treat it aggressively. However, it is known that patients with PH as underlying comorbidity in the ICU have worsened outcomes if untreated.[6] This section will present a few diagnoses that are associated with significant pulmonary arterial hypertension and require more thorough investigations and consideration of advanced therapy. Furthermore, management strategies in the ICU can affect pulmonary vascular tone. Effects from mechanical ventilators and other vasoactive agents will be discussed.

HISTOPATHOLOGY

The pulmonary vasculature is lined by continuous endothelium. The subendothelial layer consists of smooth muscle cell layer that is responsible for modulating vascular tone by systemic and local factors. Over the past decade, signaling pathways and molecules are studied in order to elucidate pathogenesis of PH, as well as their therapeutic potentials (Fig. 138.1).

Nitric oxide (NO), for example, is an important vasodilator and intracellular signaling molecule. NO acts through its cellular mediator, cyclic guanosine monophosphate (cGMP), to induce vascular smooth muscle relaxation and subsequent dilation of the pulmonary vasculature.[7] Dysregulation in its synthesis can lead to vasoconstriction or pathologic hyperproliferation of the vascular endothelium. L-arginine, a precursor in the synthesis of NO, has been used clinically in the treatment of PAH, especially in patients with sickle cell disease to augment vasodilatory effects.[8,9] Other pathways and relevant molecules include arachidonic acid metabolites, prostacycline and thromboxane A2 that affect endothelial and smooth muscle cell functions and platelets aggregation; endothelin-1, a humoral factor that has potent vasoconstrictive properties especially in the pulmonary vascular endothelium.

The histological features of patients with IPAH consist of plexogenic lesions (Figs 138.2A and B). Microscopic examination demonstrates proliferation of the intima and media layers due to muscularization of the arterioles in response to shear stress. Concurrently, there is loss of elastic layers and evident of fibrosis from repair mechanisms.

RIGHT HEART PHYSIOLOGY

The Right Ventricle (RV) is a low pressure and high compliance chamber compared to the left ventricle (LV). With each cardiac cycle, the right ventricle matches the cardiac output of the left heart. Additionally, due to its less muscular conformation, RV ejection is more continuous versus the pulsatile nature of the left ventricle. Similarly, pulmonary capillaries are distensible (high capacitance) such that during exercise, for example, additional blood can be recruited for gas exchange. The pulmonary vascular reserve, therefore, enables marked increase in blood flow before significant resistance is generated, prerequisite condition for the development of pulmonary arterial hypertension.

The primary role of the right heart is to receive returning blood from the systemic venous system and deliver it across the pulmonary vasculature for gas-exchange. The systemic venous return determines the preload, where the driving pressure is the difference between the Mean Systemic Pressure and the Right Atrial Pressure (MAP-RAP). The oxygenated blood enters the left ventricle via post-capillary vasculature or pulmonary venules and veins and is then pumped through the systemic circulation by higher pressures generated by the left ventricle.

Abnormalities involving the pulmonary vasculature leading to an increase in Pulmonary Vascular Resistance (PVR) will lead to right heart strain. The ability of the right ventricle to adapt and compensate for physiologic changes depends on the acuity of the change in PVR, pre-existing right ventricular hypertrophy and its ability to extract, and utilize oxygen in different disease states. Furthermore, the transmural pressure gradient of the right ventricle is dependent upon both systole and diastole, as oppose to the left ventricle, where transmural

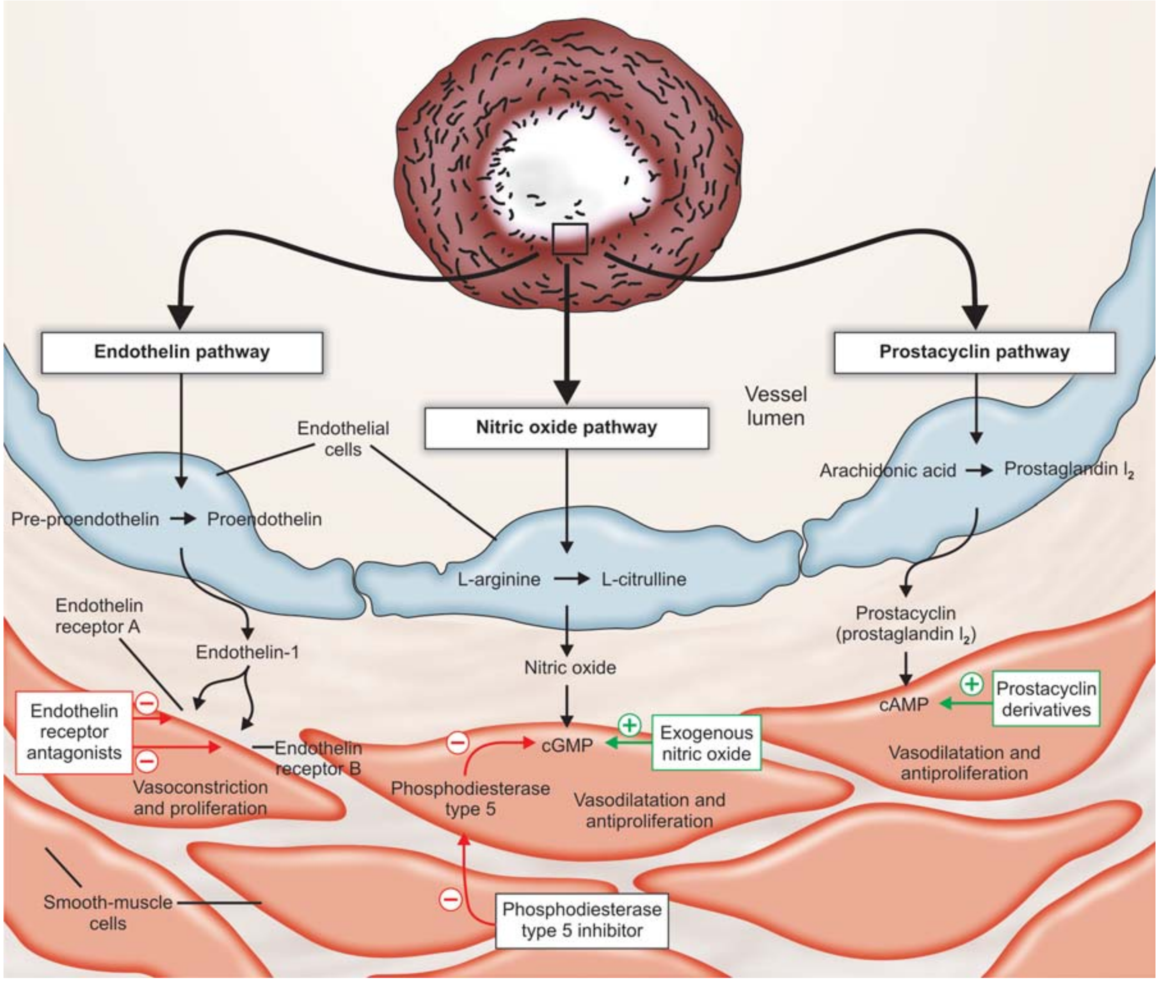

Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Pre-proendothelin → Proendothelin
L-arginine → L-citrulline
Arachidonic acid → Prostaglandin I_2
Endothelin receptor A
Endothelin-1
Nitric oxide
Prostacyclin (prostaglandin I_2)
cAMP
Prostacyclin derivatives
Endothelin receptor antagonists
Endothelin receptor B
cGMP
Exogenous nitric oxide
Vasoconstriction and proliferation
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Vasodilatation and antiproliferation
Smooth-muscle cells
Phosphodiesterase type 5 inhibitor

Fig. 138.1: The three molecular pathways that are responsible for the pathophysiology of pulmonary hypertension and through which pharmacological treatments are targeted

Adapted from: Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med. 2004;351:1425-36.

perfusion occurs during diastole. Maintenance of adequate mean systemic arterial pressure is an important aspect to be kept in mind especially for intensivists and anesthesiologists caring for critically ill patients.

It is important to recognize that the right ventricle undergoes similar adaptive responses as the left ventricle. Inability to perfuse blood across the pulmonary vascular circuit translates to inadequate left ventricular diastolic filling. Consequently, decrease in left ventricular preload causes inadequate stroke volume and inotropy. Ultimately, this compromises cardiac output to the systemic circulation. The clinical manifestations of right heart failure are peripheral edema, ascites, elevated neck veins and hypotension due to poor LV filling.

Hypertrophy is an appropriate response to RV afterload elevation, i.e. increase in PVR. In patients who cannot compensate for these changes will eventually manifest symptoms of right heart failure or cor pulmonale, as described above. Increases in pulmonary arterial pressure also increase RV afterload, which is a function of the product of RV end-diastolic volume and RV systolic pressure, the Laplace principle of wall tension. Therefore, continual elevation of RV wall stress will eventually cause cor pulmonale and hemodynamic instability. There exists a physiologic relationship among various measured and calculated variables of the right ventricle (Table 138.3). In advanced cor pulmonale, decompensatory changes occur, when the right ventricle

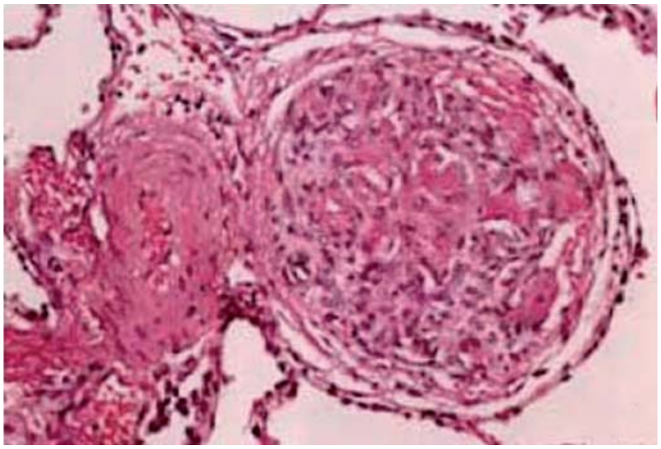
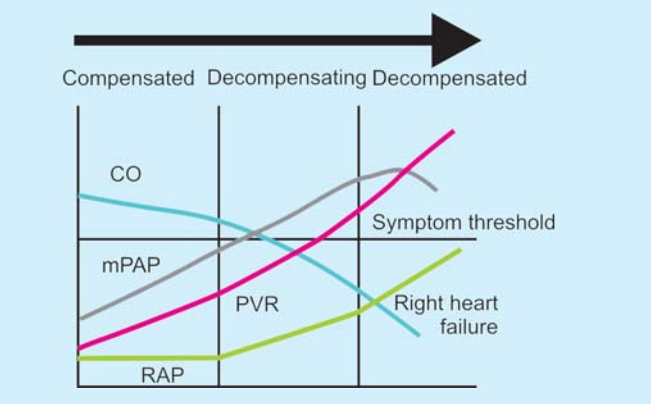


Fig. 138.2A: Plexogenic lesion typically found in PAH with smooth muscle cell proliferation and hypertrophy
Adapted from: http//www.phassociation.org/medical /advances in ph/ summer 2004/porto.asp

TABLE 138.3: Changes in cardiac output (CO), mean pulmonary artery pressure (mPAP), peripheral vascular resistance (PVR), and right atrial pressure (RAP) overtime as pulmonary hypertension progresses



Adapted from: Medscape pulmonary medicine. 2005;9(2)© 2005 Medscape
http://img.medscape.com/fullsize/migrated/513/613/mc513613.fig1.gif

can no longer adequately generate pressures to fill the left ventricle across severely high resistance.

When the right ventricle becomes markedly dilated and hypertropic, the interventricular septum is also mechanically affected and shows systolic flattening (Fig. 138.3). This D-shaped septum is a manifestation of RV pressure overload. An important consequence is interdependence, where LVEDP is elevated due to bulging of the intraventricular septum during systole and clinical manifestations of left heart failure also ensue.

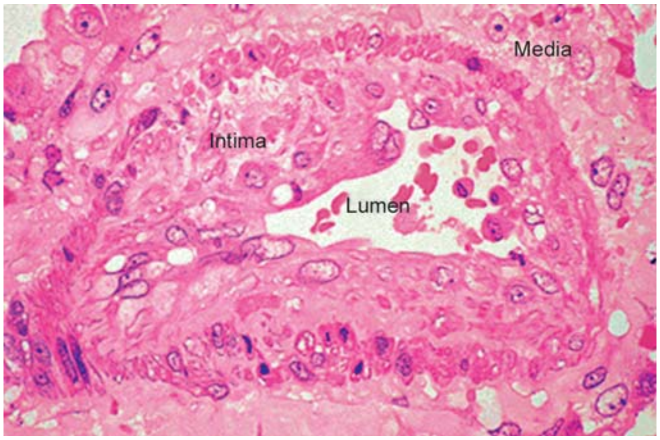


Fig. 138.2B: Vascular changes in pulmonary arterial hypertension: Pulmonary arteriole in pulmonary hypertension showing both mild medial hypertrophy and marked intimal hyperplasia, leading to partial obstruction of the lumen. *Courtesy:* Eugene Mark, MD
Adapted from: http//cmbi.bjmu.edu.cn/uptodate/vascular%20medicine/Pulmonary%20hypertension pathophysiology%20of%20secondary%20pulmonary%20hypertension.htm

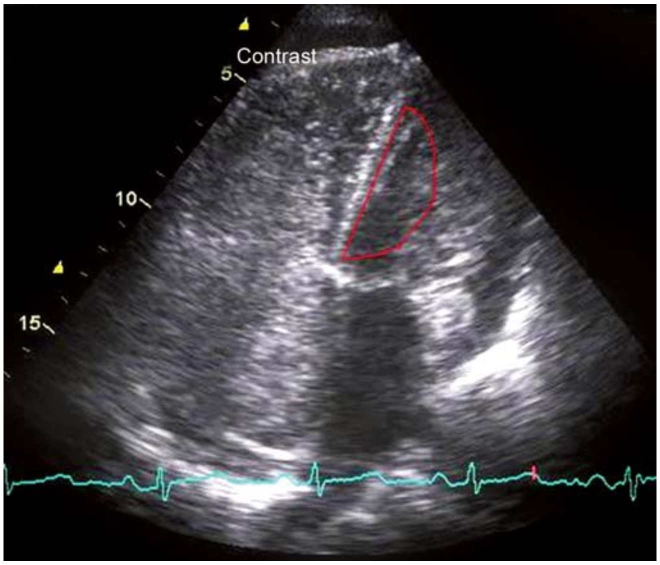


Fig. 138.3: A four-chamber echocardiographic view of the heart showing a D-shaped left ventricle, representing interventricular septal flattening

Patients in the intensive care setting are particularly susceptible to factors that can worsen pulmonary pressures. Hypoxia, leading to low alveolar FiO_2, causes hypoxic vasoconstriction that can lead to an increase in PVR. Other factors that exacerbate vasoconstriction include academia and hypothermia. Conditions that increase catecholamine release and sympathetic output such as sepsis and pain or agitation, respectively, will also worsen PVR. It is important to bear in mind that ICU patients have higher metabolic demand and they are particularly sensitive to conditions leading to right heart ischemia. Inadequate, LV filling leading to low cardiac output exacerbates global hypofusion and subsequent metabolic acidosis causes further worsening of PVR and right heart ischemia. Therefore, intensivists should be sensitive to this spiraling cycle and maximize oxygen delivery, and systemic pressures to preserve right heart function.

DIAGNOSTIC MODALITIES

Transthoracic Echocardiography

Acutely ill patients transferred to intensive care units are often too unstable for the comprehensive diagnostic modalities employed to diagnose disease, such as right heart catheterization in the laboratory. For patients with suspected pulmonary hypertension and right ventricular decompensation, bedside transthoracic echocardiography (ECHO) is an ideal diagnostic tool given its portability, non-invasive nature, as well as the ability to be repeated frequently. These attributes have positioned echocardiography as the first line modality in the assessment of right ventricular structure and function, and to estimate pulmonary artery pressure.[10,11]

Echocardiography allows clinicians to evaluate cardiac chamber dimensions, interventricular septal motion and tricuspid regurgitant jet velocity. These are important parameters for estimation of pulmonary artery pressure. Additionally, echocardiography can help establish an etiology, such as left heart failure resulting in pulmonary venous hypertension.

Doppler ECHO incorporating bubble contrast via agitated saline can detect intra- and extra-cardiac shunts. A pulmonary artery systolic pressure >40 mm Hg by ECHO is generally regarded as abnormal[12] although overestimation and underestimation of pulmonary artery pressure is frequent.[13] Nevertheless, studies indicate that echocardiographic estimates are a good correlation to actual pulmonary artery systolic pressure.[14] Raymond and collegues found in their investigations that certain parameters seen on ECHO can prognosticate patients to poorer outcomes, i.e. pericardial effusion, right atrial enlargement and septal displacement.[15]

Patient size, difficulty in positioning a critically ill patient and the level of experience of the technician can result in a poor study. This can decrease the ability for diagnosis and prognosticating pulmonary hypertension. For patients who can tolerate the procedure, a transesophageal echocardiogram yields a higher sensitivity and specificity.[16]

Pulmonary Artery Catheterization

Right heart catheterization is the gold standard for the diagnosis of pulmonary hypertension.[17] This is accomplished in the ICU setting by using a pulmonary artery (PA) catheter that is inserted through either the right internal jugular (RIJ) vein, the left subclavian vein, or femoral veins (right preferred). The RIJ is the preferred route of access as the PA catheter may be left in place for continuous monitoring of cardiac pressures. In the ICU setting, the femoral access sites although performed, are not preferred due to increased risk of infection from proximity to groin area.[18-20] Values measured include right atrial pressure (CVP), pulmonary artery systolic and diastolic pressure, and the Pulmonary Capillary Occlusion Pressure (PCOP). A PCOP $\geq$15 mm Hg suggests left sided disease while a PCOP $\leq$15 mm Hg is consistent with pulmonary arterial hypertension. In the instance of an indeterminate range of PCOP, for example, 15 to 18 mm Hg, a left heart catheterization is the only method able to confirm left heart disease or lack thereof. Therefore, collaboration with cardiology is important in this setting.

Cardiac output and cardiac index can be measured by thermodilution method. Although patients with severe tricuspid regurgitation, especially in the PH population, may give erroneous results by thermodilution. Do to this effect, the Fick's method for measuring cardiac output is preferred. The Fick's principle relies on knowing the uptake of oxygen by an organ and the concentration of oxygen in the arterial and venous circulations. Due to the cumbersome nature of calculating oxygen consumption, the Fick's determination uses a fixed value for oxygen consumption allowing one to more easily calculate the cardiac output.

$$CO = O_2\ Consumption/[(Arterial\ O_2) - (Venous\ O_2)]$$

An important calculation during right heart catheterization is pulmonary vascular resistance (PVR) expressed in Wood units. An abnormal value greater than 3 Wood units is consistent with pulmonary hypertension.

Vasodilator Challenge

Vasoreactivity challenge testing is used to differentiate patients with PAH who may benefit from high dose calcium channel blocker therapy in the outpatient setting.[21,22] Therefore, this test is not commonly performed in the ICU. For patients in the ICU on vasopressors a challenge should not be performed as the agents used can lead to systemic hypotension. Three agents are accepted for use in the vasodilator challenge: inhaled nitric oxide, intravenous adenosine and intravenous epoprostenol.[21] The test is considered positive if the mPAP drops at least 10 mmHg and is <40 mm Hg with no decrease in cardiac output after administration of the vasodilator agent.[23]

BIOCHEMICAL MARKERS

Biochemical markers have been used as a means for prognostication in the outpatient setting. Their utility in the acute setting is unclear, especially for patients in the ICU.

Troponins

Serum troponin has been extensively studied as a marker of pulmonary hypertension primarily in disease prognosis. Troponin-T release due to RV myocyte injury was found to be associated with higher heart rates and serum NT-proBNP levels, over six minutes walk distance and mixed venous oxygen saturation.[24] Serum troponin I elevation was shown to be associated with right ventricular pressure overload secondary to pulmonary embolism.[25]

Brain Natriuretic Peptide

As plasma Brain Natriuretic Peptide (BNP) and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), the biologically inactive form of BNP, are easily reproducible and relatively inexpensive, they have become useful in the assessment of right heart failure.

BNP is secreted from the cardiac ventricles and is commonly used to stratify patients with left heart failure[26] but has also been shown to be increased in right ventricular dysfunction in proportion to the level of compromise in patients with pulmonary hypertension.[27] Leuchte et al. found BNP levels to be inversely correlated to six minutes walk distance and VO_{2max} in patients with idiopathic pulmonary hypertension.[28]

THERAPY

Therapy for patients with PH in the ICU should be aimed at treating underlying causes that lead to cor pulmonale. As discussed earlier, the most common type of PH encountered in the ICU setting is pulmonary venous hypertension. There are many causes of PVH, but passive venous congestion from post-capillary vasculature is the main physiologic cause of right ventricular dysfunction. When clinical and diagnostic testing data are compatible, improving left ventricle compliance and afterload, as well as preload reduction are the primary goals of therapy.

Preload reduction of intravascular volume is the major goal of therapy in the treatment of both left and right heart failure. Pulmonary hypertension can lead to RV failure, which in turn can lead to decreased cardiac output due to under-filling of the left ventricle. Patients with signs of right ventricular failure, i.e. peripheral edema, warrant the introduction of diuresis, along with sodium and fluid intake restriction, to maintain a negative fluid balance. Judicious administration of fluid or blood products should be carefully considered due to right ventricular dysfunction, such as in the setting of sepsis. While fluid restriction and diuresis is the major goal of patients with pulmonary hypertension, the choice of which drug to use is not clear. Most patients are started on a loop diuretic with furosemide being the drug of choice. There is mounting evidence that torsemide may be a more efficacious agent.[29-32]

Patients with an established diagnosis of PAH on appropriate therapy, in general, should not have their PH medication dose adjusted or stopped, unless continuation is felt to be harmful. This is especially important with continuous prostacyclin therapy, as a reduction or discontinuation of IV infusion may cause exacerbation, or rebound pulmonary hypertension, leading to cardiovascular collapse.[33]

Inhalational pulmonary vasodilators should be considered in patients with respiratory failure and/or hemodynamic instability. Inhaled Nitric Oxide (iNO) has been studied extensively for patients with ARDS and refractory hypoxemia.[34] Although effective in the pediatric intensive care population, iNO has not been shown to improve mortality for adult ARDS, despite improvement in oxygenation.[35,36] ARDS will be discussed specifically in a later section. iNO, however, can be appropriate for the acutely unstable PAH patient with hemodynamic compromise.[37,38] The inhalational route and drug absorption is highest in ventilated areas of the pulmonary parenchyma, this optimizes drug delivery while improving ventilation and perfusion matching. On the other hand, continuous intravenous infusion of vasodilators may have significant systemic effects causing hypotension, as well as blunting the hypoxic vasoconstrictive response.

Epoprostenol is a prostaglandin with potent vasodilatory effects and is currently the only therapy with a grade A recommendation for the treatment of class IV pulmonary hypertension.[39] In trials, epoprostenol has been shown to improve hemodynamics and improve six minutes walk distances.[40,41] Intravenous treprostinil, boasting a longer half-life than epoprostenol (>4 hours vs. 6 minutes) was studied for the treatment of class III and IV pulmonary hypertension and found to also improve hemodynamics.[42]

Vasopressors

Vasopressor therapy is indicated in patients with shock, when there is inadequate cardiac output to meet metabolic demands. There are a number of vasopressor agents available in the ICU setting; with different hemodynamic effects on pulmonary vasculature (Table 138.4).

Norepinephrine is a commonly used vasopressor in the intensive care setting. It increases systemic blood pressure through vasoconstriction and a positive inotropic effect on the heart. Although norepinephrine increases the pulmonary arterial pressure to systemic arterial pressure ratio, its effect is less than that of phenylephrine.[43] Furthermore, phenylephrine was shown to worsen right ventricular function, as evidenced by an increase in the right ventricular end-diastolic pressure in patients with chronic pulmonary hypertension.[44]

Dobutamine and milrinone are agents that support inotropic states and in fact may have favorable physiologic effects on reduction of PVR. Dobutamine is a beta-1 adrenoreceptor agonist that causes increased systemic inotropic activity and vasodilation, thereby reducing left ventricular afterload. In animal models, dobutamine induced a dose-dependant decrease in PVR while also decreasing MAP with increases in cardiac output.[45]

Milrinone is a phosphodiesterase III inhibitor which potentiates the effect of cyclic adenosine monophosphate. It has been shown to significantly reduce pulmonary artery pressures in patients with pulmonary hypertension undergoing cardiac bypass and valvular surgery during the perioperative period.[46,47] As with dobutamine, its vasodilatory effects can lead to systemic hypotension. However, it can be used concurrently with vasopressin causing a lesser increase in the PVR than when combined with norepinephrine.[48]

SPECIFIC ICU DIAGNOSIS AND MANAGEMENT ISSUES

Idiopathic Pulmonary Arterial Hypertension

Patients with idiopathic pulmonary arterial hypertension (IPAH) (WHO group 1) admitted to the intensive care unit have poor prognosis. For patients already on continuous treatment with IV prostacyclin therapy, dose changes in the acute setting are neither recommended nor safe. Furthermore, nursing staff should be educated and oriented in managing the patient's pump system or transitioning to the hospital system. Even a minimal interruption of the medication infusion due to void volume in peripheral IV access can elicit significant rebound pulmonary hypertension and potential cardiovascular collapse in some patients.

For patients without a pre-existing diagnosis of IPAH, an echocardiogram is usually the first diagnostic test that detects right heart pressure elevation. It is difficult to differentiate whether right heart strain is due to long-standing undiagnosed pre-existing disease or a primary disease in the ICU setting. The decision to place a PA catheter in patients with primarily right heart dysfunction causing hemodynamic compromise is appropriate in order to of rule out other causes. In the setting of hypotension where the patient cannot tolerate fluid

TABLE 138.4: Vasoactive agents commonly employed in pulmonary hypertension management in the ICU, the receptors they act on, effects on inotropy, chronotropy, PVR, SVR, and dosing ranges

Vasoactive agents						
Medication	*Receptors*	*Inotropy*	*Chronotropy*	*Dose*	*PVR*	*SVR*
Dopamine	Dopaminergic	Vasodilatation		$\leq$5 mcg/kg/min	-	↑
	α=β	Yes	Yes	5-10 mcg/kg/min		
	α>β	Vasoconstriction		>10 mcg/kg/min		in α range
Dobutamine	β_1 & β_2	Yes	Yes	2-20 mcg/kg/min	↓	↓
Norepinephrine	α>β	Yes	+/-	0.03-1.5 mcg/kg/min	↑	↑
Vasopressin	V_1/V_2	Vasoconstriction		0.01-0.04 units/min	↓	↑
Differing Results						
Phenylephrine	α	No	No	0.05-8 mcg/kg/min	↑	↑
Milrinone	Phosphodiesterase-3	Yes	Yes	0.375 mcg/kg/min	↓	↓

resuscitation, i.e. rising CVP with worsening cardiac index, vasoactive agents should be instituted.

Initiation of continuous IV therapy needs to be performed with caution, as $\dot{V}/\dot{Q}$ mismatch and hypoxemia can ensue with nonselective vasodilatation in patients with concurrent primary respiratory disorders. Inhalational therapy, such as nitric oxide or prostacyclin, can be advantageous in this setting, as the drug is being delivered to vasculature coupled with alveolar units that are functional and thus maintaining $\dot{V}/\dot{Q}$ matching relationship.

Connective Tissue Related PH

Vasculopathies associated with connective tissue disease, such as scleroderma, are a significant contributing factor especially for patients in the ICU. Rheumatology consultation should be sought for a complete management plan in these patients. Pharmacotherapy for these patients is similar to IPAH however should transition to advanced therapies soon due to the poor expected outcome of this patient population.[49,50] Concurrent cytotoxic therapy or high-dose steroids may be indicated in patients who have a crisis related to connective tissue disease.[51]

Portopulmonary Hypertension

Portopulmonary hypertension (PoPH) is classified as group 1 disease according to the WHO. Histology of PoPH is similar to IPAH, which is characterized by plexogenic lesions in the vascular endothelium. It is hypothesized that factors including hyperdynamic state with increased shear stress, portosystemic shunting, bacterial translocation and hepatic injury, cause the imbalance between vasoconstrictive and vasodilatory mechanisms affecting vascular tone. Endothelin-1, TNF -alpha and nitric oxide pathways have all been implicated in its pathogenesis.[52,53] Furthermore, in patients with advanced liver disease, which usually lead to a hyperdynamic state, a normal cardiac output may in fact reflect a more advanced state of right heart failure. A cardiac index of 2.5 dyn/second/centimeters[5] seen in these patients is consistent with mild-to-moderate PoPH. Post-transplant survival data largely comes from multicenter liver transplant databases.[54] Advance vascular vasodilator therapy has been used as a bridge to transplantation.

Pulmonary Thromboembolic Disease

Pulmonary Thromboembolism (PTE) is a complication that can be life-threatening if not treated. With acute PTE, where the patient has no previous pulmonary vascular disease, the right ventricle will adapt but cannot generate a significant compensatory response. Therefore, these patients may present with shock secondary to right ventricular failure. This group of patients requires initial fluid resuscitation and vasopressors, similar to circumstances with right ventricular infarction. Thrombolysis therapy should be considered in patients with refractory hypotension and in dire conditions, surgical or catheter directed embolectomy may be required.[55,56] The majority of patients who survive the initial insult achieve complete recanalization and normalization of the right ventricular function.[57-59] However, a small proportion of patients with recurrent subclinical embolism or incomplete thrombolysis, are at risk for chronic thromboembolic pulmonary hypertension (CTEPH).

CTEPH is a disease that begins in the proximal vasculature of the lung. Progressive worsening is propagated by subsequent vascular remodeling and *in situ* thrombosis. Pulmonary pressures in patients with advanced disease can often rise to systemic ranges (mPAP > 65 mm Hg). The only curative therapy is surgical thromboendarterectomy which is performed in select centers with surgical and perioperative expertise.[60] For patients who are not surgical candidates, with more distal disease, limited medical literature has described the use of advanced vasodilator therapy for long-term management.[22]

Acute Respiratory Distress Syndrome

In patients with ARDS, mechanical ventilation is the primary supportive treatment modality. However, positive pressure ventilation has significant and complex interactions with pulmonary vascular mechanics. The current standard of care is to provide low tidal volume with accompanying optimal PEEP to achieve lung protection and provide adequate oxygenation. Due to poor compliance of the lung, the functional residual capacity (FRC) is reduced with alveolar collapse causing intrapulmonary shunting. Therefore, improvement in FRC by the application of PEEP counteracts the derecruitment of alveoli units and reduces intrapulmonary shunting. On the other hand, the opposite effect can lead to increased pulmonary vascular resistance when there is over-distention of the alveolar units, resulting in compression of the capillaries (Fig. 138.4).

The right ventricular filling pressure, as discussed previously, is dependent on systemic venous return. In the setting of positive pressure ventilation, an increased intrathoracic pressure impedes venous return and therefore compromises preload. Additionally, PEEP has

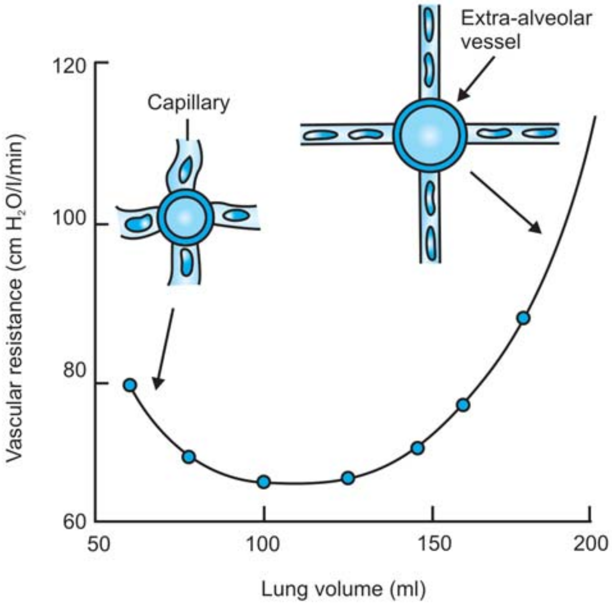


Fig. 138.4: Demonstrates the relationship between pulmonary vascular resistance and lung volumes. Illustrations represent the effects of this relationship on the alveolar vessels

Adapted from: http://rfumsphysiology.pbworks.com/Control-of-Pulmonary-Blood-Flow from JB West, Pulmonary Physiology—The Essential, 7th Edition

multiple effects on right ventricular afterload. While high intrathoracic pressure may worsen PVR by compression of the capillaries, improving oxygenation will also blunt the hypoxic vasoconstrictive response and therefore improve PVR. It behoves the clinician to exercise clinical judgment with ventilator management. Jardin and colleagues have reported a high incidence of right ventricular failure in patients with ARDS.[61] Upto 25% of this patient population manifests cor pulmonale.[62] The outcome is also worsened with greater than three times the likelihood of death.[61] The recommendation for patients with ARDS needing mechanical ventilation management is to be judicious in applying PEEP and limiting the plateau pressure at 30 mm H_2O or less.[63,64]

Perioperative Management

Pulmonologists and intensivists are often requested to evaluate patients in the ICU for perioperative management of PH. It is crucial that close communications are maintained among the consultant, surgeon and especially the anesthesiologist. The preoperative period allows the opportunity to optimize the patient's cardiovascular status. For patients with advanced disease with clinical signs of decompensation, earlier admission to the ICU is reasonable to manage volume status as well as in improving right ventricular function.

There are no clear advantages of performing surgical procedures under general versus local for example, spinal epidural anesthesia. On the other hand, the type and duration of a surgical procedure pose significant impacts on the outcomes of patients with PH. Cardiothoracic and major vascular surgeries entail the highest perioperative risks. More specifically, in cases where patients undergo valvular replacement in order to improve pulmonary venous congestion, cardiac surgery historically has the highest risk of death with advanced disease. In general, for patients with PH associated with severe mitral regurgitation, replacing or repairing the mitral valve can improve pulmonary vascular resistance to a certain extent. Performing a right heart catheterization before and after valvular replacement is indicated for patients who may have significant residual precapillary disease (vascular remodeling) and may benefit from advanced vasodilator therapy.

Certain clinical factors have predictive values for postsurgical outcomes. Patients with functional class III or IV, elevated right atrial pressure greater than 12 mm Hg and reduced cardiac output, confer an increased morbidity and mortality. Ramakrishna and colleagues also described morphologic features on ECHO, such as interventricular septal diastolic flattening and pericardial effusion to be worse predictors.[15]

SUMMARY

Physicians working in the intensive care setting should be knowledgeable in the diagnosis and management of patients with PH. With the advent of advanced therapies, it is essential to understand the vascular physiology and pharmacotherapy, due to co-morbid conditions often existing in this population. Similarly, conditions that can worsen pulmonary vascular resistance, such as increasing airway pressures from mechanical ventilation and metabolic derangements, should be recognized and managed promptly, as decompensation can occur abruptly. Finally, communication and education with other clinicians and specialists is essential to ensure optimal outcomes of patients with this complex disease.

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Pediatric Critical Care

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INTRODUCTION

After birth, lungs of a neonate undergo a change that involves a transition from fetal to neonatal circulation and the absorption of the lung fluid. The first few breaths facilitate the drainage of lung fluid and establish Functional Residual Capacity (FRC). The process of the maintenance of the FRC is facilitated by the presence of endogenous surfactant. Thus, surfactant deficiency or its inactivation can lead to decrease in FRC and inadequate gas exchange.

Transition from fetal to neonatal circulation involves decrease in pulmonary resistance as a result of the expansion of lungs, fall in arterial CO_2, rise in pH and O_2, an increase in systemic blood pressure and the closure of ductus arteriosus.[1-3]

The causes of respiratory distress in a neonate include surfactant deficiency, delayed absorption of lung fluid, aspiration of meconium into the lungs and failure of decrease in pulmonary resistance leading to persistent of fetal circulatory pattern. Group B Streptococcal infection is also a leading cause of neonatal respiratory distress.[4-7] Furthermore any anatomical abnormality in the respiratory tract or related structures may also lead to respiratory difficulty.[8]

Significant advances in the understanding of the physiology of premature neonate and the advancement in technology have markedly improved the outcome of these patients. Newer modes of treatment include the use of Inhaled Nitric Oxide (iNO) to lower the pulmonary resistance, High Frequency Oscillatory Ventilation (HFOV), and Extracorporeal Membrane Oxygenation (ECMO).[9]

Lung Fluid: Approximately 30 ml/kg of fluid fills the fetal lung. It contains large amount of chloride, small amounts of bicarbonate and almost no protein. Fetal lung fluid is secreted at 4–5 cc/kg/hr as a result of the active secretion of chloride ions into the pulmonary fluid.[10] The pressure in the trachea exceeds that in the amniotic fluid by about 2 mmHg. Thus amniotic fluid rarely enters the developing lung, except in the circumstances of fetal distress. The lung must clear this liquid soon after birth in order for the fetus to complete the transition from intrauterine to extra uterine life. The process of clearing begins two to three days before birth with a decrease in the rate of secretion of fetal lung liquid. During active labor and delivery, the fetal lung fluid decreases to about 35% of the earlier volume.[11,12] The remaining amount must be absorbed after the birth. When the lungs expand, water moves rapidly from the air spaces into the interstitium, subsequently absorbed by lymphatics and pulmonary blood vessels. Delayed absorption of the pulmonary fluid leads to transient tachypnea of newborn,[13] more common among infants born by a C-section to mothers who did not go into active labor.[14,15]

Clinical Assessment of Respiratory Distress in a Neonate

Clinical signs commonly used to assess the pulmonary function in a neonate are: respiratory rate, retractions, nasal flaring, grunting and cyanosis.[16]

Respiratory Rate: Patients with abnormal elastic and resistive components of the work of breathing tend to adjust their respiratory rate to minimize the work. Thus, in patients with decreased lung compliance, such as Respiratory Distress Syndrome (RDS), respiratory rate is rapid and shallow, whereas patients with increased airway resistance (such as caused by subglottic stenosis) may exhibit respiration that is slower and deeper.

Retractions: The negative intrapleural pressure generated during inspiration is determined by the balance between the force of the diaphragm and the compliance of the lung and the chest wall. The neonatal chest being very compliant, substernal, subcostal, and intercostal retractions are readily seen with relatively small changes in lung mechanics. In neonates with respiratory distress, retractions become more apparent as the lungs compliance decreases. Sever retractions may also indicate the complications of respiratory diseases, such as airway obstruction, misplacement of an endotracheal tube, pneumothorax or atelectasis.

Nasal Flaring: The enlargement of the effective air passage produced by the activation of alae nasi results in the reduction of the resistance. Because newborns are obligatory nose breathers, nasal resistance contributes significantly to the total lung resistance. It is commonly observed in infants with respiratory distress.

Grunting: During normal respiration, the vocal cords abduct during inspiration and adduct during expiration with out producing any sound. In the presence of increased work of breathing, neonates attempt to compensate by closing their vocal cords during expiration there by increasing lung volume that leads to an improved ventilation/perfusion ratio. Expiration through partially closed vocal cords produces the grunting sound.

Cyanosis: Cyanosis reflects the presence of a minimum of 5 g/dl of reduced hemoglobin in systemic capillaries. Peripheral cyanosis is often a manifestation of peripheral vascular constriction in response to low environmental temperature or low cardiac output state. Central cyanosis is always pathological and manifestation of significant hypoxia.

PERSISTENT PULMONARY HYPERTENSION OF THE NEONATE (PPHN)

Because of the high pulmonary vascular resistance prior to birth, blood is diverted away from the lungs through the foramen ovale and the patent ductus arteriosus into the low resistance systemic and placental circulation.[17] After abolition of placental circulation, pulmonary resistance should decrease and allow the increased amount of blood flow to lungs accompanied by, increase in systemic vascular resistance, increase in the left ventricular and left atrial pressure that in turn results in functional closure of the foramen ovale. The ductus functionally closes in the full-term infant by 24–36 hours after birth.

Persistent pulmonary hypertension of the newborn is the result of elevated pulmonary vascular resistance to the point that venous blood is diverted through the ductus arteriosus and foramen ovale away from the lungs into the systemic circulation resulting in systemic arterial hypoxemia. It is essential to rule out cyanotic heart disease that can clinically mimic PPHN. It can be classified into three forms:

i. Primary pulmonary hypertension: No evidence of parenchymal disease with radiographically normal lungs.
ii. Secondary: PPHN associated with parenchymal diseases, such as hyaline membrane disease, meconium aspiration or pneumonia.
iii. PPHN associated with hypoplasia of the lungs and reduction of capillary number—diaphragmatic hernia.

Pathophysiology

Failure of pulmonary vascular resistance to decrease after birth, despite improved alveolar oxygenation, lung expansion and increased systemic resistance results in continuing blood flow through the foramen ovale and ductus arteriosus from right to left. With inability to increase pulmonary blood flow, the arterial oxygen tension falls to very low levels. In order to pump blood to either vascular bed, right heart is subject to a large mechanical load in the presence of high pulmonary (suprasystemic) and systemic resistances. Several mechanisms have been proposed that may lead to persistent pulmonary hypertension:

1. High dose intake of aspirin by mothers near term may lead to the intrauterine closure of the ductus with the redirection of blood flow into the high-resistance fetal pulmonary vasculature may occur.
2. There is pathologic evidence that babies with PPHN have greater thickness of medial muscle in pulmonary arteries than in normal full-term infants. This has been attributed to repeated intrauterine hypoxia that stimulates the hypertrophy of medial smooth muscle that surrounds pulmonary arterioles, resulting in the constriction of vessels to an extreme degree for the long periods of time. This may lead to abnormal responsiveness of the pulmonary vasculature to

hypoxia with an inability to relax after the stimulus for vasoconstriction is removed, i.e. birth asphyxia.

3. Poor regional ventilation and alveolar hypoxia may lead to localized vasoconstriction.
4. Congenital Diaphragmatic Hernia (CDH) or other causes of pulmonary hypoplasia are frequently accompanied by the undergrowth of the pulmonary vascular tree and increased vascular resistance.
5. Nitric oxide, eicosanoids, endothelin leukotrienes, tumor necrosis factor and platelet-activating factors are among some of the vasoactive mediators that play a role in transitional circulation. Alterations in the levels of these substances may lead to pulmonary vasoconstriction.
6. Pathological evidence of platelet-fibrin microthromboembolism has been reported in infants who succumb to PPHN. The mechanical obstruction caused by these microthrombi and vasoconstriction caused by the accompanying released vasoactive mediators may induce pulmonary hypertension.[17]

Diagnosis

Primary PPHN presents in the early postnatal period as cyanosis and tachypnea that closely mimic the presentation of cyanotic congenital heart disease. There may be differential cyanosis between the upper and the lower body. The lung fields are usually clear on a radiograph. The degree of hypoxia is variable and the $PaCO_2$ is normal or low.

Secondary PPHN presents primarily as respiratory distress due to the underlying lung disease. As the lung disease deteriorates and patient needs increasing respiratory support, PPHN becomes apparent. Chest radiograph findings are consistent with the underlying disease.

Echocardiography should be performed to exclude congenital heart disease, determine the pulmonary artery pressure, presence, degree and direction of shunt through the duct and foramen ovale, and right or left ventricular function and output. In both the groups of PPHN, the evidence of tricuspid incompetence may be present.[18-21]

Management

The treatment is aimed at the maintenance of normal arterial levels of oxygen and its delivery to the organs of the body, minimizing pulmonary vasoconstriction. The most potent natural pulmonary vasodilators are oxygen and optimal lung inflation.

Oxygen

Early improvement of alveolar oxygenation with supplemental oxygen in the presence of pulmonary parenchymal disease is particularly useful as it often results in the relaxation of the pulmonary arteries and improved pulmonary blood flow. The PaO_2 should be maintained between 80–100 mmHg. Higher levels of inspired oxygen offer no benefit, but may instead contribute to secondary lung injury.

Conventional Ventilation

This is the mainstay of respiratory support. The ventilatory strategy should be based according to the underlying pulmonary disease, if any. Patients should be well sedated, the term and near term babies even paralyzed to ensure optimal ventilator efficiency. It is often necessary to ventilate with high minute volumes (>300 ml/kg) in order to achieve normal blood gases. Small reductions in minute volume that may occur with retained secretions or minor painful procedures may lead to significant changes in oxygenation.

Sedation

Catecholamines stimulate the alpha-adrenergic receptor release, thereby increase pulmonary vascular resistance. Use of a strong narcotic analgesic, like fentanyl at a dose of 3–8 micrograms/kg/hour can prevent pulmonary vasospasm due to minor variability in oxygenation. Alternatively, continuous infusion of morphine sulfate starting at 10 micrograms/kg/hour and/or bolus or continuous infusion of lorazepam may be used. *Paralysis* is usually achieved with Pancuronium bromide administered every 1–3 hours, intravenously at 0.1–0.2 mg/kg/dose. $PaCO_2$ should be maintained between 35 to 40 mm Hg, lower levels than this may cause cerebral vasoconstriction.[22,23]

High Frequency Oscillatory Ventilation (HFOV)

The best effect of HFOV is seen in babies with underlying severe lung disease. It probably works by allowing better lung inflation and alveolar recruitment.[23,24]

Inotropes

Low ventricular outputs are common in these babies. Low output may reflect the inability of right ventricle to pump blood through the lungs against high resistance, which in turn causes a low left ventricular output. In animal studies, dopamine has similar vasoconstrictor activity on the pulmonary as on the systemic vasculature, so at an empirical level, dobutamine is the preferred inotrope starting at 10 micrograms/kg/min.

Significant increase in ventricular outputs with nitric oxide in term babies has been reported, this may be a more rational approach to circulatory support than inotropes.[17]

Vasodilators

Vasodilators that have been used to treat pulmonary hypertension include tolazoline, prostacyclin, magnesium sulfate and nitric oxide. Tolazoline and prostacyclin have been widely used and both drugs have similar vasodilator effects on the systemic and the pulmonary circulation and may cause systemic hypotension. Prostaglandin I_2 (prostacyclin) one of the major endogenous pulmonary vasodilators, is normally produced by the lung when lung vessels are in a constricted state. Whether PPHN is the result of faulty PGI_2 production is not known. Administration of pharmacologic doses of PGI_2 to babies with persistent pulmonary hypertension has proven successful even when tolazoline failed.

Inhaled nitric oxide, a more specific pulmonary vasodilator has become the therapy of choice in term infants with PPHN. In babies with secondary PPHN, the effects of NO are augmented by HFOV.[25] Inhaled nitric oxide directly activates soluble guanylate cyclase resulting in the increased levels of cyclic-GMP in vascular smooth muscle cells. This results in vascular relaxation by prohibiting myosin protein cross-bridge formation in smooth muscle.[26-28] Extracorporeal membrane oxygenation should be considered only in babies who fail to respond to HFOV and NO. Since the introduction of NO and HFOV, the need for ECMO has declined.[29,30]

APNEA

Apnea in a neonate is defined as the cessation of inspiratory gas flow for 20 seconds, or for a shorter duration if accompanied by bradycardia (heart rate less than 100 beats per minute), cyanosis, pallor or desaturation as observed on pulse oxymeter.

Types of Apnea

Obstructive apnea is characterized by the presence of inspiratory muscle activity without inspiratory airflow where as *central apnea* is defined as the absence of inspiratory muscle activity. An obstructive apnea may be followed by central apnea, thus both types may occur during the same episode; termed as *mixed apnea.*

Apnea of Prematurity: Incidence and severity of apnea in premature infants are both inversely related to gestational age. Approximately 50% of infants of less than 1,500 grams birth weight require either pharmacological intervention or ventilatory support for recurrent prolonged apneic episodes. The peak incidence occurs between five and seven days postnatal age. It usually resolves between 34 to 36 weeks postconceptual age. However, apnea of prematurity has been reported to occur up to 41 weeks of postconceptual age in extremely low birth weight infants.[31,32]

Epileptic Apnea: Neonates can develop apnea during seizures. It may be difficult to distinguish this type of apnea from the one due to other causes. Epileptic apnea is usually accompanied by initial tachycardia followed by bradycardia if seizures are prolonged, where as nonepileptic apnea is frequently accompanied by early bradycardia. Continuous EEG monitoring can also be useful in distinguishing the two types.

Etiology

Apnea of prematurity is the most common cause of apnea in the neonatal intensive care unit. It is a specific diagnosis of exclusion. Other causes should be looked for if the apnea progresses in severity, fails to respond to appropriate therapy, severe episodes occur on the first day of life, or if it appears at a gestational age when it should not occur. Apnea in a term or near term infant in the absence of maternal sedation or hypoxia at birth should raise suspicion of some serious underlying cause.

Several factors that can lead to apnea include cardiac and lung disease, sepsis, neurological disorders (such as intracranial hemorrhage of various types, neonatal seizures, hypoxic ischemic encephalopathy or other disorders that lead to increased intracranial pressure), exposure to various drugs (narcotics, beta-blockers), hypoglycemia, hyponatremia, hypocalcemia or hypercalcemia, acidosis, hypothermia or hyperthermia, hematological (severe anemia), and gastrointestinal factors like NEC or gastroesophageal reflux.

Pathophysiology of Apnea

Developmental Immaturity: More frequent occurrence of apneic episodes in immature infants and decrease in their frequency during the period in which brainstem conduction time of the auditory evoked response shortens with advancing gestational suggests that the immaturity of brainstem control of central respiratory drive may be a contributory factor for the apnea of prematurity.[33]

Sleep State: Rapid Eye Movement (REM) sleep is marked by irregularity of frequency, as well as the depth of breathing. Since REM sleep predominates in the preterm infants, they are prone more frequently to apneic episodes.[34,35]

Immature Response to Peripheral Vagal Stimulation: Stimulation of laryngeal receptors in the adult results in coughing while the stimulation of the same receptors in the premature infant results in apnea. Gavage feeding, aggressive pharyngeal suctioning and gastroesophageal reflux may also induce this reflex apnea.

Chemoreceptor Response: Increased breathing effort and ventilation in response to elevated carbon dioxide level reflects predominantly central medullary chemoreceptor response and to a lesser extent, carotid body chemoreceptor activity. The ventilatory response to increased carbon dioxide is decreased in preterm infant with apnea than in those without apnea, which suggests that abnormal respiratory control may contribute to the causation of apnea.

Adults respond to decreased inspiratory oxygen by a sustained increase in ventilation. In contrast, preterm neonates respond to decrease inspiratory oxygen by initial increase followed by a sustained depression of ventilation, or even apnea. This biphasic response may represent initial peripheral chemoreceptor stimulation followed by the overriding depression of the respiratory center as a result of hypoxia. Progressive decrease in inspiratory oxygen also causes a significant flattening of carbon dioxide response in preterm infants.[36]

Obstructive Apnea: A pause in alveolar ventilation occurs due to the obstruction of airflow within the upper airway, particularly at the level of the pharynx. Because the muscles (genioglossus and geniohyoid) that are responsible for keeping the airway open are too weak in the premature infant, the pharynx tends to collapses from negative pressure generated during inspiration. Neck flexion may worsen this form of apnea.[37,38]

Mixed Apnea: A combination of both types of apnea represent as much as 50% of all episodes.[39]

Monitoring

All newborns less than 34 week gestational age should be monitored for both apnea and bradycardia. An alarm should sound if respiration ceases for more than 20 seconds or if the heart rate drops below 100 bpm. Impedance monitors routinely used in neonatal intensive care units cannot detect obstructive type of apnea because chest movement is present with no airflow. Such apneic episodes may only be detected when the monitor displays bradycardia. Also reflex apnea can lead to bradycardia within the seconds of onset, thus setting off the cardiac alarm 10 to 15 seconds ahead of the apnea alarm.

Management

When the monitor alarms sounds, the infant should be observed for the signs of breathing and skin color. If detected to be apneic, pale, cyanotic or bradycardic*, tactile stimulation* should be provided. If the infant does not respond, *bag and mask ventilation* along with suctioning should be applied. Oxygen saturation should be maintained between 88 to 92% with supplemental oxygen if needed.

Nasal Continuous Positive Airway Pressure (CPAP) of 3–4 cm of water may be needed in patients in whom the apnea is recurrent. CPAP splints the upper airway with positive pressure during both inspiration and expiration, thereby preventing pharyngeal collapse. Its use can reduce the frequency of both obstructive and mixed types of apneas. Other mechanisms include the alteration of the Hering-Breuer reflex, stabilization of the chest wall musculature and elimination of the intercostal inspiratory inhibitory reflex. Extreme degrees of flexion and extension of neck should be avoided. Suctioning of pharynx should be performed cautiously since suctioning itself may stimulate reflexes that lead to apnea. Infant should be evaluated for any underlying cause, so that therapy can be directed accordingly.

Pharmacological Therapy: The most common drugs used to treat the apnea of prematurity are the *methylxanthines* (caffeine and theophylline).

Methylxanthines antagonize adenosine, a neurotransmitter that inhibits the respiratory drive and cause respiratory depression. By blocking inhibition, stimulation of respiratory neurons results in an enhancement of minute ventilation, chemoreceptor sensitivity to CO_2, and cardiac output. Other mechanisms by which methylxanthines may reduce apnea include an improvement of diaphragmatic activity and the stimulation of the respiratory center.

Aminophylline is administered as a loading dose of 5–6 mg/kg (PO or IV infusion over 30 min) followed by a maintenance dose 1.5–2 mg/kg/dose (IV or PO given q8–12 hr) started 8–12 hours after the loading dose to achieve the therapeutic level (6–13 mcg/ml). Plasma half life of aminophylline is about 20–30 hours. Trough level should be obtained at 48–72 hours after loading dose. Levels of >20 mcg/ml are considered toxic.

Aminophylline has a narrower difference between toxic and therapeutic range compared to caffeine.

Caffeine citrate is administered as a loading dose of 20 mg/kg (PO or IV as a single or divided in two doses of 10 mg/kg each) followed by a maintenance dose of 2.5–5 mg/kg/dose (PO/IV Q24 hours), started 24 hours after the loading dose. Therapeutic level of caffeine is seen between 5–25 mcg/ml. Trough level may be obtained on day 5 or 6 after the loading dose.

Since toxic level is greater than 40–50 mcg/ml, there is greater margin of safety routine monitoring of blood levels may not be needed. Caffeine citrate has a longer plasma half-life of 40–230 hours and has fewer side effects. Methylxanthine therapy is usually continued until the infant has reached 32–37 weeks postconceptual age and apneic episodes have ceased. Patients should be monitored for any recurrence of apnea, at least for five days after the medication has been discontinued. Major side effects of methylxanthines are tachycardia, vomiting, feeding intolerance, jitteriness and seizures. Generally the dose is held if heart rate exceeds 180/minute.[40]

Intermittent Mandatory Ventilation (IMV) may be needed, if significant apnea persists despite using both pharmacotherapy and CPAP administration. It has been recently suggested that Nasal Intermittent Positive Pressure Ventilation (NIPPV) is more beneficial than CPAP alone in reducing frequency of apnea of prematurity.[41]

SIDS and apnea of prematurity: Although preterm infants constitute about 18% of all infants with SIDS, only 2 to 4% of SIDS cases had a hospital record of apnea of prematurity. The factors that reduce the risk of SIDS include sleeping on the back, encouraging breast feeding, avoiding exposure to smoking and overheating.[42]

Meconium Aspiration Syndrome

Meconium Aspiration Syndrome (MAS) is defined as respiratory distress in an infant born through Meconium-Stained Amniotic fluid (MSAF) whose symptoms cannot be otherwise explained. It is caused by the aspiration of meconium that may occur in utero or after delivery with the first few breaths. About 13% of all live births are associated by MSAF while only 5% of those born through MSAF develop MAS. MAS accounts for about 1,000 deaths annually in the United States.[43,44]

Pathogenesis

Passage of meconium by the fetus into the amnion fluid does not necessarily indicate fetal distress. It may represent an adaptation reflux developed by a mature fetus with age appropriate levels of motilin in gastrointestinal tract. Cord or head compression also may lead to the passage of meconium through vagal stimulation in the absence of fetal distress. Passage of meconium may also be secondary to an "in utero" stress as a result of fetal hypoxia and acidosis producing relaxation of the anal sphincter. Term and postmature fetuses are more likely to pass meconium in response to such a stress than preterm. Perinatal conditions that increase the risk of MAS include maternal hypertension, diabetes mellitus, heavy cigarette smoking, preeclampsia, eclampsia, intrauterine growth retardation, oligohydramnios and intrauterine hypoxia due to any other cause.

Chronic fetal hypoxia and acidosis may lead to fetal gasping leading to "in utero" aspiration of meconium. Vigorous infant who aspirates meconium-stained fluid from the nasopharynx at birth, usually develops milder form of disease as compared to the severe cases caused by chronic fetal hypoxia.[45]

Mechanisms of Injury

Aspiration of meconium can adversely affect the lung function secondary to partial or complete mechanical obstruction of airways, inactivation of surfactant, vasoconstriction of pulmonary vessels, and chemical pneumonitis.[46] "Ball-valve" effect secondary to partial obstruction leads to air trapping in the alveoli with ventilation and perfusion mismatch and increased risk of air leak syndromes, complete obstruction of the small airways leads to atelectasis. The risk of pneumothorax is estimated to range from 15 to 33%.

Full-term infant with MAS can develop secondary surfactant deficiency due to inactivation that leads to increased surface tension with atelectasis, diminished lung compliance, decreased lung volumes and resultant poor oxygenation. Meconium has a direct inhibitory effect on the function of surfactant and displaces surfactant from the alveolar surface.[47-50] It causes chemical pneumonitis associated with the release of cytokines, such as tumor necrosis factor-α, interleukin-1β, and interleukin-8, may directly injure lung parenchyma or lead to vascular leakage, which causes toxic pneumonitis with hemorrhagic pulmonary edema. Vasoconstriction caused by several underlying factors like hypoxia, acidosis, release of vasoactive mediators like eicosanoids, endothelin-1, and prostaglandin E_2 (PGE_2) may lead to persistent pulmonary hypertension.[47]

Diagnosis

Diagnosis of MAS should be considered in any infant born through MSAF who develops respiratory distress.

The radiographic findings include diffuse, asymmetric patchy infiltrates, consolidation or atelectasis, over aeration leading to air leak syndromes, such as pneumothorax, pneumomediastinum or pulmonary interstitial emphysema.[51] A two-dimensional echocardiogram to evaluate for pulmonary hypertension, may be useful early in an infant's course.

Perinatal Management

MSAF should be considered a possible warning sign of fetal distress. It is recommended that obstetricians should monitor the fetal heart rate tracing and have a low threshold for performing additional testing, such as fetal scalp pH.

Amnioinfusion: It involves infusion of a sterile isotonic solution into the amniotic cavity in order to dilute the meconium. It also increases the volume of amniotic fluid and thereby, decrease the risk of cord compression, which could be a cause for fetal hypoxia and fetal gasping. A recent meta-analysis found a 76% reduction in MAS with amnioinfusion. However, benefits of prophylactic amnioinfusion for MSAF when the fetus otherwise seems well, are not clear.[52-54]

Intrapartum Suctioning: It involves suctioning the mouth, pharynx, and nose as soon as the head is delivered, before the shoulders are delivered in a cephalic presentation or immediately after the head is delivered with a breech presentation. Although intrapartum suctioning has been considered a standard procedure for more than two decades, a multicenter, randomized controlled trial has demonstrated that routine intrapartum oropharyngeal and nasopharyngeal suctioning of term-gestation infants born through MSAF does not prevent MAS.[55-58]

Neonatal Management: The nature of pediatric intervention in infants born through MSAF depends on whether the infant is depressed or vigorous. An infant with a strong respiratory effort, good muscle tone, and a heart rate more than 100 beats/min is defined as vigorous. In such an infant, intubation is not indicated.[59] When an infant is depressed, the upper airway and the oropharynx should be cleared as soon as possible in order to minimize the amount of meconium aspiration. The infant is placed under a radiant heater, drying and stimulating is delayed. Direct laryngoscopy should be performed, mouth and hypopharynx suctioned under direct vision with a 12F or 14F suction catheter, followed by intubation. A negative suction (approximately 100 mm Hg) is directly applied to the endotracheal tube as it is slowly withdrawn. The process may be repeated until no additional meconium is recovered.[56-59] Most infants born through MSAF do not require any intervention and can stay with their mother. However, these infants should be closely monitored for signs of respiratory distress. These infants may exhibit features of postmaturity, such as peeling, yellow staining of skin, long fingernails, and stained umbilical cord. Besides the other signs of respiratory distress, the chest may appear barrel shaped as a result of over inflation. Rales and rhonchi may be heard on auscultation. Most infants who develop symptoms do so in the first few hours of life. Infants at risk for MAS who show signs of respiratory distress, must be transferred to the Neonatal Intensive Care Unit (NICU). The type of respiratory support depends upon the severity of respiratory distress. It varies from simple oxygen hood to mechanical ventilation, iNO and even ECMO. *In sever cases of MAS, a vicious cycle of hypoxemia that leads to acidosis, which together cause pulmonary vasoconstriction and lead to PPHN.* PPHN should be managed as described in section on PPHN.[60]

Surfactant

Use of surfactant in the severe cases of MAS has been demonstrated to decrease the need for ECMO and a possible reduction in the risk of pneumothorax.[50, 60]

Surfactant Lavage: It has been suggested that the use of large-volume lung lavage with dilute surfactant may be effective in removing particulate meconium from the lung, minimize obstruction, and simultaneously offset the inactivation of surfactant by meconium. Its use in the newborn with severe MAS may carry increase in the risks of hemodynamic instability.[61-65]

Inhaled Nitric Oxide (refer to section on PPHN): A large, randomized, multicenter trial has demonstrated that infants with MAS responded better to the combination of iNO and HFOV, possibly because of improved lung inflation and better delivery of nitric oxide to alveoli pretreatment with surfactant may enhance the delivery of iNO to the alveoli, with a resultant increase in oxygenation.[23,65-67]

Extracorporeal Membrane Oxygenation: Infants with MAS make up approximately 35% of those neonates who require ECMO. However, use of iNO for the treatment of PPHN, has markedly reduced the need for ECMO.

RESPIRATORY DISTRESS SYNDROME (RDS)

RDS, also called *hyaline membrane disease,* is the most common cause of respiratory morbidity in neonates. RDS occurs in up to 50% of infants born at 28–32 weeks, the incidence approaches to nearly 100% at 24 weeks.[68,69,70]

Surfactant System: Surfactant is the surface tension lowering substance produced by the alveolar type II cells. It is composed of two main fractions: Lipids and surfactant-specific proteins. Lipids account for 90% and phospholipids form the bulk of the lipids. Other lipids that are found are: Cholesterol, triacylglycerol, and free fatty acids. Phosphatidylcholine (PC) forms 70 to 80% of the total amount of lipid. Approximately 50 to 70% of PC is saturated, especially in the dipalmitoylated form (DPPC). The anionic PG accounts for approximately 8%. Other lipids are phosphatidylethanolamine (PE, ±5%), phosphatidylinositol (PI, ±3%); and phosphatidylserine (PS), lysophosphatidylcholine, and sphingomyelin in small quantities (less than 2%).

About 10% of surfactant consists of four surfactant-associated proteins: The SP-A and SP-D are hydrophilic, and SP-B and SP-C are hydrophobic. Surfactant is stored and exported to the alveolar surface as lamellar bodies. After secretion, surfactant is transformed into specific structures, called tubular myelin, from which phospholipids are inserted into an air-liquid interface, thus reducing the surface tension during expiration. During the next inhalation, surfactant components are lost from the interface and taken back into the type II cell for recycling.[71-75]

Etiology/Pathophysiology

RDS is the result of primary absence or deficiency of surfactant. Without surfactant, the alveoli collapse at the end of expiration. The preterm neonates have both the structural immaturity of the lung, as well as surfactant deficiency.[76-78] Surfactant replacement therapy is the standard of care for preterm neonates suffering from RDS, and has significantly decreased the mortality.

Clinical Features

Surfactant deficiency leads to progressive atelectasis, loss of functional residual capacity, hypoventilation and $\dot{V}/\dot{Q}$ inequality. This, in turn leads to hypoxia, hypercarbia, metabolic acidosis and respiratory failure. It is further complicated in premature infants by week respiratory muscles and compliant chest wall that impair alveolar ventilation. The infants present at birth or within several hours after birth with the signs of respiratory distress that include tachypnea, expiratory grunting, retractions, nasal flaring, cyanosis and increasing oxygen requirement. Other clinical features include pallor, cardiovascular instability, extremity edema that develops after several hours due to altered capillary permeability.

Chest radiographs are characterized by diffuse reticulogranular pattern caused by alveolar microatelectasis, giving the classical ground glass appearance. Aerated bronchioles superimposed on collapsed alveoli give rise to widely distributed air bronchogram. In more severe cases, complete white out of the lungs with the loss of cardiac borders may be seen. Neonatal pneumonia especially caused by group B Streptococcal pneumonia, may present with radiographic features similar to RDS.

The clinical course depends upon the severity of RDS, the gestation age and the birth weight. The uncomplicated clinical course is characterized by the progressive worsening of symptoms with the peak severity by 2–3 days following which recovery begins. When the disease process is severe enough to require assisted ventilation, recovery may take several days or even weeks. However, surfactant therapy may shorten this course.

Clinical Management

S*upportive therapy* constitutes the basic principle of management. Adequate oxygenation, ventilation, temperature and circulation must be assured before the baby is transferred from the delivery room. *Oxygen therapy* by the means of CPAP or positive pressure ventilation is often initiated in the delivery room for the smaller infants, continued in NICU. The infant is placed in thermoneutral environment to reduce oxygen consumption. Close monitoring of vital signs, oxygen saturation, blood gases by noninvasive monitoring and an umbilical arterial line for frequent sampling and accurate blood pressure is often necessary.

Mild or moderate RDS is often managed by *CPAP.* Usually, 3–6 cm of water pressure applied to infant's airways helps to open up the alveoli and prevent atelectasis. Mandatory ventilation should be instituted well in advance of respiratory failure, to avoid hypoxemia, respiratory acidosis and secondary pulmonary vasoconstriction. Pressure cycled ventilators are most frequently used in the NICU, controlled by setting Positive Inspiratory Pressure (PIP), Positive End Expiratory Pressure (PEEP), rate, inspiratory pressure (IT), and FiO_2. Oxygen saturation, PaO_2, $PaCO_2$ and pH should be maintained within the acceptable limits with minimal ventilator parameters to avoid barotraumas and oxygen toxicity to the immature lung. Frequent adjustments are needed in the face of rapidly changing compliance of the lungs after surfactant therapy or during the recovery phase. *Hyperoxia is associated with retinopathy of prematuriy, a leading cause of blindness among premature infants.* PO_2 *is generally maintained between 50 to 80 mm Hg. Hypocarbia of less than 30 mm Hg has been associated with the higher incidence of periventricular leukomalacia.* In severe forms of RDS, non responsive to conventional ventilation and surfactant therapy, use of other modes of ventilation like high frequency oscillation or jet ventilators may be necessary.[79,80,81,82]

Surfactant therapy: Several forms of natural, as well as synthetic surfactant have been used in various regimens. Surfactant therapy appears to decrease the incidence of air leaks, improve oxygenation, and reduce the mortality from RDS among the preterm ventilated neonates. The incidence of Bronchopulmonary Dysplasia (BPD), intraventricular hemorrhage, sepsis and symptomatic PDA seems to be unaltered. Surfactant is administered through the endotracheal tube either through a side-hole adapter connected to an endotracheal tube or a catheter. Dramatic improvement in oxygenation after surfactant therapy correlates well with the improvement in lung volume and stabilization of FRC. If ventilator pressures are promptly lowered, a significant improvement in compliance is seen. The dose is repeated if the oxygen requirement stays more than 30% after 8–12 hours. It is unclear whether a prophylactic dose of surfactant administered intratracheally within the first minutes after birth has any advantage over its use as a rescue therapy after the symptoms have developed. Though earlier therapy has been shown to reduce the need for subsequent treatment, supplemental oxygenation and mechanical ventilation, it should be reserved for infants who need endotracheal intubation and likely to develop a more severe lung disease.

The currently available surfactant preparations are not ideal, require further refinement. Since the role of surfactant proteins in the surface tension lowering function of lipids has been defined, recombinant DNA technology may aid in the production of protein containing surfactant preparations.[78-87]

Prevention of RDS

Although the incidence of premature birth has remained unchanged in the United States, the incidence of RDS has shown a significant decrease at each gestational age. *Use of two doses of antenatal steroids* administered to mother at least 24–48 hours before the birth seems to decrease both the incidence and the severity of RDS. Its effectiveness is enhanced if used prior to gestation of 34 weeks. Although the role of thyroid hormone in lung development and surfactant maturation has been demonstrated in the lung cell culture of humans, subsequent multicenter studies did not show any significant synergistic effect of combined steroid and TRH therapy as compared to steroids alone.[88,89]

SURGICAL DISORDERS PRESENTING AS RESPIRATORY DISTRESS IN A NEONATE

Two to three percent of infants are born with a congenital anomaly that may require intervention soon after birth. Disorders like diaphragmatic hernia, bilateral choanal atresia or hydrops fetalis with pericardial and pleural effusion can be life threatening while other problems like esophageal atresia with tracheoesophageal fistula may present later with aspiration pneumonia. A quick and thorough screening examination for congenital anomalies should be conducted in delivery room.[90]

Choanal Atresia

Choanal atresia is the congenital absence of the posterior nasal aperture (the choanae). It results from the bony fusion or persistence of buccopharyngeal membrane or mixture of both, thus classified as bony, membranous or mixed,[91] unilateral or bilateral. Neonates being obligatory nasal breathers for four to six weeks after birth, bilateral choanal atresia can present as upper airway obstruction leading to respiratory distress and hypoxia. Bilateral choanal atresia presents at birth. The patient becomes cyanotic and struggles for air when quiet, becomes pink while crying.[91, 92]

Unilateral choanal atresia may not be symptomatic. Infants may initially present with foul smelling secretions on the effected side or with respiratory distress associated with upper respiratory obstruction. Inability to pass a 6Fr catheter through the nares into the pharynx suggests the diagnosis. Bilateral choanal atresia is the most common cause of complete upper airway obstruction at birth with an incidence of 1 in 7,000 live births. Twenty to fifty percent of patients with bilateral choanal atresia have associated anomalies that include various syndromes like CHARGE association, Treacher Collins, Aperts, Lenz-Majewski hyperostosis, Antley- Bixler Downs and Crouzon's syndromes.[90-92]

Management at birth depends upon the severity of symptoms and if bilateral or unilateral. *An appropriate oral airway* (size 0 or 00) should be placed and properly secured to prevent dislodging. Thorough *evaluation for other congenital anomalies* should include an echocardiogram, since 70% have associated heart defects.[93,94] CT scan should be performed to differentiate between the bony, membranous and mixed type of choanal atresia.[95]

If patient tolerates oral airway, *surgical correction* may be deferred till 4–6 weeks of age. Immediate repair is recommended if the patient needs endotracheal intubation. *Transnasal endoscopic repair* has been used with better results.[96] Some of the patients may need repeated dilatation in the postoperative period.

Esophageal Atresia

The proximal and distal portions of the esophagus do not communicate, the upper segment is a dilated blind-ending pouch with a hypertrophied muscular and the distal esophageal portion is an atretic pouch with a small diameter and a thin muscular wall. An abnormal communication between the trachea and esophagus may exist and occurs most commonly between the distal esophageal segment and the trachea just above the carina. Esophageal and tracheoesophageal atresia are congenital malformations that are typically diagnosed in neonates within the first few hours of life.[97-101]

Once tracheoesophageal fistula is suspected following steps should be taken in order to stabilize the patient and to *prevent aspiration pneumonia*. *Evaluate for other congenital anomalies* that may have an effect on surgical intervention.[102,103]

Clinical Signs

The inability to swallow and absorb amniotic fluid through the gut leads to polyhydramnios, seen in 95% of infants with Esophageal Atresia (EA) without fistula and in 35% of patients who have EA with a distal fistula.[104-108]

Diagnosis can be made by the inability to pass a large radio opaque (10F) catheter into the stomach. The catheter gets coiled up in the upper pouch and can be seen in posterior-anterior and lateral chest radiographs. Injection of 10 ML of air into the catheter while simultaneously taking an X-ray of the chest and abdomen may outline the pouch. Injection of barium and other contrast materials are not necessary and may pose a risk of aspiration through the fistula.[109,110]

The inability of the infants with esophageal atresia to clear their secretions leads to persistent regurgitation, frothy bubbles in the mouth and sometimes in the nose, drooling and aspiration of secretions. Any attempt at feeding results in choking, coughing, cyanotic episodes and regurgitation of feeds. The reflux of gastric secretions may also occur through the fistula into the tracheobronchial tree and contribute to pneumonia and atelectasis.[100-107]

With atresia alone, the abdomen appears scaphoid. Fifty to seventy percent of children with esophageal atresia may have other anomalies that include vertebral, anorectal, cardiac, tracheal, renal and limb (VACTERL association). Cardiac abnormalities are the most common, especially Ventricular Septal Defects (VSD) and Tetralogy of Fallot (TOF).

The severity of complications after EA repair is often dictated by the extent of the repair required. Primary anastomosis and fistula closure has fewer complications than esophageal replacement. The most common complications include anastomotic leak (14–21%), recurrent fistula, stricture and Gastroesophageal Reflux (GER). Most leaks are small, occur usually after the first 48 hours after surgery, and require only conservative management with the cessation of oral intake and antibiotic therapy. Ninety percent of leaks heal spontaneously. Major anastomotic disruptions occur in only 3 to 5% of leaks, but large leaks can be fatal and require surgical repair. An anastomotic leak can present with choking episodes during feeding and/or recurrent pneumonia. The best methods of diagnosis are bronchoscopy and esophagography. Tracheomalacia is seen postoperatively in almost all patients of tracheoesophageal fistula.[111-116]

Congenital Lobar Emphysema

Congenital lobar emphysema is the result of a group of disorders that lead to the over distention of and air trapping within the alveoli involving a part or whole lobe of a lung. Left upper lobe is most commonly involved (50%), followed by right middle lobe (24%) and right upper lobe (18%). Partial bronchial obstruction has been attributed to defective or overtly compliant cartilage, valve like obstruction created by mucosal folds, bronchial stenosis, and external compression by aberrant blood vessels, mediastinal or intrapulmonary masses. Familial form has also been reported. Males suffer more often than females (1.8:1). About 30% of cases have associated heart anomalies like tetrology of Fallot, ventricular septal defect or anomalous pulmonary venous return.[117-120]

The obstruction is check valve type and progressive distension of the alveoli compress the surrounding normal lung tissue and in some cases, the contralateral lung by crossing over the mediastinum. Patients usually present at 1–2 months of age, but many infants may exhibit symptoms soon after birth or within the first six months of life. Rarely some patients remain undiagnosed up to the school age. Severity of symptoms depends upon the size of the over inflated lobe. Physical findings include hyperresonant note on percussion, decreased breath sound over the affected lobe, and the signs of mediastinal shift.[121,122]

Chest radiograph shows unilateral hyperinflated lobe, bronchovascular markings in the periphery of involved lobe, possibly mediastinal shift and/or atelectasis or collapse of adjacent lobe.[123]

For infants with severe respiratory symptoms, segmentectomy or lobectomy is the treatment of choice. The incidence of complications is low. Asymptomatic patients may not require any definitive treatment. Most respiratory symptoms do not progress, resolve within a year of age. Lobectomy has been successfully avoided in occasional cases by the use of selective endotracheal intubation on the unaffected side or high frequency ventilation.[123,124]

Diaphragmatic Hernia

Congenital Diaphragmatic Hernia (CDH) is characterized by a defect in the diaphragm that occurs due to failure of closure of pleuroperitoneal canal during the sixth to eighth week of gestation. In approximately 85 to 90% of cases, the hernia occurs through the posterolateral lumbocostal triangle, called Bochdalek hernia, whereas 10 to 15% are anteromedial hernias called Morgagni hernia. Bilateral hernia occurs in less than 1% patients, is usually fatal. Left-sided hernia allows the herniation of both small and large bowel, as well as of intra-abdominal solid organs into the thoracic cavity. In right-sided hernias, only the liver and a portion of the large bowel tend to herniate. Depending upon the size of defect, a variable degree of pulmonary hypoplasia is associated with a decrease in the cross-sectional area of the pulmonary vasculature, dysfunction of the surfactant system and increased musculature in the intra-acinar pulmonary arteries. Right-sided hernias may not be symptomatic early because the liver may seal the defect. [119,120,121,125]

CDH occurs in 1/2,000–4,000 live births, isolated posterolateral CDH being 1.5 times frequent in males than females. The risk of recurrence of isolated CDH for future siblings is approximately 2%. Familial CDH has been reported, may be due to a multifactorial or autosomal recessive pattern. As many as 10% of patients with CDH may present after the newborn period, and even during adulthood. Outcome in patients with the late presentation of CDH is extremely good, with low or no mortality.[119,120]

No single gene mutation has been identified as producing or contributing to this anomaly. A variety of chromosomal anomalies, including trisomy 13, trisomy 18, and tetrasomy 12p mosaicism have been reported in 4% of infants with CDH. CDH may be associated with non-chromosomal disorders, such as the de Lange syndrome.[119]

Majority of the patients are diagnosed by an antenatal sonogram. Infants most commonly present with the history of cyanosis and respiratory distress in the first minutes or hours of life, although a later presentation is possible. The infants frequently exhibit a scaphoid abdomen, respiratory distress and cyanosis. In left-sided hernia, auscultation of the lungs reveals poor air entry on the left side. Posterolateral hernia may occur as an isolated defect or in association with other congenital anomalies. CDH can occur as a part of multiple malformation syndrome in up to 40% of infants, principally with cardiovascular, genitourinary, and gastrointestinal malformations. Lethal anomalies are present in up to 16% of infants.[119-121]

Infants with prenatal diagnosis or with symptoms should immediately undergo endotracheal intubation and mechanical ventilation. The resuscitation team should consider the possibility of early pneumothorax if the infant does not stabilize.[122-124,126] High frequency oscillatory ventilation should be considered if high peak inspiratory pressures are needed. Surfactant administration may be helpful because of associated lung immaturity and surfactant deficiency. Inhaled nitric oxide may be used to lower the pulmonary vascular resistance. However, its use has not been shown to reduce mortality or the need for ECMO in infants with CDH. Arterial Blood Gases (ABG) should be monitored frequently because of persistent pulmonary hypertension. Placement of venous and arterial lines is essential because many infants may require the use of inotropic agents, multiple infusions and frequent blood sampling. Associated PPHN should be managed, and patients should be adequately sedated or paralyzed in order to achieve optimal oxygenation. Placement of pulse oxymeter probes at preductal (right-hand) and postductal (either foot) sites may help in assessing a right-to-left shunt at the level of the ductus arteriosus.[125,127-129] ECMO is indicated if optimal oxygenation and perfusion is not achieved by ventilation and medical therapy.

Typical findings in left-sided posterolateral CDH include air- or fluid-filled loops of the bowel in the left hemi thorax and shift of the cardiac silhouette to the right. Due to underlying lung hypoplasia, these patients are prone to the development of pneumothorax. Placement of an orogastric tube prior to the study helps to determine the position of the stomach. *Echocardiogram* should be performed to rule out PPHN and associated cardiac anomalies. If the infant is being considered for ECMO, it is essential to perform cranial ultrasonographic examination to evaluate for intracranial bleeding and anomalies. Patients should also have a renal sonogram.[119,123]

Preoperative stabilization significantly decreases morbidity and mortality. Many surgeons prefer to operate when echocardiographic evidence for normal pulmonary artery pressures is maintained for at least 24–48 hours. Delays of upto 7–10 days are often well tolerated. Surfactant therapy for term infants with a prenatal diagnosis of isolated CDH does not offer any significant benefit.[129] A single lung transplant has been successfully performed. It allows the remaining hypoplastic lung to increase in size and recover from injury while allowing for optimal ventilation and oxygenation.[126,130-132]

ACUTE PULMONARY DISORDERS IN THE PEDIATRIC PATIENT

The pediatric airway differs from the adult airway as it is shorter and narrower, the epiglottis is long and floppy. Therefore, a relatively small amount of airway obstruction can cause significant reduction in airway diameter with increased airflow resistance and work of breathing. Over the last few years, advances have been made in ventilatory management. More recently, ventilatory strategies have involved moving away from mimicking the volumes and pressures of physiologic ventilation, towards using low pressure and low volume strategies, as well as prone position ventilation.[133-138]

Inhaled nitric oxide and extracorporeal membrane oxygenation are now routinely used in the treatment of Persistent Pulmonary Hypertension of the Newborn (PPHN). The outcome figures for pediatric ECMO are not as good as for neonates, with an overall survival rate of 40 to 50%.[139-145] There are recent reports that the use of Volumetric Diffusive Respirator in combination with nitric oxide may have a place in the treatment of respiratory failure unresponsive to conventional modes of treatment.[146]

Croup

The term *croup* refers to a clinical syndrome characterized by barking cough, inspiratory stridor and hoarseness of the voice, also referred to as laryngotracheobronchitis. Most cases of croup are viral in etiology, the most common being parainfluenza virus.

A short history suggestive of a viral upper respiratory infection may be elicited. Subsequently the child develops a hoarse voice, brassy cough and stridor, which is usually inspiratory. The child may appear cyanotic and pale due to hypoxemia—this can eventually progress to respiratory failure.

The steeple sign, which refers to subglottic narrowing of the upper airway, may be evident on radiography.

Management

Mild Croup (no stridor at rest): These children can generally be managed at home, the child should be disturbed as little as possible. Cold mist from a humidifier by the bedside could be more helpful. Treatment of fever, if present, by antipyretics, is also indicated.

Moderate to Severe Croup (Stridor at Rest)

Mist Therapy: Misting through a tent or humidifier has historically been the mainstay of the treatment of croup. However, placing the child in a croup tent may agitate the child and therefore worsen the spasm.

Corticosteroids: Dexamethasone in a dose of 0.15–0.6 mg/kg p.o. or i.m. is recommended. Budesonide, 2 mg by nebulizer, can also be used.[147,148]

Epinephrine: Racemic epinephrine, in a dose of 0.05 ml/kg, to a maximum of 0.5 ml/dose, diluted in normal saline, can be given by nebulization every two hours. Patients requiring more frequent administration of racemic epinephrine should be considered for admission to the pediatric intensive care unit.[149,150]

Intubation and mechanical ventilation should be considered if the child with croup shows the evidence of impending or imminent respiratory failure.

Epiglottitis

Epiglottitis refers to the inflammation of the epiglottis and the supraglottic portion of the airway. This disease has become much less common after the introduction of the Hib vaccine. The commonest causative organism is *H. influenzae*.

The child with epiglottitis may present with a history of high fever, may have a “toxic” look, with drooling, may adopt a “tripod position” sitting with both arms extended and face in the sniffing position. The pharynx should be examined in the operating room by trained personnel ready to intubate. The epiglottis will be seen inflamed and “cherry red” in color.

X-rays may show an enlarged epiglottis, the aryepiglottic folds may be markedly thickened.

The child with suspected epiglottitis should not be agitated or disturbed, this could increase laryngospasm and worsen respiratory distress. Humidified oxygen by mask should be administered if this does not upset the child.

An airway team should be called to the emergency room and should accompany the child to the operating room. Swabs should be taken from the pharyngeal and epiglottic surface, and the child should be intubated under anesthesia and put on mechanical ventilation.[151,152] Tracheostomy may be indicated if the vocal cord edema is severe. Antibiotics, such as ceftriaxone, should be administered for 7 to 10 days.

Bronchial Foreign Body Aspiration

Foreign Body Aspiration (FBA) is a common cause of mortality and morbidity in children, especially in those younger than 2 years of age. A common site for lodgement is the right mainstem bronchus, as it is shorter, straighter and wider than the left mainstem bronchus.[153]

A foreign body lodged in the right mainstem bronchus may cause either partial or complete obstruction. Partial ball valve obstruction, results in overinflation and emphysema of the segment distal to the obstruction, with poor air exchange. If the obstruction is complete, the air in the segment distal to the bronchus, eventually gets absorbed and cause atelectasis. Both of the above situations can lead to secondary infection and abscess formation.

Clinical Features

Immediately after the foreign body is aspirated, there may be paroxysmal coughing. The coughing and wheezing may last for an indefinite period. Reduced air entry on the affected side may be perceived by dullness to percussion. The physical examination may reveal generalized wheezing or localized findings, such as focal monophonic wheezing or decreased air entry. Fever and respiratory distress may develop in the case of superadded infection.

Plain radiographic evaluation of the chest may or may not be helpful in establishing the diagnosis of FBA, depending upon whether the object is radiopaque, and whether the airway obstruction is present. A normal chest radiograph does not rule out foreign body aspiration.

In case of complete foreign body obstruction, chest X-ray may show atelectasis and mediastinal shift to the same side. A radiopaque foreign body may be visualized. In the case of check valve obstruction with emphysema, expiratory films may show mediastinal shift to the side opposite to the obstruction. Rigid bronchoscopy should be done for both diagnosis and management, in case aspiration is strongly suspected. Infection often develops distal to an obstructed airway. Therefore, a consolidated infiltrate is also a possible finding.

Treatment

If in respiratory distress the child should be administered oxygen, and appropriate respiratory support should be provided.

Children, who are symptomatic, with strong suspicion of foreign body aspiration, should be admitted to the hospital. Rigid bronchoscopy should be performed, and the foreign body removed, if visualized. Treatment with antibiotics should be instituted if superadded infection is suspected.

Status Asthmaticus

Asthma is characterized by diffuse, reversible lower airway obstruction with the evidence of inflammation and edema, bronchial smooth muscle spasm and mucous plugging. Some authors characterize a patient with severe asthma as being in status asthmaticus if they fail to respond to at least three doses of nebulizers or bronchodilators.

Clinical Features

Children with acute severe asthma who fail to improve with initial treatment in the emergency department should be admitted to the pediatric intensive care unit. The child will usually present with cough, wheezing and increased work of breathing. Bilateral wheezing may be heard on auscultation, with reduced air entry. However, if air entry is significantly reduced, wheezing may not be heard, a “silent chest” may be an ominous sign.[154] The child may also present in respiratory failure or with cardiopulmonary arrest. The child may have low oxygen saturation on pulse oximetry, may also demonstrate pulsus paradoxus.[155-157]

The diagnosis of status asthmaticus is mainly clinical. Arterial blood gas may show the evidence of respiratory and metabolic acidosis.

Management

Adequate humidified oxygen to keep saturations above 95% should be provided via non-rebreather mask. Albuterol should be administered, either by frequent nebulization or as continuous nebulization. Most studies have used low doses (4 to 10 mg/hr) of continually nebulized albuterol, but recent studies recommend much higher doses (up to 150 mg/hr at 10 to 12 lit/min. flow). Intravenous methylprednisolone (0.5 to 1 mg/kg every 4 to 6 hours), or hydrocortisone (2 to 4 mg/kg every 4 to 6 hours), should be administered. Ipratropium can be used by nebulization in a dose of 250 to 500 micrograms every six hours. Intravenous bronchodilators, such as IV terbutaline in a dose of 0.1 to 10 micrograms/kg/minute should be considered in children unresponsive to continuous nebulization. Some trials suggest using aminophylline, but this remains controversial.[158]

Intravenous magnesium sulfate has been recommended for the treatment of severe asthma (in a dose of 75 mg/kg IV over 20 minutes).[159,160]

Helium-oxygen mixture with a concentration of helium from 60 to 80% can be used.[161,162] However, this cannot be used in children with a relatively high oxygen requirement due to the relatively lower concentration of oxygen in the mixture.[163]

Mechanical ventilation should be avoided, if possible, in patients with severe asthma, as it increases the incidence of complications of barotrauma and air trapping.[164-166] The indications for ventilation include deterioration in the child's mental state, cardiac and respiratory arrest and evidence of severe hypoxia.[167]

Ketamine can be used in children on mechanical ventilation (2mg/kg bolus followed by a continuous infusion of 0.5mg/kg/hr).[168] It should be used with caution in patients with hypercarbia as it may cause increased intracranial tension due to its ability to cause cerebral vasodilatation.[169]

Smoke Inhalation

Smoke inhalation is associated with over half the burn deaths in the US. Advances in technology have been contributing to reducing the mortality due to surface burns.

Injury due to smoke inhalation results due to injury at a cellular level, or due to local or systemic effects. Injury immediately after exposure may be due to the effects of hypoxia or Carbon Monoxide (CO), which causes the poor release of oxygen to the tissues, and may also have a myocardial depressant effect, leading to ventricular arrhythmias.[170] Its effect at the cytochrome oxidase level may cause neurologic manifestations.

The mechanism and effects of smoke inhalation injury may be divided into five phases. Immediate heat transfer may result in severe mucosal injury, acute respiratory distress due to bronchospasm and laryngeal edema. This may go on for 6–12 hours, the bronchospasm may not be reversible by administering β-agonists. In the second phase, from 6–72 hours, pulmonary edema may occur, initially due to increased capillary permeability and subsequently worsened by surfactant deficiency. In the third phase, at two to four days, respiratory distress may occur or be worsened by the presence of a cervical eschar.[171] After two to four days, pneumonia may develop as a result of either restrictive disease or decreased ability of the mucociliary apparatus to clear the airways of bacteria. The late effects of smoke inhalation may be manifest by increased predisposition to airway hyperactivity.[172]

Investigations

In the absence of respiratory signs, early chest films may not be useful in the diagnosis of inhalation injury.[50] Diagnostic bronchoscopy is a useful investigation in evaluating inhalation injury with upto 86% diagnostic accuracy. It has been also used for therapeutic purposes in the presence of atelectasis.[173]

Management

Airway, breathing and circulation should be assessed and appropriately managed. Oxygen 100% through a non-rebreathing mask should be provided. Carboxyhemoglobin levels, blood counts and biochemistry to be sent. Skin burns, if present, should be assessed and managed, and appropriate IV fluids provided.

Asymptomatic, low risk children should be observed for 4 to 12 hours. Severe respiratory distress should be managed with endotracheal intubation and oxygenation. Bronchospasm, if present, can be treated with bronchodilators.

The role of corticosteroids is debatable, their use has been reported to be associated with the increased rate of pulmonary infection.[174] If cyanide toxicity is suspected, antidote in the form of sodium nitrate and sodium thiosulfate should be used. The use of prophylactic antibiotics is controversial. Hyperbaric oxygen has been tried for management of CO poisoning.

Drowning and Near-Drowning

Epidemiology and Definition

Drowning is responsible for about 5,00,000 deaths around the world every year.[175] Drowning is defined as death resulting from suffocation within 24 hours of submersion in a liquid medium, near-drowning is survival atleast 24 hours after an episode of suffocation caused by submersion in a liquid medium. The immersion syndrome is defined as syncope provoked by bradycardia, tachycardia or arrhythmia precipitated by sudden contact with water at a temperature of atleast 5 degrees less than body temperature.

In its 2000 Resuscitation Guidelines, the American Heart Association suggests that the term drowning should refer to a mortal submersion event in which the victim dies within 24 hours, while the term submersion injury should be used up until the time of drowning-related death. In this classification scheme, the term near-drowning is abandoned.[176-178]

Pathophysiology

The pathophysiology of drowning and near-drowning involves hypoxia and metabolic acidosis, and hypercarbia leading to respiratory acidosis.[179] There is initial laryngospasm or breath holding, followed by the aspiration of water. This leads to pulmonary surfactant depletion, alveolar damage, pulmonary edema, intrapulmonary shunting and hypoxia. Ventricular fibrillation may occur due to hypoxia and acidosis, there may be severe peripheral vasoconstriction due to hypoxia, catecholamine release and hypothermia.

Management

Artificial or assisted breaths must be started at the site of rescue of the drowning victim, should not be deferred. Time should not be wasted in trying to extrude the water from the lungs before Cardiopulmonary Resuscitation (CPR) is started. The water would have quickly dissipated into the vascular compartment in case of fresh-water immersion, and would continue to cause fluid to be poured into the lungs (pulmonary edema) in the case of salt-water drowning. Suctioning fluid from the airways may be necessary in the case of salt-water drowning, due to pulmonary edema. Cardiopulmonary resuscitation should be continued as long as needed, until an emergency care facility is reached.[180]

Admission for a minimum of 24 hours is indicated for any drowning victim who was submerged for atleast one minute, was apneic or cyanotic, or required pulmonary resuscitation. Fulminant pulmonary edema despite normal chest X-ray has been reported to develop as long as 12 hours after the episode. Monitoring should be done by serial measurements of blood gases, electrolytes, urea, creatinine and hemoglobin.

Adequate respiratory support should be provided in the form of high-flow oxygen, CPAP or mechanical ventilation, if indicated. Cardiac dysfunction, if present, should be treated with vasopressors, such as dobutamine. Cerebral anoxia and edema should be appropriately monitored and treated. Hyperpyrexia due to the failure of the hypothalamic thermostat has been treated with body cooling, dexamethasone can be used for management of cerebral edema. Any drowning victim should be examined for the presence of cranial and spinal trauma.

Pediatricians, in consonance with parents, children, caregivers and the community must be proactive in implementing the AAP recommendations for the prevention of drowning.[181]

Bronchiolitis

Bronchiolitis is a common viral respiratory infection in children. Respiratory Syncytial Virus (RSV) is responsible for bronchiolitis in over 50% of the cases. Less common causes include parainfluenza virus, human metapneumovirus, influenza virus, adenovirus, coronavirus, and human bocavirus.[182,183] Pathophysiologic processes occur both at the cellular and molecular level. Infection by the virus causes edema and the accumulation of cellular debris, thus causing airway obstruction, air trapping and atelectasis. [184] At a molecular level, cytokines, interleukins and IgE are involved.[185]

Clinical Features

These are often more severe in the younger age groups, especially in the babies of less than 1 year of age. There may be evidence of a mild upper respiratory tract infection with sneezing and rhinorrhea, with or without fever, followed by respiratory distress and wheezing. Very young infants may have apnea. Examination may show the evidence of respiratory distress in the form of nasal flaring, retractions and crackles or wheezing on auscultation. Pulse oximetry may show the evidence of hypoxia. There may not always be a correlation between the degree of respiratory distress and hypoxemia.

Differential Diagnosis

In a younger child, the diagnosis of asthma rather than bronchiolitis may be entertained if there are repeated episodes of wheezing, absence of a viral prodrome and presence of a family history of atopy or asthma. In babies and children presenting with wheezing or stridor, tracheomalacia or bronchomalacia, vascular rings and slings should be ruled out. Pertussis should be entertained as a differential diagnosis in babies with persistent and continuous coughing. Chest X-ray may show the evidence of hyperinflation or atelectasis. Total and differential leukocyte count may be normal or affected. Viral testing can be done by rapid immunofluorescence, this may often avoid the need for sepsis evaluation in an infant.

Management

The management of bronchiolitis is mainly supportive. Babies with significant respiratory distress should be hospitalized, and so should very young infants because of the risk of apnea.[186-188] Cool humidified oxygen should be provided. Oral intake is avoided and parenteral fluids provided if there is risk of aspiration.

Bronchodilators may provide some short-term improvement, although there is little data to support their administration to all patients. Nebulized epinephrine has also been tried as a therapeutic modality, although trials have not shown this to be efficacious.[189-191]

There is little evidence to show that corticosteroids are beneficial, except in the cases of recurrent wheezing where reactive airway disease is the underlying diagnosis.[192]

Ribavirin, an antiviral agent, has been administered by aerosol to infants with chronic lung disease or congenital cardiac disease, but there is no convincing evidence of its efficacy.[193] Respiratory syncytial virus immune globulin has no role in acute bronchiolitis, antibiotics are indicated only in the presence of bacterial pneumonia.[194] Palivizumab, a monoclonal antibody to the RSV F protein, has been effective in reducing the risk of RSV infection before and during RSV season. The latest recommendations for the administration of palivizumab should be followed, which involve monthly intramuscular injections for high-risk groups.[195] Through handwashing is an extremely effective method to prevent nosocomial transmission of RSV.

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Mechanical Ventilation: General Principles and Modes

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INTRODUCTION

Mechanical ventilation is an important method to save life of critically ill patients. In both forms, invasive as well as noninvasive, positive pressure ventilation is widely used worldwide. About one third of adult Intensive Care Unit (ICU) patients receive mechanical ventilation.[1,2] Conceptually, mechanical ventilation is the process to provide O_2 and CO_2 transport between the environment and the alveolar pulmonary capillary interface, with the help of a device. The target of this process is to maintain appropriate PaO_2 and $PaCO_2$ in arterial blood along with reduction in work of breathing. Originally, Mechanical Ventilator (MV) consisted of simple, manually-driven pump device, which over the period has developed into advanced positive pressure ventilator for continuous support of patients in respiratory failure. The earlier MVs delivered fixed volumes or pressures with fixed rates and breath durations, however later advancements allow the patient to trigger the ventilator with their own effort, which can then be cycled-off on time criteria or when certain flow criteria are met.[3] Latest MVs provide many variables, which may be controlled to provide the ventilatory support depending on the underlying disease in an intermittent fashion, mimicking natural breathing. With these advancements, survival rate in patients requiring mechanical ventilation has significantly improved.[4]

An important aspect of mechanical ventilation is a thorough understanding of the equipment being used. There are a wide variety of MVs available for use in the modern pulmonary care. It would be extremely difficult for anyone to master on all the equipment and their functioning. The basic principles and application of different ventilators are similar.

Indications of Mechanical Ventilation

Mechanical ventilation is often used to manage ventilatory or oxygenation failure or an impending failure. Failure to ventilate or oxygenate adequately may be caused by several pulmonary or extrapulmonary conditions, belonging to three distinct groups:

1. *Depressed Respiratory Derive*: This group includes drug overdose (narcotic, sedative, alcohol, etc.), acute spinal cord injury, head trauma, neurologic disorders (coma, stroke, etc.), sleep disorders (e.g. sleep apnea) and metabolic alkalosis.
2. *Excessive Ventilatory Workload*: This group includes acute airflow obstruction, e.g. Chronic Obstructive Pulmonary Disease (COPD), asthma or epiglottitis, dead space ventilation (pulmonary embolism and emphysema), Acute Lung Injury (ALI), e.g. Acute Respiratory Distress Syndrome (ARDS), cardiovascular decompensation (decreased cardiac output, Ventilation/Perfusion ($\dot{V}/\dot{Q}$) mismatch), shock, increased metabolic rate (fever), drugs and decreased compliance (atelectasis, pneumothorax and obesity).
3. *Ventilatory Pump Failure*: This includes chest trauma (flail chest, tension pneumothorax), premature birth (idiopathic respiratory distress syndrome), electrolyte imbalance (hyperkalemia or hypokalemia) and geriatric patients (muscle fatigue).

Phase Variables

The actual factors that provide the four components of a ventilator-delivered breath are called the phase variables. These factors or variables are responsible for changing of one phase of the respiratory cycle into the next and for controlling what occurs during that portion of the breath. The four phases of a breath consists of:

1. Inspiratory phase
2. Change from inspiration to expiration
3. Expiratory phase
4. Change from expiration to inspiration

In each of these four phases a certain variable (time, pressure, volume or flow) is measured and used to initiate, maintain and end the phase.

There are three terms used to describe phase variable:

Triggering of Breath

Triggering is the term applied to the variable that changes from expiration to inspiration.

When a variable, such as time, pressure, volume or flow reaches a preset value and causes the ventilator to change from expiration to inspiration, the ventilator is said to be triggered by that parameter. The ventilator is said to be time-triggered, where inspiration begins when a certain time has elapsed. This occurs independently from a patient's spontaneous effort. In pressure-triggering, the ventilator senses the patient's inspiratory effort sufficient to cause a drop in the baseline airway pressure by preset value and initiates inspiration. The breath occurs regardless of the set rate. It is essential to find the individual patient's need and set sensitivity accordingly, otherwise patient has to either work hard or there will be auto-triggering. A ventilator is said to be flow-triggered, when the baseline flow variable drops below a preset flow and initiate inspiration. Ventilators can also be manually triggered in most cases. This is accomplished by activating the "manual breath" control.

Limiting a Breath

Limiting is a term used to describe the variables that have a limiting value during inspiration or expiration, which could be time, flow or pressure. The length of inspiration is the time from the beginning of inspiratory flow to the start of expiratory flow. During the inspiratory phase, the ventilator can control pressure, volume or flow as described previously in this section. In addition, the ventilator can also limit these variables. Limiting in simple words means the variable can reach the preset value, but never goes higher than it.

Cycling of Breath

Cycling is defined by the preset variable, causing the ventilator to end the inspiration and switch it to expiration. During this process a preset variable (time, pressure, volume or flow) is actually measured by the ventilator, this information is used by the ventilator to determine when to end the inspiratory flow.

Time-cycled ventilation: This is one of the common cycling mechanisms used in clinical practice. Here, time-cycling terminates the inspiratory gas flow and changes to the expiratory phase, when a preselected time interval has elapsed after the start of inspiration. At the designated time, the exhalation valve opens and the delivered Tidal Volume (VT) is vented to the ambient atmosphere. At a constant gas flow and controlled time interval, VT can be predicted according to the following relationship:

Volume = Flow (volume/unit time) × Time

Pressure-cycled ventilation: In this cycling, ventilation terminates the inspiratory phase, when a preselected airway pressure has been achieved. The exhalation valve then opens, initiating the expiratory phase. Tidal volume and the time of active flow delivery will vary in pressure-cycled ventilation, depending on the airway resistance, chest wall and lung compliance and the integrity of the ventilator circuit. As the volume delivery is unpredictable with pressure cycling, this mode is uncommonly used in intensive care settings. They are used predominately for intermittent positive pressure breathing, ventilatory support at home and while using inverse ratio ventilation.

Volume-cycled ventilation: In volume-cycled ventilation, the inspiration is terminated when a preselected volume of gas has been delivered. There is fear of development of excessive airway pressure, in case of airway obstruction therefore, volume-cycled ventilators have pressure-limiting valves that prevent excessive pressure within the system. Without this pressure-limiting valve, excessive pressure may lead to barotrauma.

There has been a belief that volume-cycled ventilation maintains constant VT delivery to the patient, regardless of changes in resistance and compliance. This alleged characteristic is largely responsible for the popularity of these devices in critical care settings. However, the volume of gas received by the patient may vary considerably with volume-cycled ventilation. The variability occurs, since the gas flows into the circuit and the patient. When the ventilator triggers on, its distribution depends on their relative compliance. If there is a decrease in patient's compliance, a larger proportion of the volume is lost within the circuit due to expansion of the tubing and compression of the inspiratory gas within the humidifier or nebulizer, water traps, bellows or cylinder and connectors. Conversely, if the patient's compliance improves, less inspiratory gas is retained within the circuit.

Flow-cycled ventilation: If a preset flow, ends the inspiratory flow, the breath is flow-cycled. Flow-cycled ventilation is independent of airway pressure, VT or duration of inspiration. Flow-cycled mode is most commonly used during pressure support ventilation, in which it is common for the ventilator to cycle into exhalation when the flow during inspiration has dropped to 25% of the peak inspiratory flow.

Patient-Ventilator Interactions

Most of the modern MVs utilize piston or bellow systems of high pressure gas source to drive the gas flow. However, newer MVs provide "interactive" modes, in that patient can interact with ventilator and affect its functions. These interactions can range from simple triggering of mechanical breaths to more complex processes, which can affect various aspects of tidal breath, such as the flow pattern and breath timing.

The patient interacts with ventilator based on three physiological variables:[5]

1. Ventilatory drive when inspiration starts.
2. Ventilatory requirement, i.e. how much flow and volume is required to satisfy the metabolic demand.
3. Timing of the integrated circuits generating the respiratory rhythm, as measured by the duration and ratio of inspiratory time to total breath cycle duration.

Similarly, ventilator interacts with the patient based on three technologic variables:

1. The inspiratory trigger or when the ventilator starts to deliver flow, volume and pressure.
2. The delivery of the gas, i.e. the algorithm used by the ventilator to assist ventilation through delivery of flow, volume or pressure.
3. Cycling or when the ventilator stops assisting the inspiratory effort and lets the patient exhale spontaneously.

Interactive modes allow for muscle activity, which when done at nonfatiguing or physiologic levels may prevent muscle atrophy and facilitate fatigue recovery.[6,7] In addition, permitting spontaneous patient ventilatory activity and using comfortable interactive modes may reduce the need for sedation and/or of neuromuscular blockers, that are often required to prevent patients from "fighting" controlled ventilation.[8]

For the ventilation to be effective, these interactions should be synchronous during different phases of interactive breathe delivery, i.e. breathe triggering, ventilator flow delivery and breathe cycling. Synchronous interactions imply that the ventilator is sensitive to the initiation, modulation and termination of a patient's ventilatory effort. The importance of all these variables has been described below.

Interactions during breath triggering: During interactive mode of ventilation, MVs need to sense a spontaneous effort (a drop in airway pressure or flow change), in order to trigger a mechanical response. Even with modern advanced sensors, there is some unavoidable dyssynchrony in the triggering process due to the artifacts triggering the ventilator (i.e. autocycling) or a certain inherent delay (system responsiveness) in opening of demand valve. Both of these factors can result in a significant work of breathing during the triggering process. In the setting of air trapping and auto-Positive End Expiratory Pressure (PEEP), the elevated alveolar pressure at end expiration can serve as a significant triggering threshold load on the ventilatory muscles. In these circumstances, appropriate use of external PEEP can equilibrate expiratory pressure throughout the lungs and ventilator circuit to reduce this triggering load.[9,10]

Interaction during ventilator-delivered flow: During an interactive breath, ventilatory muscles are contracting.[11,12] At this point of time, the ventilator flow delivery should be adequate to meet one of three goals:

1. Fully unload the contracting ventilatory muscles in patients with severely overloaded and fatigued muscles.
2. Partially unload the contracting ventilatory muscles in patients recovering from muscle fatigue.
3. Add no imposed loads on muscles in patients during spontaneous breathing trials, i.e. Continuous Positive Airway Pressure (CPAP). Synchronous flow interactions are required to achieve these goals.

There is evidence that suggests pressure-targeting breathe, by providing a variable flow, tends to synchronize better with patient effort than the fixed flow pattern of the flow-targeted breath.[13,14] Moreover, a single, consistent assisted or supported breath pattern more readily synchronizes with breath types. Thus, when partial support is desired, Pressure Support/Assist (PS or PA) approach alone appear preferable to Synchronized Intermittent Mandatory Ventilation (SIMV). Although one can argue that SIMV offers the advantage of a guaranteed ventilator rate during partial support, the pressure-assist control mode can similarly, provide both interactive pressure-targeted assisted breaths, as well as backup pressure-targeted controlled breaths.

Interaction during breath-cycling: Cycling dys-synchrony can occur in one of two ways. First, if the breath lasts beyond patient effort, an inadequate expiratory time may develop (along with air trapping) and/or patient expiratory efforts may be required to terminate the breath.[15] Second, if the breath terminates before the patient's effort ends, the patient may be left demanding additional flow without any tidal breathe being delivered by the machine, which significantly imposes loading and/or double breath triggering may result. Cycle dys-synchrony can be addressed by adjusting the tidal volume or inspiratory time in flow/volume-targeted ventilation, by adjusting the inspiratory time in pressure assist-control ventilation or by adjusting the cycle criteria in PS mode of ventilation.

In recent years, certain innovations have been introduced to improve patient-ventilator synchrony during interactive modes of ventilation, such as automatic tube compensation, inspiratory pressure slope and proportional assist ventilation. These have significantly reduced the problem of patient-ventilator dys-synchrony.

MODES OF MECHANICAL VENTILATION

Technological advances have provided a number of different modes, by which a patient can be mechanically ventilated. However, the primary targets are to improve gas exchange, provide patient comfort and speed up weaning from mechanical ventilation. All the ventilators are equipped to deliver either volume-set or pressure-set ventilation. In volume-set ventilation, a preset VT is delivered at whatever pressure it is required. On the other hand, in pressure-set modes, a fixed Inspiratory Pressure (P*insp*) is applied to the respiratory system. Whatever the resulting VT, both usually achieve the same level of ventilation in fully paralyzed patients. In these patients, Plateau Pressure (Pplat) is determined by VT and static Respiratory System Compliance (Crs):

$$\text{Pplat} = \text{VT}/\text{Crs} + \text{PEEP (including auto-PEEP)}$$

Further, VT is predictable (in paralyzed patients), if Crs is known:

$$\text{VT} = (P\textit{insp} - \text{PEEP}) \times \text{Crs}$$

Though the physician's comfort level with volume-set and pressure-set modes may vary, but both modes are similarly tied to each other through the patient's Crs. The potential advantage of pressure-set ventilation is probably greater physician control over the Peak Airway Pressure (P_{rw}) and the Peak Alveolar Pressure (P_{alv}), hence reduction of Ventilator-Induced Lung Injury (VILI). However, could be also attainable with low VT (typically 5 to 8 ml/kg) in volume-set ventilation. Other advantages of pressure-set modes are greater control over inspiratory flow rate and therefore, potentially increased comfort. The disadvantage of pressure-set modes is the increased airflow resistance or lung stiffness, which decreases the minute ventilation. Volume-set modes provide ventilation, but require pressure alarms to detect new abnormalities in respiratory mechanics.

Controlled Mechanical Ventilation (CMV)

The term CMV has been used to describe a volume or pressure-controlled and time-triggered form of ventilation. The operator sets the desired VT (volume controlled) or peak airway pressure (pressure controlled), respiratory rate/frequency (f), Inspiratory Time (TI) and I:E ratio. The patient's ventilation is totally controlled by ventilator and patient cannot trigger the ventilator (Fig. 140.1). However, the controlled ventilation does not guarantee that patient will not attempt to initiate spontaneous ventilation. In such situations, the ventilator will not respond, if it is used strictly in a control mode implying that the ventilator sensitivity is kept "off". This may result in patient-ventilator asynchrony, i.e. the patient attempts to take more breath than the ventilator can provide. It adds to significant patient apprehension, results in CO_2 retention and increased work of breathing. To overcome the problem, the patients need heavy sedation and/or neuromuscular blockade.

The complications observed with use of controlled mechanical ventilation include, excessive ventilation,[16,17] use of sedatives and muscle relaxants,[18] and muscle atrophy resulting from disuse.[19-21] Further, use of heavy sedation/neuromuscular blockade imposes a great risk of apnea/hypoxia in case of accidental ventilator disconnection.

Volume-Controlled (Targeted) Ventilation

Volume-controlled (targeted) mode requires that the operator set a desired VT. Usually, the operator also sets the rate or inspiratory time and gas flow, including flow pattern. During this mode of ventilation, the peak pressure varies from breath-to-breath depending on several factors, primarily patient's lung compliance. However, volume delivered is usually constant.

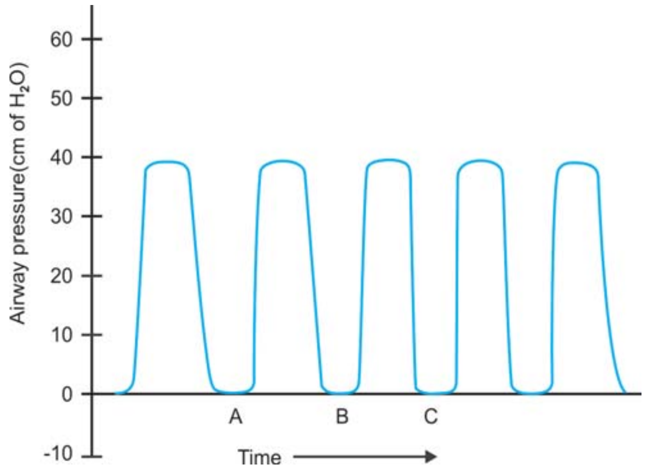

Fig. 140.1: A graphical presentation of CMV

Pressure Controlled (Targeted) Ventilation (PCV)

Pressure controlled ventilation, unlike volume targeted modes, is pressure and time cycled and generates tidal volumes that vary with the impedance of the respiratory system. The ventilation is determined by f, the inspiratory pressure increment (Pinsp-PEEP) and I:E ratio. A working understanding of the factors that determine volume delivery is necessary for proper implementation of this mode of ventilation.

During the inspiratory phase of PCV, gas flows briskly into the ventilator circuit to pressurize the system to a specified target. Once the target pressure has been reached, flow is adjusted to maintain a flat or "square wave" pressure profile over the remainder of the set inspiratory time.[22,23] This is achieved by measuring airway pressure approximately every 2 ms to provide critical feedback to flow controller mechanisms within the ventilator. By tracking the rate of change in pressure during inspiration, appropriate deceleration can occur as the pressure ceiling is approached. Flow is brisk, if the gradient between the circuit pressure and pressure target is large. As in patients without severe obstruction, given a sufficiently long TI, there is equilibrium between the ventilator-determined Pinsp and Palv and inspiratory flow ceases. In such cases, VT can be predicted based on Pinsp (=Palv) and the mechanical properties of the respiratory system (Crs). As the gradient between the recorded pressure and preset target narrows, flow decelerates to prevent overshoot. In situations of severe airflow obstruction or if TI is too short to allow equilibration between ventilator and alveoli, VT will fall below the predicted, based on Pinsp and Crs.

Advantages of PCV: PCV facilitates ventilation with a lung protective strategy. When one of the goals of ventilator management is to limit alveolar overdistention, PCV ensures that Palv never exceeds prefixed threshold value (usually 30 to 35 cm H_2O). Pressure limits and decelerating flow profiles are thought to produce more uniform distribution of forces within the lung, possibly reducing the risk of barotrauma. PCV leads to improved oxygenation, higher static and dynamic compliance along with improved measures of work of breathing. PCV is increasingly used in ARDS patients to deliver Inspiratory Reserve Volume (IRV), in which the TI exceeds the Expiratory Time (TE).

Disadvantage of PCV: PCV, especially when done as IRV, generally requires sedation and sometimes paralysis, which may have adverse effects on weaning.

Assist Control Mode of Ventilation (ACMV)

This is the most commonly used mode of ventilation all over the world. It delivers controlled breaths as well as assists patient triggered breaths. During ACMV, operator can set the inspiratory flow rate ($\dot{V}$), frequency (f) and tidal volume (VT). In some ventilators, one must set the total minute ventilation and rate, thereby determining VT and indirectly determining $\dot{V}$. In fully paralyzed or sedated patients, ACMV behaves like CMV delivering tidal breaths per minute at a operator set rate. Tidal volume and $\dot{V}$, determine the TI, TE and I:E ratio. In turn, Pplat depends on VT and Crs. Patient having their own adequate respiratory effort can trigger the ventilator (Fig. 140.2). During such a breath, the ventilator assists the patient and delivers the set VT at patient's respiratory rate. This ability to trigger extra breaths may change TI, TE, and I:E ratio, may create or increase auto-PEEP. This can be overcome by setting controlled ventilator frequency, a few breaths per minute below the patient's rate, so the control rate serves as an adequate support should the patient stop initiating breaths. If high inspiratory effort continues during the ventilator-delivered breath (few patients may trigger a second or third superimposed/stacked breath), it will lead to breath stacking.

On ACMV mode, patients continue to perform inspiratory work even on ventilator.[7,24] This may not be easily appreciated, despite careful examination of the patient, unless intrathoracic pressures (esophageal pressure or central venous pressure) are measured. Since effort at the end of the breath will affect the Peak Pressure (Ppk) and Pplat, determination of respiratory system mechanics may be unreliable. Clues to patient effort are

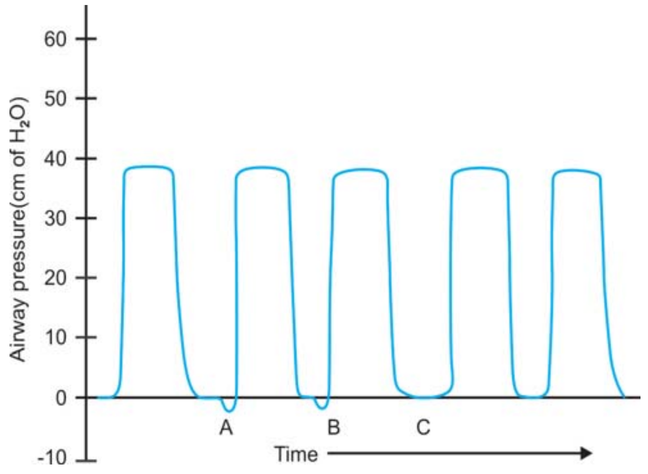

Fig. 140.2: A graphical presentation of Assist Controlled Mechanical Ventilation (ACMV). Each assisted as well as controlled breath, triggers a mechanical ventilator to deliver tidal volume. The assisted breath is characterized by a negative deflection at the beginning of inspiration (breath A and B). While in controlled breathing, there is no negative deflection at the onset of inspiration (breath C)

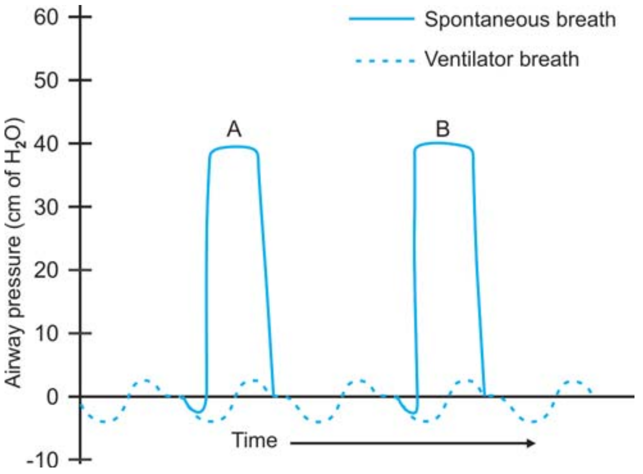

Fig. 140.3: A graphical presentation of Synchronized Intermittent Mandatory Ventilation (SIMV). Tracing is showing two mandatory breaths (A and B) and five triggered breaths. In SIMV the mandatory breaths may be delivered slightly sooner or later (during a small window period) than the preset time, so that the anticipated breath during this is converted into mechanical breath

also often available from the airway pressure tracing (Fig. 140.2). If patient is assisting every breath, the work of breathing can be increased, by either increasing the magnitude of the trigger or by lowering VT. Lowering of "f" at the same VT, generally has no effect on work of breathing.

Indications of ACMV Mode

The ACMV mode is most often used to provide full ventilatory support in the first place. Typically, these patients are having stable respiratory drive (an adequate inspiratory effort of atleast 10 to 12 breaths per minute) and therefore can trigger the ventilator into inspiration. The time-triggering control rate (back up rate) is generally considered as safety net, to provide adequate ventilation in case the patient stops triggering the ventilator. In general, the accepted minimum control rate for ACMV mode is 2 to 4 breaths per minute, lower than the patient's assist rate or a minimum control rate of 12 to 15 breaths per minute.

Advantages of ACMV Mode

There are two advantages of ACMV mode. First, the work of breathing, which is required is minimal when trigger sensitivity is set appropriately and when ventilator supplies adequate flow that meets or exceeds patient's inspiratory demand. Second, if the patient has an appropriate ventilatory drive, this mode allows the patient to control the respiratory rate and hence the minute ventilation.

Complications of ACMV Mode

Alveolar hyperventilation or respiratory alkalosis is the most important complication associated with ACMV mode. Patients on ACMV had higher pH and lower $PaCO_2$, when compared to Intermittent Mandatory Ventilation (IMV).[25,26] This may be an important consideration in patients having inappropriately high respiratory drive/rate due to disease/injury to respiratory center.

Synchronized Intermittent Mandatory Ventilation (SIMV)

SIMV works as CMV in fully paralyzed patients, where ventilation is determined by the mandatory f, VT and V. However in SIMV, if the patient is having breathing effort, he or she may perform respiratory work during the mandatory breaths also. Moreover, the patient can trigger additional breaths, by lowering Airway Opening Pressure (Pao) below the trigger threshold (Fig. 140.3). If this triggering effort comes in a brief, defined interval (synchronization window) before the next mandatory breath is due, the ventilator will deliver the mandatory breath ahead of the scheduled breath, in order to synchronize with the patient's inspiratory effort. If a breath is initiated outside the synchronization window,

V_T, V and I:E ratio are determined by patient's effort and respiratory mechanics, not by ventilator settings. These spontaneous breaths tend to be small and variable from breath to breath. In the absence of breathing effort by the patient, ventilator will deliver a tidal breath with preset V_T and rate. The SIMV mode is often used to gradually augment the patient's work of breathing for weaning. This can be achieved by lowering either the mandatory breath or the V_T. This approach prolongs the process of weaning.[27,28]

Indications for SIMV mode

The primary indication of SIMV is to provide partial ventilatory support, so patient is actively involved in providing part of minute volume. For practical purpose, full ventilatory support is provided usually for the first 24 hours. After this initial period of full ventilatory support, the usual practice of partial ventilatory support, such as SIMV is tried. SIMV have been used for weaning by gradually reducing the rate, but it prolongs weaning, as compared to that with pressure support or spontaneous breathing trial.

SIMV promotes spontaneous breathing and use of respiratory muscles, which results in:

1. Maintenance of respiratory muscle strength and avoids muscle atrophy.
2. Reduced ventilation-perfusion mismatch.
3. Decreased mean airway pressure.
4. Help in weaning. SIMV has inherent property to provide a spontaneous breathing work load that gradually increases patients' muscle strength and endurance. The primary disadvantage is breath wasting, which may occur when patient breathes outside the synchronization window. Although SIMV is commonly used for weaning, this approach prolongs the process of weaning.

Pressure-Support Ventilation (PSV)

Pressure support ventilation is delivered to the mechanically ventilated patient during spontaneous breathing. It is a triggered mode, with changes in airway pressure or flow used as the trigger signal. Ventilation is determined by Pinsp, patient-determined f and patient effort. Following detection of spontaneous patient effort, the ventilator delivers a breath that is flow cycled but time limited. Once a breath is triggered, the ventilator attempts to maintain Pao at the preset Pinsp using whatever flow is necessary. Eventually, flow begins to fall due to cessation of the patient's inspiratory effort, or due to increasing elastic recoil of the respiratory system as VT rises. The termination point is determined by the algorithm within the ventilator, it is usually a function of the delivered tidal volume. At the termination point, inspiratory flow ceases and the breath cycles directly into expiration.

PSV, although is commonly used for weaning purpose, has a potential for providing full ventilatory support. A potential advantage of pressure-support ventilation is improved patient comfort.[29] When a patient is well maintained (on clinical and ABG parameters) at a PS of 5–7 cm of H_2O, it indicate that patient can be extubated.

Patients' own effort is essential for PSV. PSV can account for a large fraction of total minute ventilation, even when set at rather low levels in patients with normal respiratory system mechanics. Old ventilators do not have a back support with PSV, therefore there is risk of apnea/hypoxia. Pressure support ventilation is commonly used for weaning.

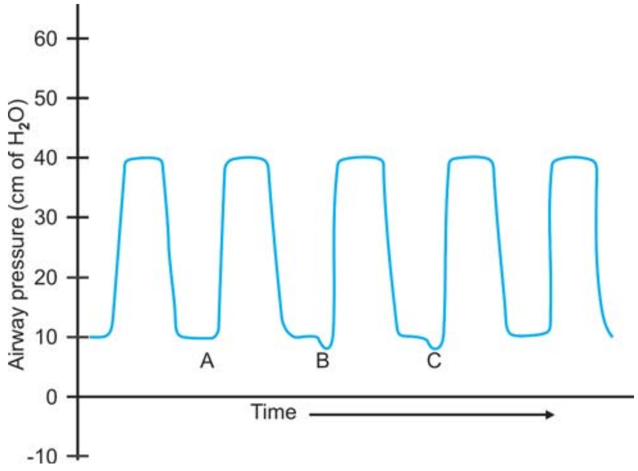

Fig. 140.4: A graphical presentation of Positive End-Expiratory Pressure (PEEP). It is a pressure tracing of assist controlled mode of mechanical ventilation with a PEEP of 10 cm of H_2O. "A" is controlled breath, while "B" and "C" is an assisted breath with PEEP

Positive End Expiratory Pressure

Positive end expiratory pressure increases the end expiratory or baseline airway pressure to a value greater than atmospheric pressure (Fig. 140.4). Positive end expiratory pressure is not commonly regarded as a stand-alone mode, rather it is applied in conjunction with other ventilatory modes. It is used mainly to recruit or stabilize lung units and improve oxygenation in patients with hypoxemic respiratory failure.

Advantages of PEEP

Use of PEEP has positive effects on both the gas exchange and lung mechanics.[30,31] Following are the advantages of PEEP:

Gas Exchange

1. Redistributes fluid within the alveoli and reduces intrapulmonary shunting.
2. Improves arterial oxygenation (PaO_2).
3. Reduces FIO_2 requirement and risk of oxygen toxicity.

Lung Mechanics

1. Helps in preventing alveolar collapse.
2. Stabilizes and recruits lung units.
3. Increases functional residual capacity.
4. Improves lung compliance.
5. Shifts tidal deflections to the right along the inspiratory pressure-volume curve, minimizing potential for ventilator-induced lung injury, by preventing repetitive collapse of lung units at end-expiration followed by reopening during inspiration.
6. May decrease the inspiratory work of breathing due to auto-PEEP in patients with obstructive airway disease.

Indications of PEEP

Indications of PEEP include the respiratory failure due either to intrapulmonary shunting or decreased functional residual capacity, for example, acute lung injury and acute respiratory distress syndrome, cardiogenic pulmonary edema, diffuse pneumonia requiring mechanical ventilation, atelectasis associated with severe hypoxemia and other forms of severe hypoxemic respiratory failure. PEEP is also used in patients with COPD, where there is significant intrinsic PEEP. External PEEP is given approximately at the level of 80% of the intrinsic PEEP. It helps in the easy triggering of breath by counteracting intrinsic PEEP.

Complications of PEEP

The hazards associated with use of PEEP include:

1. Decreased venous return and cardiac output leading to hypotension.
2. Barotrauma.
3. Increased intracranial pressure.
4. Alteration in renal function and water metabolism.

Continuous Positive Airway Pressure (CPAP)

Conceptually, CPAP is not a mode of ventilation, but rather a means of raising functional residual capacity while patient is breathing spontaneousoly. In this mode, ventilatory support is pressure-limited and pressure or flow-triggered, i.e. the spontaneous breath has a pressure limit that remains nearly the same, (within few centimeters of water) during both inspiration and expiration (Fig. 140.5). The patient's inspiratory effort causes the ventilator to increase the flow to the patient to maintain the same pressure during inspiration. During expiration, the flow out of the exhalation valve maintains the expiratory pressure fairly uniform. No mechanical positive pressure breaths are given.

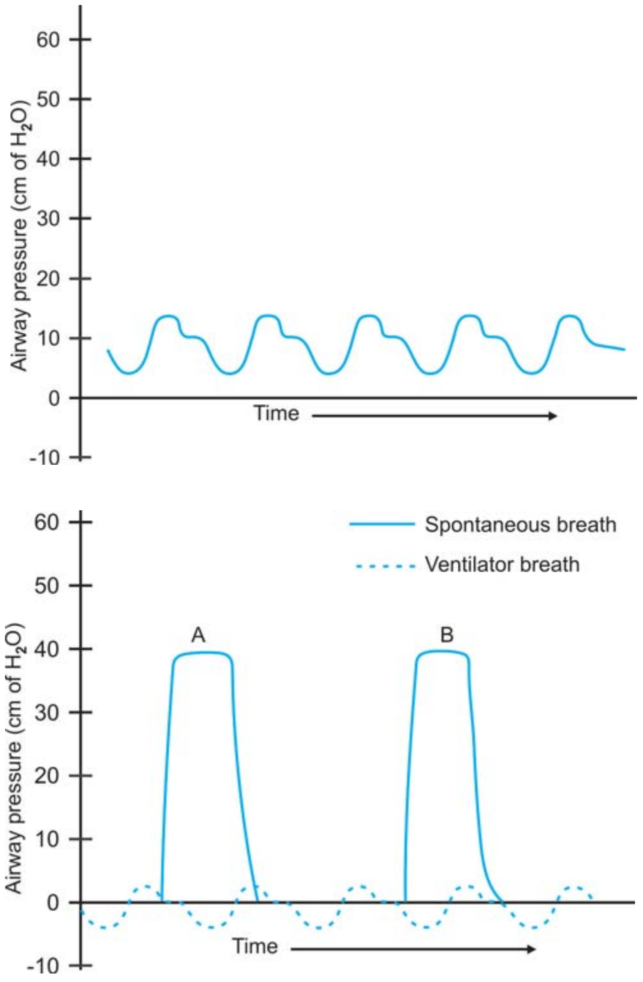

Fig. 140.5: Graphical presentation of CPAP of 14 cm of H_2O

Indications of CPAP

This approach is frequently used to assess the patient's ability to breathe without ventilatory support.
The advantages of CPAP over T-piece breathing are:

1. Improved oxygenation.

2. Detection of low minute ventilation and apnea (as ventilator alarms remain in place).
3. The patient's spontaneous tidal volumes and rate can be easily read.
4. The work of breathing is reduced, if auto-PEEP is present.[32,33]

Bi-Leveled Positive Airway Pressure (Bi-PAP)

Conceptually, Bi-PAP is a mode which combines PEEP with PS and is used more in context of Non-Invasive Ventilation (NIV) using a nasal or oronasal mask. In this mode, both Expiratory Positive Airway Pressure (EPAP) as well as Inspiratory Positive Airway Pressure (IPAP) are adjustable. IPAP helps in improving alveolar ventilation, normalization of $PaCO_2$ and reduction in work of breathing, whereas EPAP improves oxygenation by reducing intrapulmonary shunting. Previously, Bi-PAP was given by dedicated NIV machines. However, majority of the newer ventilators have this facility with inbuilt pressure-controlling valve to maintain a desired EPAP and IPAP levels. Inspiration is triggered at the inspiratory flow of greater than 40 ml/sec for more than 30 milliseconds. Expiratory flow is detected when the inspiratory flow decreases below a manufacturer-determined threshold level (flow cycled) or when IPAP is longer than 3 s (time cycled).

Usual initial setting of EPAP and IPAP are 4 cm of H_2O and 8 cm of H_2O, respectively. Further adjustments are done based on the cardiopulmonary response. If the response is positive, the IPAP may be increased with increment of 2 cm of H_2O to improve alveolar ventilation. Similarly, EPAP may also be increased to improve oxygenation. When EPAP and IPAP are equal, it behaves like CPAP.

Indications of Bi-PAP

Bi-PAP has value in preventing endotracheal intubation in many conditions leading to respiratory failure, such as COPD, pulmonary edema, pneumonia, acute lung injury and ARDS. It also helps in weaning and avoiding intubation in patients with respiratory failure during postextubation period.

NEWER MODES OF MECHANICAL VENTILATION

Inverse Ratio Ventilation (IRV)

IRV is not a different mode of ventilation, instead it is a maneuver to improve oxygenation in cases with severe hypoxic respiratory failure. During IRV, inspiratory time is kept equal/more than expiratory time resulting in I:E ratio is greater than 1. There are two general ways to apply IRV:

1. Pressure-Controlled IRV (PC-IRV), in which a preset airway pressure is delivered for a fixed period of time.
2. Volume-Controlled IRV (VC-IRV), in which a tidal volume is delivered at a slow (decelerating) inspiratory flow rate, keeping I:E ratio greater than 1.

For PC-IRV, variables controlled by the physician must specify the inspiratory airway pressure, f and I:E ratio, while VT and flow profile are determined by respiratory system impedance as discussed for PCV. The commonly used initial settings for PC-IRV are:

Pinsp = 20–40 cm H_2O (or 10–30 cmH_2O above the PEEP),
f = 20/min and the I:E = 2:1 to 4:1

For VC-IRV, the operator selects a tidal volume, f, V (a low value), flow profile and possibly, an end-inspiratory pause. The chosen values result in an I:E ratio greater than 1:1 and as high as 5:1. As there a risk of auto PEEP, the PC-IRV is preferred over VC-IRV.

Compared with conventional modes of ventilation, lung oxygen exchange is often improved on IRV. The mechanisms involved are increased mean alveolar pressure and volume, creation of auto PEEP, which reduces shunt by redistributing alveolar edema into the pulmonary interstitium.[34,35] Major disadvantage of IRC (both PC-IRV and VC-IRV) is requirement of heavy sedation with or without muscle paralysis, which may have adverse effect on the outcome.

High Frequency Ventilation

High Frequency Ventilation (HFV) attempts to achieve adequate gas exchange, by using asymmetrical velocity profiles when combining very high respiratory rates with V_T smaller than the volume of anatomic dead space (Fig. 140.6). These modes include High Frequency Oscillatory Ventilation (HFOV) and High Frequency Jet Ventilation (HFJV). It is used more commonly in neonates and infants with neonatal respiratory failure. There has been a renewed interest in using HFV in adult patients with ALI/ARDS, with the rationale that the small tidal volumes may cause less ventilator associated lung injury. Theoretical benefits of HFV include, lower risk of barotrauma due to smaller tidal excursions, improved gas exchange through a more uniform distribution of ventilation and improved healing of bronchopleural fistulas.[36] A substantial risk is that dynamic hyperinflation is the rule. However, more trials are necessary to determine, if HFV can improve mortality outcomes in these patients. [37]

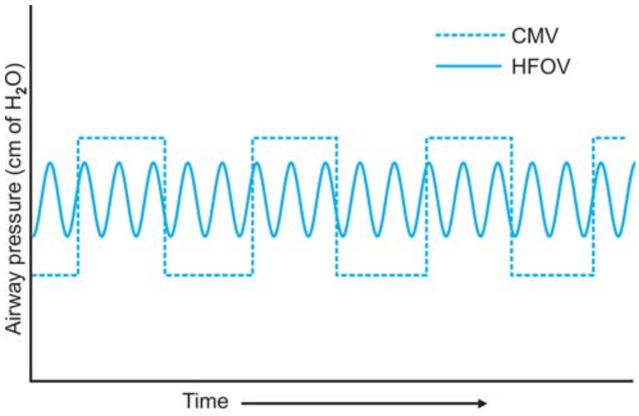

Fig. 140.6: A graphical presentation of high frequency ventilation (solid line), comparing the controlled ventilation (dotted line)

Airway Pressure Release Ventilation (APRV)

Airway pressure release ventilation is similar to CPAP, in that patient is allowed to breathe spontaneously without restriction. During APRV, the clinician sets a "pressure high", "pressure low" and a time at each level (time high and time low) (Fig. 140.7). Ventilation occurs during the release from pressure high to pressure low. The "time low" is typically 0.2–0.8 seconds in restrictive lung disease and 0.8–1.5 seconds in obstructive lung disease. It is probably most prudent to start at 0.8 and titrate to meet individual patient requirements. The time low is also referred to as the release phase.[38] During spontaneous exhalation, the PEEP is dropped (released) to lower level, this action simulates the process of exhalation. A common occurrence in this mode is setting the "time low" too long. This essentially mimics a pressure-targeted SIMV strategy. The patient typically spends 4–6 seconds in "time high".

In the paralyzed patient APRV/Bi-Level is identical to pressure targeted inverse ratio ventilation. For these reasons, some have described this mode as Inverse Ratio Ventilation (IRV). However, a major difference between APRV/Bi-Level and IRV is that IRV typically requires chemical paralysis or heavy sedation. APRV/Bi-Level allows for spontaneous breathing throughout both pressure levels, making it relatively more comfortable and typically does not require heavy sedation or paralysis. APRV/Bi-Level has gained popularity in patients with hypoxemic respiratory failure because it improves oxygenation by optimizing alveolar recruitment and V/Q matching.[39]

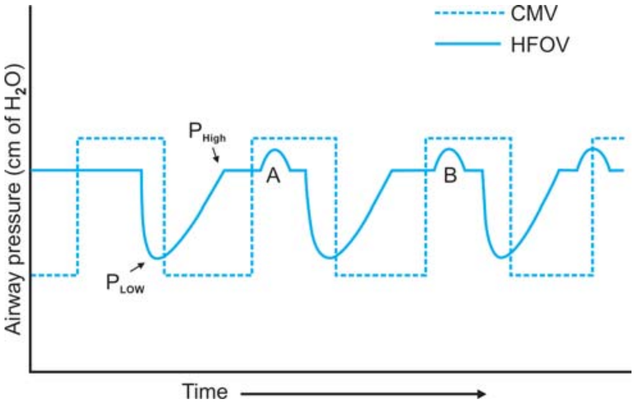

Fig. 140.7: A graphical presentation of airway pressure release ventilation (solid line), as compared to controlled ventilation (dotted line). This pressure-time tracing is showing two spontaneous breaths (a and b) at P_{High}

Proportional Assist Ventilation (PAV)

This is a form of partial ventilatory support developed to avoid some of the adverse effects of CMV, such excessive ventilation, use of sedative/paralytic agents and muscle disuse atrophy. Proportional Assist Ventilation (PAV) is based on the principle that during partial support, the Pressure applied to the Respiratory System (P_{RS}) is contributed by the Pressure produced by the Respiratory Muscles (P_{MUS}) and the Ventilator (P_{AW}), the latter of which represents the amount of assistance delivered.

$$P_{RS} = P_{MUS} + P_{AW}$$

The load imposed on the respiratory muscles during assisted ventilation can be described by the equation of motion as follows:

$$P_{MUS} = R \times \dot{V} + E \times VT + PEEPi - P_{AW}$$

where V is flow, VT indicates volume displacement, R is respiratory system resistance, E is respiratory system elastance, and PEEPi is the end-expiratory elastic recoil pressure, which the respiratory muscles must overcome at the onset of inspiration to trigger the ventilator. During PAV, the ventilator instantaneously delivers positive pressure throughout inspiration, in proportion to patient-generated flow (flow assist, units cm $H_2O/l/s$) and volume (volume assist, units cm H_2O/l). The pressure applied by the ventilator (P_{AW}) therefore is:

$$P_{AW} = FA \times \dot{V} + VA \times VT$$

During PAV, the ventilatory support depends on patient's efforts, the more the demand, the greater will be the delivered pressure, flow and volume.[40] It does not apply a set pressure, flow or volume, instead it boosts the sensed patient effort according to a proportion set by the clinician. This contrasts with volume assist ventilation, where flow and volume may be "pulled down" by the effort. PAV also contrasts with pressure assist/support, in which flow and volume are affected by the effort but pressure is not.

Advantages of PAV

PAV has been shown to be effective in unloading the respiratory muscles,[33,41-43] without imposing a fixed breathing pattern,[44] in enhancing patient comfort,[45] and patient-ventilator interaction.[46] Two recent, randomized clinical trials have demonstrated, improved patient comfort during noninvasive ventilation with PAV compared with PSV. [47,48]

Complications of PAV

Despite these positive results, PAV still seems to be more of an intellectually satisfying research tool than a ventilatory treatment in the clinical setting. There are number of practical limitations which hinder the use of PAV.[40] The most important limitation is that proper adjustments of PAV settings require knowledge of the mechanical characteristics of the respiratory system, this information is not easy to obtain in patients receiving partial support.[49-53] Furthermore, the PAV algorithm is based on the equation of motion, which assumes resistance and elastance to be linear within the tidal breathing range. This assumption may not always be valid in ICU patients. Moreover, neuromechanical coupling, the transformation of respiratory muscle activation into mechanical output (P_{MUS}) is important for tidal breaths. There are several factors which can lead to neuromechanical uncoupling in ICU setting, such as fatigue, electrolyte, acid-base disorders and shock contributing to decreased P_{MUS}.[54-57] Other problems which may be observed during PAV include, ventilator-patient asynchrony and the presence of air leaks. [48]

Proportional Assist Ventilation Plus and Proportional Pressure Support

Proportional Assist Ventilation Plus (PAV+) and Proportional Pressure Support (PPS) are forms of synchronized ventilatory assistance, where the ventilator generates pressure in proportion to the patient's effort, i.e. the greater the effort, the more the pressure the ventilator generates. Therefore, the clinician determines the level of resistive and elastic unloading, irrespective of volume or flow requirements.

Neurally Adjusted Ventilatory Assist (NAVA)

Neurally adjusted ventilatory assist was developed in an attempt to overcome the limitations of PAV, while maintaining all of its potential advantages. During this mode of ventilation, the electrical activity of the inspiratory muscles is used as an index of the inspiratory neural drive.[58] The neural drive is measured as crural Diaphragm Electrical Activity (EAdi), detected by means of esophageal bipolar electrodes, as it express global diaphragm activation.[59-63] Further, esophageal electrodes are not affected by the activity of postural and expiratory muscles (cross-talk) or by the subcutaneous tissues, which can be a problem with skin surface electrodes. The array of bipolar electrodes can be mounted on a nasogastric tube, which is introduced in almost all critically ill patients. The signal obtained by these electrodes is then transferred to the ventilator to regulate the ventilation support, which is therefore instantaneously applied in relation to EAdi. Thus, cycling and the intrabreath assist profile are determined directly by the EAdi, whereas the amount of assistance for a given EAdi depends on a user-controlled gain factor. As the ventilator is triggered directly by EAdi with NAVA, the synchrony between neural and mechanical inspiratory time is guaranteed both at the onset and at the end of inspiration, regardless of PEEPi, air leaks and respiratory mechanics.

Advantages of NAVA

In the absence of any significant disease of the respiratory centers, phrenic nerves and neuromuscular junctions and drugs suppressing the ventilatory drive, the ventilatory support provided corresponds to the ventilatory demand of the patient, irrespective of variations in muscle length or contractility. The use of neural control of mechanical ventilation has the capability to dramatically enhance the coordination between mechanical ventilation and respiratory muscle activity, thereby improving patient comfort.

Limitations of NAVA

Although NAVA may be considered as a major advance in the care of the critically ill, it is not currently available for clinical use and serves only as a research tool. It has been used primarily in healthy subjects for short-term studies, by only a few investigators. The effects of this mode on breathing pattern and gas exchange have yet to be evaluated and it remains to determine, whether NAVA can maintain adequate levels of support in different kinds of respiratory failure from admission to weaning.

Biologically Variable Ventilation

Biologically Variable Ventilation (BVV) is a new mode, which was designed to improve the management of ARDS. Controlled mechanical ventilation is often required for treatment of ARDS, however the loss of physiological variability of breathing pattern may contribute to deterioration in respiratory mechanics and gas exchange.[64] Biologically variable ventilation mimics spontaneous breath-to-breath variability, incorporating natural variable noise into volume-targeted controlled mechanical ventilation, which may overcome this limitation. The ventilator has a programme to modulate respiratory rate and VT, while maintaining a fixed minute ventilation based on a previously generated data file.[64]

It is important to recollect that recruitment is a continuous and progressive phenomenon that depends not only on PEEP, but also on the inflation volume.[65-68] The rationale behind BVV is based on the concept that the alveolar recruitment achieved by high volumes exceeds the derecruitment caused by small volumes, resulting in improvement in lung compliance and oxygenation without an increase in mean airway pressure.[69]

Advantages of BVV

Biologically variable ventilation has been compared with conventional controlled ventilation in a series of animal studies. BVV significantly improved oxygenation in healthy animals during general anesthesia.[70] It has been shown to be useful after re-expansion of a collapsed lung and in ARDS, with and without PEEP.[64, 71, 72] Boker et al., also compared the low tidal volume ARDS network protocol with BVV in a porcine model of ARDS and found a decreased concentration of proinflammatory cytokines in the tracheal aspirate, improved oxygenation and decreased shunt fraction.[73] BVV variability results in periodic deep inflations and the mere application of periodic sighs has also been shown to provide beneficial effects.[65,74] Comparing these two strategies, BVV is found to be more effective than periodic sighs of the same magnitude and frequency as the higher BVV tidal volumes.[71]

Limitations of BVV

Although there are impressive results with BVV use in animal studies, no human study has been conducted yet. There are dissimilarities between different animal species, therefore the effects observed in animals should be carefully extrapolated to humans. Indeed, others have failed to reproduce the benefits of BVV in a canine model of oleic acid-induced ARDS.[75] Further, its effects on conditions of different severity or diverse origins are also not clear.[69]

Hybrid or Mixed Modes

Some ventilators allow combinations of modes, most commonly SIMV plus PSV. There is little reason to use such a hybrid mode, although some physicians use the SIMV mode as a means to add sighs to PSV, an option not otherwise generally available. It is advantageous in that SIMV plus PSV guarantees some backup minute ventilation (which PSV does not). It is many times used for difficult to wean patients.

INITIATING MECHANICAL VENTILATION

Initial Ventilator Settings

Initial ventilator settings depend on the goals of ventilation, i.e. full respiratory muscle rest versus partial exercise, the patient's respiratory system mechanics and the needed minute ventilation. Each critically ill patients present unique challenges. Some common clinical scenarios are described below:

Patients with Normal Lung Mechanics and Gas Exchange[76]

These patients may require mechanical ventilation because of:

1. Loss of central drive to breathe (drug overdose or structural injury to the brainstem).
2. Due to neuromuscular weakness (high cervical myelopathy, myasthenia gravis).
3. Treatment of shock (as adjuvant therapy).
4. To achieve hyperventilation (treatment of raised intracranial pressure).

Following are the acceptable initial setting after intubation:

FiO_2 of 0.5 to 1.0
VT 8 to 12 ml/kg, f of 8 to 12 per minute
Inspiratory flow rate of 40 to 60 l/min

In patients with preserved respiratory derive and without profound weakness, PSV can be used. The pressure support is adjusted (usually 10 to 20 cm H_2O above PEEP), to bring the respiratory rate down into the low twenties, usually corresponding to tidal volumes of about 500 cc. It should be noted that PSV is entirely spontaneous, with no machine backup. Therefore, hypoventilation may occur despite the use of PSV, if there is further deterioration of muscle strength or blunting of respiratory drive. Once stabilized, effort should be made to bring down FiO_2 less than 0.6. For hyperventilation, the initial respiratory rate should be increased to the range of 16 to 20 breaths per minute. If patient complains of air hunger, the inspiratory flow rate can be increased, but 40 to 50 l/min is often sufficient,[24] flow greater than 60 l/min is rarely required.

Airway pressure and flow waveforms should be inspected for evidence of patient-ventilator dys-synchrony or undesired patient effort. To provide full rest, the patient's drive can be suppressed by increasing the inspiratory flow rate, frequency or tidal volume.[77] If such adjustments are ineffective, then sedation may be necessary. If sedatives also do not abolish inspiratory efforts and full rest is essential (as in shock), muscle paralysis should be considered.

Preventive measures for atelectasis should include sighs (6 to 12 per hour at 1.5 to 2 times the VT) or small amounts of PEEP (5 to 7.5 cm H_2O). This is specially required in patients with neuromuscular diseases. Three-point turning and chest physiotherapy are desirable in all patients, unless other conditions preclude their use. Rotating beds are effective in some patients in preventing atelectasis and pneumonia.[78]

Patients with Severe Airflow Obstruction

The common conditions included in this category are bronchial asthma and Chronic Obstructive Pulmonary Disease (COPD).

Bronchial asthma: Patients with acute severe asthma requiring mechanical ventilation are usually extremely anxious and distressed. Deep sedation should be routinely provided, a few patients may require therapeutic paralysis, although paralytic drugs occasionally causes long lasting weakness.[79,80] These interventions help to reduce oxygen consumption (and hence carbon dioxide production), to lower airway pressures and to reduce the risk of self-extubation.

The gas exchange abnormalities of airflow obstruction are largely due to ventilation-perfusion mismatch. Ventilation should be initiated using the A/C mode (or SIMV), the tidal volume should be small (5 to 7 ml/kg) and the respiratory rate should be 12 to 15 breaths per minute. A peak flow of 60 l/min is recommended, higher flow rates do not increase expiratory rate significantly. An FiO_2 of 0.5 suffices in the vast majority of patients.[81] Requirements for a higher FiO_2 should prompt a search for an alveolar filling problem or for lobar atelectasis. Finally, if the patient is triggering the ventilator, some PEEP should be added to reduce the work of triggering, although this may occasionally compound the dynamic hyperinflation, potentially compromising the cardiac output. Usually, auto-PEEP increases little as long as PEEP is not set higher than about 85% of the auto-PEEP.[82,83] The targets should be, to minimize alveolar overdistention (Pplat less than 30) and dynamic hyperinflation (auto-PEEP below 10 cm H_2O or end-inspiratory lung volume less than 20 ml/kg), a strategy that largely prevents barotrauma.[84] Reducing minute ventilation to achieve these goals generally causes the PCO_2 to rise above 40 mm Hg, (permissive hypercapnia) often to 70 mm Hg or higher. This requires sedation, such permissive hypercapnia is quite well tolerated.

Careful attention should be paid to the inspiratory flow and flow profile. The flow changes, which have little effect in normal individual without airflow obstruction, can have a dramatic impact in obstructed patients. Specifically, reduction in the inspiratory flow or switching to a decelerating flow profile, reduces the airway pressures and the amount of ventilator alarming. But the same actually worsens auto-PEEP, by prolonging inspiration. Therefore, a close watch should be kept on auto-PEEP and expiratory flow profile.

Chronic obstructive pulmonary disease: Unlike patients with status asthmaticus, COPD patients have expiratory flow limitation, arising largely from loss of elastic recoil. As a consequence, in a patient with COPD, the peak airway pressures on the ventilator tend not to be extraordinarily high, still auto-PEEP and its consequences are common.[85] The majority of patients with COPD will appear exhausted, at the time when mechanical support is instituted and will sleep with minimal sedation. To the extent that muscle fatigue has played a role in a patient's functional decline, rest and sleep are desirable. Also, such a patient has underlying compensated respiratory acidosis. Hyperventilation carries the risk of severe respiratory alkalosis and bicarbonate wasting by the kidney. The initial ventilator settings of a tidal volume of 5 to 7 ml/kg and a respiratory rate of 24 to 28 breaths per minute, with either an SIMV or an A/C mode, set on minimal sensitivity can achieve the goal of rest and relative hypoventilation. Usually, good oxygenation can be achieved with a FiO_2 of 0.4. Inspiratory flow rates may be adjusted for patient comfort, but usually in the range of 60 l/min. PEEP should be used, when the patient is triggering the ventilator, but is not required in sedated patient.

Usually, two to three days of rest restore biochemical and functional changes associated with muscle fatigue, but 24 hours is probably not sufficient.[54] A few patients on the ventilator are difficult to rest and continue to demonstrate a high work of breathing. Airway pressure and flow waveforms may be used to identify these patients and strategies for improving the ventilator settings. Auto-PEEP may be responsible for this problem, when addition of extrinsic PEEP to nearly counterbalance the auto-PEEP may dramatically improve the patient's comfort.[83] Another approach is to increase minute ventilation, although this worsens auto-PEEP and bicarbonate loss. A careful search should be made for problems that might drive the patient to a respiratory rate higher than is desirable, e.g. hypoperfusion, pleural effusion or pain. If the patient continues to make significant inspiratory efforts after correction, judicious sedation is advised. Once the patient improves and the respiratory muscles are adequately rested, the patient should assume some of the work of breathing and be evaluated for weaning. During this phase, some extrinsic PEEP is typically useful to reduce the work of triggering.[83]

Patients with Acute Lung Injury (ALI) or Adult Respiratory Distress Syndrome (ARDS)

Acute lung injury and ARDS are inflammatory conditions, resulting from a broad spectrum of lung injury leading to mild respiratory abnormality to severe respiratory derangement. Respiratory dysfunction often develops during early phase of (within 48 hours) of the physiologic insult,[86] may take weeks to months to resolve. Regardless of the cause, the pulmonary physiology and the mechanics are altered, leading to hypoxemic respiratory failure. The use of positive pressure ventilation itself may cause lung injury (Ventilation induced lung injury), that may amplify pre-existing injury, delay lung recovery and result in adverse outcomes. In ARDS, the Functional Residual Capacity (FRC) is reduced due to alveolar flooding and collapse, leaving fewer alveoli to accept the tidal volume. This result in stiff lung, the work of breathing is increased dramatically. The ARDS lung should be viewed as a small lung (baby lung), rather than a stiff lung. In line with this current conception of ARDS, ventilatory strategies have evolved markedly in the past decade. The goals of ventilation are to reduce shunt, avoid toxic concentrations of oxygen and choose ventilator settings that do not amplify lung damage.

The initial FiO_2 should be 1.0, in view of the typically extreme hypoxemia. PEEP should be instituted immediately, beginning with 15 cm H_2O, rapidly adjusted thereafter either to produce an arterial saturation of 90% on an FIO, less than 0.6 ("least PEEP approach") or a value 2 cm H_2O higher than the lower inflection point of the inflation pressure-volume curve ("open-lung approach").[87] The tidal volume should be 5 to 7 ml/kg on A/C or SIMV, since higher tidal volumes usually overdistend the lung at end inspiration, as judged by the upper inflection point of the respiratory pressure-volume curve,[88] which may even contribute to systemic inflammation.[89] Alternatively, PCV can be used with an inspiratory pressure (PEEP plus the pressure increment) of 30 to 35 cm H_2O. This will generally drive VT of 350 to 550 ml/kg. In both modes the respiratory rate of 24 to 28 breaths per minute is acceptable, as long as there is no auto-PEEP. The combination of high levels of PEEP (especially when the open-lung approach is used) and low end-inspiratory pressures, leaving only a small range for tidal ventilation is called as Lung Protective Ventilatory (LPV) strategy. A common consequence of LPV is hypercapnia ("permissive hypercapnia").

The ventilatory settings, which are followed most widely are based on ARDSnet trial.[90] The same protocol is summarized below:

A. *Target a tidal volume* of 6 ml/kg Predicted Body Weight (PBW), with a goal of plateau pressures of 30 cm H_2O or lower and adjust tidal volume according to ARDSNet guidelines. For patients who develop ALI, while receiving tidal volumes in excess of 6 ml/kg, stepwise reductions in tidal volume of 1 ml/kg every 15 minutes, with concomitant increases in respiratory rate to maintain constant minute ventilation is advised to ease the transition.
    1. Choose a mode of ventilation: Although any mode may be used, the sentinel ARDSNet trial results were based on the use of continuous mandatory ventilation (assist/control) mode with volume-controlled ventilation setting. Importantly, plateau pressure may not reflect transpulmonary pressure in pressure-limited modes (pressure-

controlled ventilation and pressure support ventilation). If the patient is making active inspiratory efforts that lower the pleural pressure, in this situation, delivered tidal volumes and transpulmonary pressures may approximate those in the control arm (12 ml/kg) of the ARDSNet trial.

2. Calculate PBW:
   - Males: PBW(kg) = 50 + 2.3 [height(inches) 60]
   - Females: PBW(kg) = 45.5 + 2.3 [height (inches) 60]
3. Choose tidal volume goal of 6 ml/kg PBW
4. Set PEEP to 5 cm H_2O or higher
5. Measure and record plateau pressure, atleast every 4 hours and after any changes in tidal volume and PEEP:
   a. If plateau pressure greater than 30 cm H_2O, reduce tidal volume to 5 ml/kg and then to 4 ml/kg PBW, if necessary and to decrease plateau pressure to 30 cm H_2O or lower.
   b. If tidal volume less than 6 ml/kg PBW and plateau pressure less than 25 cm H_2O, increase tidal volume by 1 ml/kg PBW to a maximum of 6 ml/kg.
6. Adjust respiratory rate or tidal volume according to pH goals:
   a. If pH less than 7.30, consider increasing the respiratory rate to as high as 35/min, while monitoring for development of auto-PEEP.
   b. If pH less than 7.15 and respiratory rate greater than 35/min, consider increasing tidal volume and suspending the plateau pressure limit, depending on patient tolerance of the acidemia.
7. If severe dyspnea (less than three double-triggered breaths per minute or if airway pressure remains at or below PEEP level during inspiration), increase tidal volume to 7 or 8 ml/kg PBW, if plateau pressure remains less than 30 cm H_2O. If plateau pressure greater than 30 cm H_2O on 7 or 8 ml/kg PBW, revert to lower tidal volume, consider ventilator adjustments to improve patient synchrony and consider more sedation.
8. Set PEEP or FiO_2, to achieve oxygenation target of PaO_2 55 to 80 mm Hg or SpO_2 of 88% to 95%, using the PEEP and FiO_2 combinations.
   a. Increase FiO_2 or PEEP within 5 minutes of consistent measurements below the oxygenation target range.
   b. Reduce FiO_2 or PEEP within 30 minutes of consistent measurements above the oxygenation target range.
   c. Assess lung recruitability for patients with PaO_2/FiO_2 lower than 150 (with PEEP = 5 cm H_2O), consider using the higher PEEP/lower FiO_2 to set PEEP and FiO_2, if either or both of the following occur when PEEP is increased:
      i. Increase in respiratory system compliance (when PEEP is increased from 5 to 15 cm H_2O).
      ii. Reduced dead space fraction (or decrease in $PaCO_2$ at constant minute ventilation and tidal volume), when PEEP is increased from 5 to 15 cm H_2O.

B. *Select PEEP and FiO_2,* according to oxygenation criteria, using PEEP-FiO_2 combinations within the two ranges tested in the alveoli trial. In patients with high FiO_2 requirements (PaO_2/FiO_2 less than 150 with PEEP 5 cm H_2O), who demonstrate a reduction dead space fraction (or a fall in $PaCO_2$ at constant minute ventilation and tidal volume) or an improvement in respiratory system compliance, when PEEP is increased from 5 to 15 cm H_2O, the authors advise use of the higher PEEP/lower FiO_2 table. For patients who experience a fall in respiratory compliance or a rise in dead space fraction, when PEEP is increased to 15 cm H_2O (indicating overdistension) or who have active barotrauma or adverse PEEP-induced cardiovascular changes, the authors advise use of the lower PEEP/higher FiO_2 table. The two approaches produce similar clinical outcomes, when applied to patients who have ALI/ARDS, regardless of lung recruitability. This stratification aims at targeting higher PEEP, to the recruitable subset of patients, although such an approach is logical, it remains to be shown, whether such an approach improves outcomes.

C. *Minimize contributors to patient-ventilator dys-synchrony* (e.g. adequate sedation, trigger sensitivity, flow and other factors).

COMPLICATIONS OF MECHANICAL VENTILATION

Mechanical ventilation is associated with multiple complications as demonstrated in Table 140.1. Some of them may be related temporally and not caused by ventilatory support per sec, but many are a direct result of positive-pressure ventilation.

TABLE 140.1: Common complications associated with MV

Endotracheal intubation	*Complications*
a. During intubation	Trauma to teeth and soft tissue
	Esophageal intubation
	Vomiting and aspiration
	Hypoxia
	Arrhythmia
	Bradycardia
b. While intubated	Obstruction
	Pneumonia and atelectasis
	Aspiration
	Kinking of ET tube
	Mucosal injury
	Improper position
	Accidental extubation
c. Post extubation	Aspiration
	Laryngospasm
	Hoarness
	Laryngeal or subglottic edema
	Laryngeal stenosis
	Tracheal stenosis
Positive pressure ventilation	
a. Pulmonary	Barotrauma
	Ventilator associated pneumonia
	Deconditioning of respiratory muscles
	Oxygen toxicity
b. Extrapulmonary	Raised intracranial tension
	Hypotension
	Stress ulcer and cholestasis
	Renal dysfunction

A successful outcome of mechanical ventilation depends upon the avoidance and presentation of complications. Comprehensive intensive care of patient can therefore, be considered as essential component of mechanical ventilation.

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Noninvasive Ventilation

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INTRODUCTION

Assisted ventilation is an integral part of critical care which has significantly improved the outcome of these patients. However, conventional mechanical ventilation is associated with several complications, a large proportions of these are related to endotracheal intubation. Noninvasive Ventilation (NIV) refers to technique of augmenting alveolar ventilation without an endotracheal airway, thereby avoiding many of these complications. Since its first use in 1980s in patient with neuromuscular respiratory failure, NIV is considered as one of the most important addition in the field of mechanical ventilation and critical care armamentarium. Over the last two decades, it has gained widespread acceptance as a mode of assisted ventilation for the management of acute, as well as chronic respiratory failure in different settings including in emergency departments, Intensive Care Units (ICUs), wards and at home.[1-7]

Technically, NIV refers to the provision of inspiratory pressure support plus Positive End-Expiratory Pressure (PEEP) via a nasal or face mask. Although continuous Positive Airway Pressure (CPAP) does not actively assist inspiration and is not a ventilatory support mode, it is considered a form of NIV, when used as a therapy for respiratory failure. The use of NIV therapy in selected patients with acute respiratory failure is associated with significantly reduced need for endotracheal intubation and conventional ventilation. The available evidence suggests that the benefits of this therapy are not limited to hypercapnic acute respiratory failure but extend to hypoxemic acute respiratory failure as well. The successful application of NIV requires the training and collaboration of an experienced ICU team, including intensivists, nurses and respiratory physiotherapists.[1, 8] Proper selection of the patient based on various clinical and laboratory parameters cannot be ignored as an important factor deciding the success of this therapy. An expanded awareness of NIV devices and techniques promises to increase the therapeutic options for patients with severe respiratory insufficiency. This chapter summarizes the technique and mechanism of action of NIV, along with its efficacy in acute and chronic form of respiratory failure, clinical uses and limitations.

TECHNICAL ASPECT OF NONINVASIVE VENTILATION

Types of Noninvasive Ventilation

Noninvasive mechanical ventilation support can be either negative pressure ventilation or positive pressure ventilation.

Negative Pressure Ventilation

The negative pressure ventilators were widely used during polio epidemics, the classical example was the ‘iron lung’. The principle of negative pressure ventilation involves the application of external sub-atmospheric pressure to the chest wall, resulting in its expansion during inspiration, expiration occurs as the pressure around the chest wall is allowed to return to atmospheric level.[9] During negative pressure ventilation, tidal volume is related to peak inspiratory negative pressure (more the negative pressure, more the tidal volume) and the pressure waveform (a square wave produces a greater tidal volume than a half sine wave) generated by the ventilator pump. This type of ventilation has been used in patients with respiratory failure due to chest wall deformity, neuromuscular diseases or central hypoventilation.[9-11] Recently, negative pressure ventilation has been shown to be associated with a higher PaO_2, a lower $PaCO_2$ (despite identical minute ventilation), and less lung injury in an animal study.[12] It may motivate the researchers for similar trials in human subjects. However, the use of negative pressure ventilation is limited by their propensity of causing upper airway obstruction leading to oxygen desaturation and poor acceptance by patients due to the awkward size of devices.[10] The positive pressure ventilation administered by nasal mask, overcame some of these shortcomings, especially ameliorating the nocturnal oxygen desaturation.[13]

Noninvasive Positive Pressure Ventilation (NIPPV)

For several decades, positive pressure ventilation has been delivered by endotracheal intubation as standard of care to patients with various forms of respiratory failure. Noninvasive Positive Pressure Ventilation (NIPPV) refers to the positive pressure ventilation provided without the use of endotracheal intubation. The technique requires a mechanical ventilator, connected by tubing to an interface (nasal, orofacial and other types of mask). The ventilator delivers continuous or intermittent positive airway pressure through the upper airway and actively assists the ventilation. NIPPV is used in selected patients with various forms of respiratory failure.[1,14-17]

The Equipment of NIPPV

Ventilator Device

The primary requirement for NIPPV is a device to deliver positive pressure ventilation (ventilator) and an appropriate patient-ventilator interface (orofacial or nasal mask). The choice of ventilators available to provide noninvasive ventilatory support has continued to expand. Noninvasive ventilatory support may be provided either by using large bedside critical care volume ventilators or a specialty ventilator devoted to noninvasive ventilation. A dedicated NIPPV ventilator is a small, compact, portable machine connected to the interface (nasal, orofacial or other types of mask) via tubing (Fig. 141.1). Many critical care ventilators currently in use also have a NIPPV option, either as part of the original device or available as an upgrade option. While the critical care ventilators have more options of several modes and better oxygen blending, they are also less tolerant of leaks. The specialty ventilators have fewer options and range, but are more leak-tolerant. The ideal device is dependent on a number of factors, including the familiarity of the staff and the availability of options. The differences between the bedside critical care ventilator and specialty noninvasive ventilator continue to diminish as the differences related to ventilator options, range of support and leak tolerance are corrected in both devices. The size is an important consideration. Therefore, specialty ventilators which are small in size (Fig. 141.1) are used both in hospitals and in home.

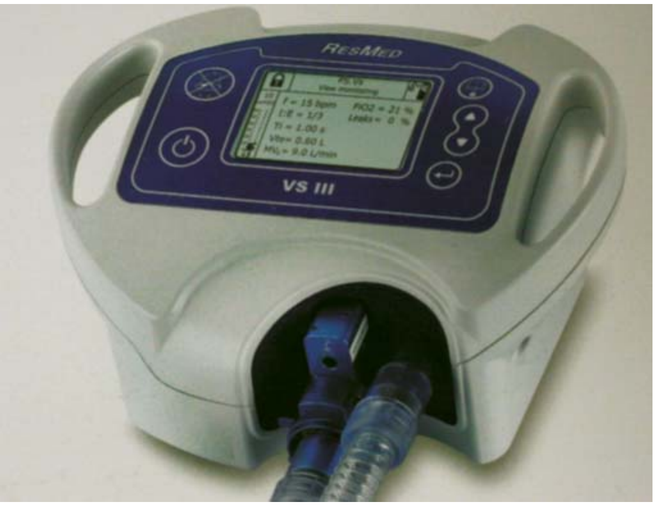
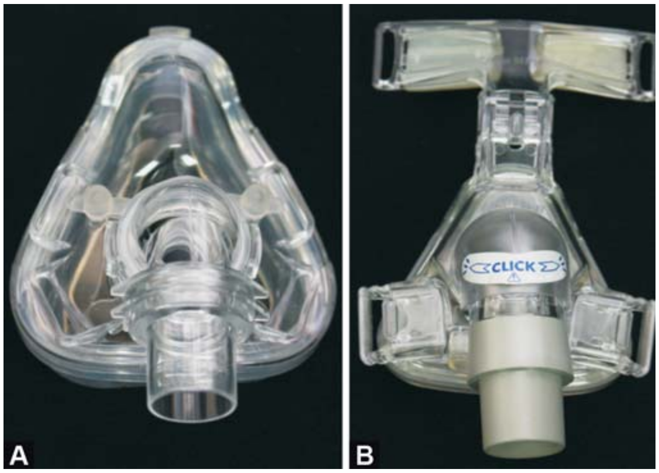


Fig. 141.1: Noninvasive mechanical ventilation machine

Interfaces

The interface between the machine and the patient is a tight fitting mask that is made of silicon (Figs 141.2A and B). Nasal masks and orofacial masks were the earliest interfaces, with subsequent development and use of full face masks, mouthpieces, nasal pillows, and helmets.[8] This advancement gives liberty to the care provider to select interface as per indication and tolerance of the patient. Nasal masks and orofacial masks are still the most commonly used interfaces. Both nasal and a full-face mask are held in place by cloth straps or Velcro (Fig. 141.3). These masks are available in various sizes. The choice of mask depends upon the comfort and compliance of the patient, as well as on the operator choice.

Orofacial masks are the most frequently used interface for management of acute respiratory failure.



Figs 141.2A and B: Commonly used interfaces, (A) orofacial and (B) nasal masks

Fig. 141.3: Typical headgear used to hold the interface

Use of these masks compared to nasal masks lead to faster correction of blood gases. Orofacial masks are preferred in patients who are less cooperative, have a higher severity of illness, are mouth-breathers or pursed-lips breathers, edentulous and those requiring more effective ventilation. However, these masks are associated with claustrophobia, hindrance in speaking and coughing and carry a small risk of aspiration with emesis. Nasal masks are best suited for more cooperative patients with a lesser severity of illness. These are not claustrophobic, allow speaking, drinking, coughing, secretion clearance, carry lesser risk of aspiration and emesis. However, these are associated with more air leaks (e.g. mouth-breathing or edentulous patients) and effectiveness is limited in patients with nasal deformities or blockade.

Importantly, mask should be the proper sized, so that it snugly fits and there is no air leak. Indeed, selection of appropriate mask and its proper application is of paramount importance for success of this form of ventilation, air leak leads to ineffective ventilation. Leaks are the bane of all of the interfaces, but excess pressure applied with the straps is discomforting to the patients, increases the risk of pressure necrosis and skin breakdown. Some amount of air leak at times is inevitable; however, most of the machines have facility for leak compensation. Therefore, one should be careful to minimize excess pressure on the face or nose. Straps should be tight enough to prevent significant leaks, but with enough slack to allow passage of 1 or 2 fingers between the face and the straps.[1,8]

Various Modes of Ventilation

NIPPV usually provides a form of assisted ventilation, where every breath is supported by the ventilator. Two types of breaths can be used, either volume targeted or pressure targeted.

Volume Targeted NIPPV

During volume targeted breaths, a predetermined tidal volume is delivered, usually with a set peak-flow rate and a controlled flow wave shape, over a fixed inspiratory time. It is frequently recommended to set tidal volume higher than usual, to compensate for possible leaks (12–14 ml/kg). In "invasively" ventilated patients, much attention has been paid to the importance of the peak-flow setting in relieving the patient's dyspnoea and reducing effort.[18,19] Surprisingly, little attention is paid to the importance of this peak-flow setting, while providing volume controlled ventilation with NIPPV. The usual peak-flow rate of 45–60 l/min is essential to decrease patient's inspiratory effort. Excessive peak-flow rates, however, also have adverse effects, as they can increase the sense of dyspnoea (the patient receives "too much air").[18,20] Unfortunately, some of the "old" generation ventilators cannot be used for volume targeted NIPPV. Modern ventilators have been designed to deliver volume targeted NIPPV; however, in the case of leaks, the delivered volume is reduced, with no adaptation by the ventilator.

Pressure Targeted NIPPV

In case of pressure targeted NIPPV, the ventilator maintains a constant preset pressure after the breath has been triggered by the patient and stops when the flow decreases to a given threshold (similar to PSV) which is supposed to indicate the end of the patient's effort or after a fixed, preset inspiratory time (assist pressure control). The potential advantages of a pressure targeted NIPPV include: 1) in case of leaks, the preset pressure is maintained, which facilitates achieving an appropriate delivered volume; 2) because the pressure is limited in the mask, the likelihood of leaks and its side effects is reduced; 3) synchrony between the patient and the ventilator is usually good, since these modes have been primarily designed to facilitate the patient's effort to breathe; 4) the combination of PSV and PEEP has been shown to be very efficient in reducing the work of breathing.[21,22]

Choosing the initial mode of ventilation is based in part on the underlying disease, the ventilator available and the past experience. Pressure targeted ventilation with Continuous Positive Airway Pressure (CPAP) is the most basic level of support and is not considered as a mode of NIPPV in true sense. CPAP is most frequently used for management of cardiogenic pulmonary edema and obstructive sleep apnea.

Most patients on NIPPV require pressure support mode of ventilation with PEEP (popularly called BiPAP). During BiPAP mode, patient receives ventilatory support during both phases of respiration, as preset Inspiratory Positive Airway Pressure (IPAP) and Expiratory Positive Airway Pressure (EPAP). The difference between IPAP and EPAP is a reflection of the amount of pressure support ventilation provided to the patient and EPAP is synonymous with PEEP. Some non-invasive ventilators have facilities of proportional-assist ventilation (PAV), which provides flow and volume assistance with each breath.

While volume ventilators can be used to provide non-invasive ventilatory support, the pressure targeted modes are preferred because they provide better patient comfort and synchrony and are more tolerant of the leaks that accompany all noninvasive ventilatory interfaces.

Mechanism of Action of NIPPV

Intermittent positive pressure is transmitted through upper airway to the alveoli, increasing transpulmonary pressure, inflating the lungs and assisting alveolar ventilation, as in the case with positive pressure ventilation through an artificial airway. It has been stated that NIPPV improves day time ventilatory muscle function by reducing chronic respiratory muscle fatigue, improving respiratory system compliance through reversal of microatelectasis of lung and preventing nocturnal hypoventilation by resetting the respiratory center's sensitivity to carbon dioxide.

STEPS TO SUCESSFUL PROVISION OF NIPPV

Several considerations can enhance the likelihood of successful noninvasive positive pressure ventilation (NIPPV), such as proper selection of patient, settings (ICU/ward/home), the type of interface used, underlying disease, and patient's co-operation. In addition to these factors, the experience and expertise of health care providers including the nurses and the respiratory physiotherapist, is important for the success of NIPPV.

Choosing the Patients

It is most essential to choose the right patient for initiating NIPPV. A poor selection of patient leads to higher rate of failure of NIPPV. It is important to ensure that patient is able to understand the instructions. Although altered level of consciousness is a relative contraindication, patients with Chronic Obstructive Pulmonary Disease (COPD) with impaired consciousness may be given a trial of NIPPV for 30 to 60 minutes; quite often, there is improvement in the level of consciousness. Other contraindications to its use include hemodynamic instability, presence of copious respiratory secretions, impaired swallowing reflex, active upper gastrointestinal bleeding, and orofacial trauma. Hemodynamic parameters are important considerations; presence of hemodynamic instability or associated organ failure in a patient with respiratory failure carries a risk of failure of NIPPV. History of recent facial surgery, trauma or deformity are obvious contraindications. Patients should be carefully assessed for contraindications before the decision to initiate NIPPV is taken (Table 141.1).

Location of NIPPV Application

Initially, it was recommended that NIPPV should be initiated only in the ICU since some proportion of

TABLE 141.1: Contraindications to use of NIPPV

a. Uncooperative/obtunded patient
b. Agitated patient
c. Hemodynamic instability or presence of organ failure
d. Severe co-morbidity
e. Recent facial/upper airway trauma
f. Recent upper gastrointestinal tract surgery
g. Intestinal obstruction
h. Excessive secretions in the airways
i. Undrained pneumothorax

patients would require endotracheal intubation. It has now been recognized that this modality can be used in general wards.[5] Many other trials have demonstrated its therapeutic use outside ICUs in the emergency room, general wards and high dependency units (HDUs) subject to the availability of trained and experienced nursing staff and respiratory therapists.[3,4,6,7] The location of NIPPV therapy is largely determined by the severity of the illness. For example, patients with acute respiratory failure due to exacerbation of COPD with pH less than 7.25 are best managed in ICU.

Explanation and Evaluation

Physician should explain to the patient about the breathing support being provided to him and its benefits. Patients should also be provided a feel of the interface. It can be done by holding the mask with hands, without applying straps. It is useful to inform the patient that some discomfort might occur in the beginning due to tight fitting mask and the repeated gush of air with each inspiration. This helps the patient in understanding the working of the device which leads to reduction in the anxiety and better cooperation.

Initial Ventilator Settings and Adjustments

The primary goals of NIPPV are adequate ventilation and oxygenation, correction of respiratory failure, and adequate patient tolerance and comfort.[23] The ventilatory settings and adjustments are made to achieve these endpoints. Initial settings focus on achieving adequate tidal volumes, usually in the range of 5–7 ml/kg. Additional support is provided to reduce the respiratory rate to less than 25 breaths/minute. Oxygen is adjusted to achieve adequate oxygenation, so as to achieve hemoglobin oxygen saturation of more than 90%. Serial arterial blood gas measurements are essential to monitor the response to therapy and to guide further adjustments in the ventilator settings.

All patients should be initiated on a pressure support that is lower than the target level. To start with, an IPAP of 6 cm of water with EPAP of 2 cm of water is a reasonable setting. A pressure difference of 4 cm of water between IPAP and EPAP is desirable. Pressure may be augmented every few minutes by 2 cm of water, to reach a target level to achieve the therapeutic end points. The maximum recommended level of IPAP is 24 cm of water, whereas that of EPAP is 16 cm of water. Oxygen should be supplemented through a port provided in the mask or in the NIPPV machine at a flow rate, so as to maintain oxygen saturation above 90%.

TABLE 141.2: Indications of discontinuation of NIPPV

Major criteria (any 1 of the following)	*Minor criteria (2 of the following)*
• Respiratory arrest • Loss of consciousness • Gasping for air • Psychomotor agitation requiring sedation • Heart rate less than 50/minute with loss of alertness • Hemodynamic instability	• Respiratory rate greater than 35 breaths/minute • pH < 7.30 and decreased from onset • PaO_2 < 45 mm Hg despite oxygen • Increase in encephalopathy and decreased level of consciousness

Monitoring of Patients on NIPPV

Patient should be monitored for patient-ventilator asynchrony, deterioration of sensorium, gastric distention and development of air leaks as patient changes posture or speaks. Pulse rate, blood pressure, respiratory rate, signs of respiratory distress and oxygen saturation should be monitored during the first hour. Arterial blood gases (ABG) must be repeated within the first hour and monitored as and when necessary. A rising $PaCO_2$ with fall in pH should be taken as a sign of failure of NIPPV, invasive ventilation should be considered. Table 141.2 enumerates clinical situations where discontinuation of NIPPV should be considered. It must be remembered that a delay in decision regarding initiation of invasive ventilation is far worse than not considering NIPPV at all.

Predictors of Response to NIPPV

It is important to recognize that certain parameters may predict success or failure of NIPPV, so that patients are not subjected to unduly prolonged treatment with NIPPV, while optimal treatment requires endotracheal intubation and conventional mechanical ventilation. These parameters should be observed during a trial of noninvasive ventilation (Table 141.3). These parameters, in turn, are a reflection of the patient's ability to cooperate with noninvasive ventilation, patient-ventilatory synchrony and efficacy of noninvasive ventilation for the clinical situation. Trials of NIPPV are usually of 1 to 2 hour duration and are useful to determine if a patient can be managed by this modality. Extended trials without significant improvement are not recommended, this only delays intubation and mechanical ventilation (unless patients are "do-not-intubate" status). Trials may be as short as of a few minutes in patients with immediate

TABLE 141.3: Predictors of response to NIPPV

Predictors of success response to trial of NIPPV (1–2 hours)

- Improvement in $PaCO_2$ (a decrease of greater than 8 mm Hg)
- Improvement in pH (greater than 0.06)
- Correction of respiratory acidosis

Predictors of failure

- Severity of illness
  - Acidosis (pH <7.25)
  - Hypercapnia (>80 and pH <7.25)
  - Acute Physiology and Chronic Health Evaluation II (APACHE II) score higher than 20
- Level of consciousness
  - Neurologic score (>4 = stuporous, arousal only after vigorous stimulation; inconsistently follows commands)
  - Encephalopathy score (>3 = major confusion, daytime sleepiness or agitation)
  - Glasgow Coma Scale score lower than 8
- Failure of improvement with 12–24 hours of noninvasive ventilation

Late failures (>48 hours after initiation of NIPPV)

- Admission predictors of failure
  - Lower functional status (Activity score < 2 = dyspnea on light activity)
  - Initial acidosis (pH ≤7.22)
  - Hospital complications (pneumonia, shock, coma)

failure and probably should not exceed 2 hours if patients fail to improve.

Objective criteria for discontinuation are important to limit trials in patients in whom noninvasive ventilation ultimately fails (Table 141.2). The patients who are fulfilling these criteria are best managed by invasive mechanical ventilation, hence also referred as intubation criteria. These criteria, although carry a subjective element, have been defined in investigational studies. All these criteria are subject to some degree of interpretation in the context of the patient's clinical status. However, most patients who meet these criteria are candidates for intubation.

CLINICAL USES OF NIPPV: EVIDENCE AND RECOMMENDATIONS

Hypercapnic Respiratory Failure

Chronic Obstructive Pulmonary Disease

After several randomized controlled trials, a general consensus has been reached that NIPPV has an important role in the management of selected patients with acute respiratory failure due to exacerbation of COPD.[8,14,24] This therapeutic modality has also been used in chronic stable phase of COPD and for facilitation of extubation in patients who required intubation.[24]

NIPPV in Acute Exacerbation of COPD: Use of NIPPV for management of acute respiratory failure (ARF) secondary to acute exacerbation of COPD is now the standard of care. NIPPV acts primarily by reducing patient's effort and work of breathing in patients with COPD presenting with acute exacerbation.[25] Several randomized trials have documented reduction in requirement of endotracheal intubation, ICU and hospital stay, and mortality.[2,26,27] Brochard was the first to document these benefits in a prospective- randomized trial including 85 patients with ARF, due to acute exacerbation of COPD.[28] Subsequently, there have been several randomized trials which have documented benefit of this modality in patients with ARF secondary to COPD.[29] NIPPV also leads to reduced rate of nosocomial pneumonia and other complications related to endotracheal intubation. Therefore, all the patients with ARF secondary to COPD should receive benefit of NIPPV, unless there are contraindications. Patients with type II respiratory failure secondary to COPD with altered level of consciousness improve within 30 to 60 minutes with NIPPV. Therefore, such patients should get the therapy under close monitoring.

NIPPV in Chronic Stable COPD: The possibility that NIPPV might aid patient with severe chronic COPD has intrigued clinicians for decades. Earlier investigators thought that the intermittent use of NIPPV might give rest to the mechanically disadvantaged respiratory muscles, relieving chronic fatigue and enhance ventilatory and overall functions. Vitacca et al. demonstrated that in COPD patients with chronic hypercapnia, NIPPV led to improvement in arterial blood gases and unloading of respiratory muscles when pressures were set according to patients comfort and improvement in arterial blood gases.[30] Use of nocturnal NIPPV in chronic stable COPD patients with CO_2 retention leads to significant improvement in day time blood gases and sleep quality, compared to those receiving oxygen therapy alone.[31,32] The principal mechanisms for improved gas-exchange in patients with COPD following NIPPV include decreased gas trapping and increased ventilatory sensitivity to $PaCO_2$.[33] Changes in some volitional muscle strength measures may reflect improved patient effort.[33]

NIPPV significantly reduces ICU admissions, improves alveolar ventilation, exercise capacity, and quality of life.[34,35] However, not all the studies have shown benefit of NIPPV in chronic COPD. Some investigators have failed to show additional benefits from NIPPV over oxygen therapy and comprehensive rehabilitation programs.[36] The studies of Shapiro and Strumph discouraged the long-term use of NIPPV in severe stable COPD patients without significant hypercapnia.[36,37] Nocturnal NIPPV provides significant physiological and clinical benefits to stable patients with severe COPD with significant hypercapnia. NIPPV may be more effective in selected patients with hypercapnia and hypoxemia.[8,24]

Clearly, the data on mortality benefit of NIPPV use in long-term management of severe COPD is not robust enough to justify the routine use of NIPPV for home ventilation. However, given the positive impact of nocturnal use of NIPPV on physiological parameters, as well as subjective symptoms, there is significant benefit in terms of reduction of morbidity and possibly mortality. In fact, a selected group of patients may well benefit from domiciliary mechanical ventilation, we need to identify who they are. Moreover, NIPPV can be a new strategy to improve exercise tolerance in COPD patients. Larger studies designed to determine the impact of NIPPV on long term mortality in these patients are required and a routine use of NIPPV must await such data.[8,38]

Facilitating Extubation in COPD

Based on success of NIPPV in managing patients with ARF, there have been efforts to try the same in patients on conventional mechanical ventilation, in order to facilitate weaning and prevent reintubation in patients with COPD. In these patients, NIPPV can be used in three ways: 1) using NIPPV after early extubation, in order to reduce duration of invasive mechanical ventilation; 2) using it as a prophylactic measure to avoid respiratory failure and reintubation and 3) using as a therapeutic option in patients who develop respiratory distress after extubation, in order to avert endotracheal intubation.

The evidence suggest that NIPPV weaning was significantly associated with reduced mortality, fewer ventilator associated pneumonia, lesser length of ICU stay, hospitalization, total duration of ventilation and of duration of invasive ventilation.[39,40] Benefits in mortality and weaning failures were nonsignificantly greater in trials that exclusively enrolled patients with chronic obstructive pulmonary disease versus mixed populations.[41] Based on these findings, patients intubated for hypercapnic respiratory failure due to COPD who fail spontaneous breathing trials, should be considered for a trial of extubation to NIPPV. This approach should be reserved for patients who are good candidates for NIPPV in other respects and who are able to tolerate levels of pressure support easily administered via mask (i.e. 15 cm H_2O). In addition, there should not have been a difficult intubation.

Bronchial Asthma

Asthma exacerbations are similar to COPD exacerbations, there is increased airway obstruction, dynamic hyperinflation and impaired ventilatory effort, leading to respiratory muscle fatigue. However, there is a paucity of randomized controlled trials on the use of NIPPV in asthma. Still, positive results have been reported in a limited number of case reports, case series or uncontrolled studies with both CPAP and BiPAP.[42-47] NIPPV in asthma patients with acute respiratory failure has been associated with improved gas exchange and avoidance of intubation in an uncontrolled study.[44] A subsequent randomized pilot study in 33 patients with acute asthma but not acute respiratory failure, showed improved flow rates and decreased hospitalizations with NIPPV, compared to sham NIPPV.[48]

A trial of NIPPV before intubation and mechanical ventilation should be considered in selected patients with acute asthma and respiratory failure (evidence category B). These would include patients who can tolerate and cooperate with this therapy. NIPPV should only be used under close observation of the experienced respiratory therapists, nurses and physicians and in an area with facility of immediate intubation, if needed.[49]

Hypoxemic Respiratory Failure

Cardiogenic Pulmonary Edema

NIPPV has been used in patients with cardiogenic pulmonary edema for quite a long time; both CPAP and BiPAP have been used for the same. The favorable effects on lung mechanics include improvements in alveolar recruitment and functional residual capacity and reduction in anatomic shunting. It also reduces the work of breathing by decreasing the preload and after load. There is suggestion that the patients with cardiogenic pulmonary edema secondary to acute myocardial infarction get maximum benefits from this therapy.[50] There is always a concern of recurrence of myocardial infarction in these patients, there is enough evidence that this does not add to the risk of myocardial infarction and should not be considered as a contraindication to this therapy.[51] It may be avoided in patients who require emergency life saving procedure, such as percutaneous coronary intervention. NIPPV use has been shown to be associated with reductions in intubation and mortality rates.[52,53] Recently a large trial has challenged these findings in which no mortality benefit of NIPPV was observed in patients with acute cardiogenic pulmonary edema, although it showed a more rapid improvement in respiratory distress and metabolic disturbances than the standard oxygen therapy.[51] Thus, NIPPV should be used to treat acute cardiogenic pulmonary edema with expectations of success in terms of rapid improvement in symptoms and metabolic disturbances and probably reduced mortality and intubation rate (level A).[17]

Pneumonia

NIPPV has been used in patients with pneumonia and ARF with variable results.[54,55] The benefits of NIPPV include reduced intubation rates, ICU length of stay and mortality rate.[54,55] Among these, the patients with underlying COPD respond better than without the same. However, there is no strong evidence to support the routine use of NIPPV in patients with ARF due to pneumonia.

Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS)

Patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) require conventional mechanical ventilation using various strategies. NIPPV has been tried in patients with ALI/ARDS in an effort to avoid endotracheal intubation.[56-58] Benefits of this modality are not well documented in these trials. Therefore, NIPPV should be used in these patients with caution, endotracheal intubation should not be delayed.

Respiratory Failure in Immunocompromised Patients

Immunocompromised patients who require endotracheal intubation have higher rate of ventilator associated pneumonia. The use of NIPPV in such patients leads to reduced rate of nosocomial infection which results in reduced mortality and ICU stay.[59,60] Therefore, the current recommendations strongly favor (level A) the use of NIPPV in immune-compromised patients with acute respiratory failure.[17,61]

Postoperative Respiratory Failure

NIPPV is widely used during postoperative period in patients with abdominal and thoracic surgery[62-67] It is believed that it provide better patient comfort and oxygenation after extubation. The current evidence shows only some usefulness of this modality, it does not strongly support the routine use of CPAP or NIPPV in postoperative patients, either prophylactically in high risk patients or as an early therapy of respiratory insufficiency. Although, data is sparse to support NIPPV, it can be safely used for respiratory distress in these patients.

Weaning or Postextubation Respiratory Failure

NIPPV during weaning or postextubation period has been used in three ways: (1) a *facilitation technique* for early extubation in patients who fail to meet standard extubation criteria;[39, 40, 68, 69] (2) a *rescue or curative technique* for avoiding reintubation in patients who fail extubation[70-72] and (3) a *preventive or prophylactic technique* for preventing extubation failure.[73-75] NIPPV has been suggested as a means to avoid reintubation and improve outcomes in patients with failed weaning. The first report to assess the role of NIPPV for weaning dates back to 1992, when it was successfully used in assisting the return of spontaneous breathing in a small group of patients with chronic respiratory insufficiency and weaning difficulties.[76] There have been conflicting results from various trials in patients with extubation failure. NIPPV reduced the need for reintubation, ventilator associated pneumonia, need for tracheostomy and ICU mortality.[74, 75, 77] Notably, patients with hypercapnic respiratory failure (mainly COPD) were benefitted the most.

Currently available data suggest that the potential effectiveness of NIPPV for facilitating ventilator weaning and early extubation varies across patient population and that the benefit seems greatest for COPD patients.[41] However, early indiscriminate use in all patients with risk factors is discouraged. Patients with extubation failure treated with NIPPV should be closely monitored and delays in needed intubation be avoided. Further studies are required to better identify those subcategories of patients with non-COPD respiratory failure who are most likely to benefit from NIPPV.

Palliative Care and Do-Not-Intubate Status

NIV may be particularly useful in patients reporting to the emergency room for ARF, with a Do-Not-Intubate (DNI) status, due to advanced age or other critical conditions. There are very few studies which have addressed this issue.[78-80] The current evidence suggests that if the patient and/or family desire prolonged survival, the NIPPV use should be reserved primarily for COPD and congestive heart failure patients.[23] On the other hand, if the goal is to palliate, relieve dyspnea or to delay death, then NIPPV can be used for other

TABLE 141.4: NIPPV for various types of acute respiratory failure (ARF): Evidence for efficacy and strength of recommendation

Type of ARF	*Level of Evidence*[a]	*Strength of Recommendation*[b]
Hypercapnic respiratory failure		
COPD exacerbation	A	Recommended
Asthma	C	Option
Facilitation of extubation (COPD)	A	Guideline
Hypoxemic respiratory failure		
Cardiogenic pulmonary edema	A	Recommended
Pneumonia	C	Option
tALI/ARDS	C	Option
Immunocompromised	A	Recommended
Postoperative respiratory failure	B	Guideline
Extubation failure	C	Guideline
Do-not-intubate status	C	Guideline
Preintubation oxygenation	B	Option
Facilitation of bronchoscopy	B	Guideline

COPD, chronic obstructive pulmonary disease; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

[a]A – supported by multiple randomized controlled trials and meta-analyses; B – supported by more than one randomized, controlled trial or case control series or cohort studies; C - case series or experts' consensus/opinion; *b* recommended - first choice for ventilatory support in selected patients; Guideline - can be used in appropriate patients with careful monitoring; Option - suitable for a very carefully selected minority of patients under close monitoring.

diagnoses as well.[23] However, it should be reassessed frequently and stopped if the goal of palliation is not being met.

Other ICU Applications of NIPPV

Preoxygenation Before Intubation

Preoxygenation by face mask is standard of care for improving the oxygen status for the patients requiring endotracheal intubation. NIPPV has been tried by few intensive care providers considering the fact that it has the potential to improve oxygenation more effectively than oxygen by face mask.[81, 82] It was also noticed that NIPPV might be a useful preoxygenation technique in the hypoxemic critically-ill patient. However, the current evidence is insufficient to suggest the routine use of NIPPV for this purpose and further studies are required before reaching any conclusion.

Before Fiberoptic Bronchoscopy

Fiberoptic Bronchoscopy (FOB) is an important tool for determining the etiological diagnosis of pneumonia. Arterial oxygen tension routinely decreases by 10 mm Hg to 20 mm Hg in patients after they undergo uncomplicated FOB, may complicate hypoxemia in patients with already compromised oxygen status which puts them on high risk for developing respiratory failure or serious cardiac arrhythmias. NIPPV seems a logical approach in such situations. There is some data to suggest that its use is associated with improved oxygenation and reduces post-procedure respiratory failure in patients with severe hypoxemia undergoing bronchoscopy.[83-85] However, the ICU team must be prepared for the possibility of emergent intubation.

Chronic Ventilation Failure

Chronic ventilation failure is observed in many conditions, including the chest wall diseases, neuromuscular disease and sleep apneas. Mechanical ventilatory support in the form of NIPPV, especially at night, may be helpful in improving ventilation in these conditions. The benefits of this modality include a reduction in need of hospitalization for respiratory illness, improvement in daytime arterial blood gases and respiratory muscle strength and improvement in activities of daily living.[86-89] Data also suggest a good long-term survival benefits of home ventilation with NIPPV.[90] For sleep apnea syndrome, NIPPV is the standard modality of therapy.

CONCLUSION

The role of NIPPV in the management of acute respiratory failure has been further clarified in the recent years (Table 141.4). Evidence is strong to support its use in the initial management of acute respiratory failure in patients with COPD exacerbations, acute cardiogenic pulmonary edema, in immune-compromised state and to facilitate extubation in patients with COPD with failed spontaneous breathing trials. A trial of NIPPV is justified in patients with asthma exacerbations, postoperative respiratory failure, extubation failure or a 'do not resuscitate' status. Supporting evidence for these indications is not strong; they should be carefully selected according to available guidelines and clinical judgment. The response to NIPPV after the first hour or two is the best predictor of eventual outcome, if the patient does not have a favorable initial response to NIPPV, the clinician should consider intubation.

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Section

18

RESPIRATORY MONITORING

R Agarwal
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Blood Gas Monitoring*

Chandana Reddy, R Agarwal

INTRODUCTION

Monitoring of arterial blood gases is fundamental to respiratory critical care and oxygen therapy. It is important to recognize gas abnormalities before the appearance of clinical symptoms or signs. A patient may appear to be well oxygenated but may have a low PaO_2 values on blood gas measurements. Therapeutic interventions are required after careful monitoring of blood gases. Blood sample is usually obtained from the radial artery for this purpose. Venous sample though easy and safer to obtain, is not helpful for blood gas monitoring. Blood sample from any artery represents the sample from the left ventricle. On the other hand, venous sample is affected by the metabolism, blood flow and many other factors of different tissues. However, central venous samples have been shown to correlate well with arterial samples with respect to pH, PCO_2 and base excess in mechanically ventilated trauma patients to reach clinically reliable conclusions, but central venous sample cannot substitute arterial samples for resuscitation and management. This chapter will review the technical aspects of both invasive (arterial blood gas analysis) and noninvasive (pulse oximetry and capnography) blood gas monitoring.

INVASIVE TECHNIQUE

Arterial Sampling

Radial artery is the most commonly used site to obtain a sample for arterial blood gas analysis. This is because the radial artery is superficial and easily accessible. Moreover, there is a good collateral vascular network minimizing the risk of vascular interruption in case of complications such as vascular spasm, intraluminal clotting or periarterial hematoma formation which can compromise the blood supply. Radial artery can also be fixed against the radius bone for obtaining sample, and compressed in case of continued ooze. If radial arteries are not available for sampling, other sites such as dorsalis pedis, femoral and brachial arteries should be tried.

It is important to ensure adequate collateral circulation before performing an arterial puncture. In case of the upper extremity, this can be done with the help of a simple and reliable test, the Allen's maneuver. In this, the hand is clenched to form a fist; pressure is applied to obstruct the radial and ulnar arteries at the wrist. The hand is then relaxed (but not fully extended) when the palm and finger are seen to blanch. Thereafter, the pressure from ulnar artery is removed. The thumb and index finger get flushed within 15 seconds, followed by flushing of the entire hand. This is a positive Allen's test indicating adequacy of collateral circulation, i.e. ulnar artery alone is capable of supplying the hand. If the test is negative, it implies the inability of ulnar artery to supply the entire hand. In this situation, the radial artery should not be used for arterial puncture.

In an uncooperative or unconscious patient who cannot clench the fist, the test is done in a similar fashion by obstructing both the arteries, raising the patient's hand above the level of the heart until balancing occurs. The hand is then lowered below the level of the heart and pressure removed from the ulnar artery.

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Technique for Arterial Puncture

The process is explained to the patient, both radial and ulnar arteries palpated and Allen's test applied.

1. A 20 or 21 gauge needle and a glass syringe is taken and 0.2 ml (just enough to smear the inner aspect of the syringe) of 1,000 U/ml heparin is drawn into the syringe. Errors in PaO_2 of up to 6% in two minutes and 16% in 30 to 60 minutes due to exchange of O_2 from plastic syringes have been reported. Hence, glass syringes are generally preferred to plastic syringes unless analysis is done immediately.
2. The wrist is stabilized in the position in which maximum pulsations are felt.
3. The skin is sterilized at the puncture site and a small skin wheal is raised with a local anesthetic.
4. The radial artery is then punctured keeping the needle at a minimum angle of about 30 to 40 degrees to the artery and slowly advancing the needle in one plane. Once the artery is punctured, the blood will enter the syringe.
5. If the needle has completely gone through the artery, its tip is slowly withdrawn until it is once again in the lumen as indicated by the free flowing blood through the needle.
6. After the required amount (2–4 ml) of blood has filled the syringe, the needle is withdrawn and firm pressure is applied at the puncture site for a minimum of two minutes. The pulse distal to the pressure site is palpated to ensure arterial patency.
7. The syringe is then held vertically and air bubbles removed. The needle is then replaced by a syringe cap, the syringe rolled between palms of hand and immersed in a bag of ice and sent to the laboratory.

Arterial Cannulation

Most patients requiring critical care need repeated arterial punctures and many intensivists prefer indwelling arterial catheters/cannulae to repeated punctures. With the availability of an arterial cannula, samples can be immediately and as repeatedly drawn as required. It is also useful in patients whose cardiopulmonary status is unstable. The preanalytical errors related to improper sampling, handling and storage are minimal with samples obtained from arterial cannulae. In addition, the arterial cannulae can be used for systemic blood pressure monitoring and to obtain blood samples for other numerous clinical estimations such as electrolytes, urea, creatinine, etc.

However, arterial cannulation is not without risks. There is an increased incidence of diminished or absent blood flow through the cannulated artery. This is often reversible, although necrosis and loss of tissue have been reported in some cases. Local infection and systemic sepsis can also occur, but the incidence is believed to be no more than that with venous cannulation. Another method to obtain arterial blood, especially in infants and young children, is the arterialized earlobe capillary blood sample (ELCS) which shows strong agreement with arterial blood pH and $PaCO_2$. Simultaneous measurements of oxygen saturation through pulse oximetry may also improve the accuracy of ELCS for PaO_2 assessment.

Measurement Techniques

Measurement of blood pH, PaO_2 or $PaCO_2$ is done with the help of an electrode. It consists of an anode and a cathode immersed in an electrolyte solution. The flow of electrons (electric current) occurs from one point to another in response to a potential difference between the two points. The difference called voltage is measured with a voltmeter. The voltage can be varied predictably with the help of an electric device called potentiometer. A brief account of the different electrodes used for blood gas analysis is described below. Both pH and CO_2 electrodes employ a measuring chemical half-cell of silver-silver chloride solution (to measure small potential differences accompanying pH changes) and a reference half-cell to supply a constant reference voltage.

Oxygen Analysis

There are several techniques to analyze oxygen in the dissolved form which include manometric and volumetric measurements, chemiluminescence method, gas chromatography, physical methods using paramagnetic properties of oxygen and electrochemical techniques. It is the membrane covered oxygen electrode employing the principle of polarography which is most useful and employed in clinical laboratories.

Polarographic electrode for O_2 (Clark electrode) utilizes the principle of chemical reduction of oxygen, i.e. oxygen is dissolved in an aqueous medium and exposed to a polarizing voltage at a cathode wherein the following reaction takes place:

$$O_2 + 2(H_2O) + 4 \text{ electrons } (e') \rightarrow 4\ OH^-$$

The electrode consists of a silver anode and a platinum cathode. The silver anode is immersed in a potassium chloride solution. The chloride ion will react with the silver anode to form silver chloride producing a constant flow of electrons. The adjacent platinum cathode reacts chemically with oxygen to form hydroxyl (OH^-) ions. This reduction reaction uses the electrons. The amount of oxygen reduced is strictly proportional to the number of electrons used in the cathode reaction. The change in electron flow (i.e. current) between the anode and the cathode is measure of the amount of oxygen.

The electrode system is covered by a polypropylene membrane which allows a slow diffusion of oxygen from the blood from into the electrode. The membrane is a slow diffusion membrane to prevent oxygen depletion during the measurement. The ease with which oxygen molecules can pass through the membrane depends upon its permeability coefficient expressed in terms of the number of moles of the gas passing through a specific area and thickness at a given temperature and pressure difference across the membrane.

A galvanic electrode has also been used for oxygen analysis. It is based on a principle similar to the Clark electrode. The voltage for cathode reduction is produced internally by the galvanic cell. The cathode is usually composed of gold, the anode of lead and the electrolyte solution is potassium hydroxide.

Some of the technical difficulties in using the polarographic method of gas analysis include the alteration in the electrolyte layer thickness, changes in electrolyte concentration causing dryness, deposition of silver on the platinum cathode, artifacts due to the presence of gas bubbles in solution and changes in the sensitivity of the membrane. The response time, i.e. the time required in sensitivity of the membrane or the time required for the output to change following a change in the partial pressure of oxygen, of the electrode depends upon the membrane thickness and the permeability coefficient. The average 97.5% response time for a 1 ml teflon membrane covered electrodes is 10 seconds while for 1 ml polypropylene it is close to 40 seconds.

Calibration of the electrode is done with an oxygen concentration of 0 percent and either of 12 or 20%. The calibration of gases for PO_2 and PCO_2 are generally combined for purposes of conveniences and economy.

PCO_2 Electrode

PCO_2 is measured with the help of Severinghaus electrode. It utilizes the principle of Henry's law, i.e. the amount of the gas (CO_2) diffusing across a semi-permeable membrane is directly proportional to the pressure gradient, i.e. PCO_2 in contact with the membrane. The PCO_2 electrode consists of a silicon elastic membrane containing a measuring half-cell (silver-silver chloride) and a similar reference half-cell. It is calibrated each time with a gas mixture containing 5% and 10% CO_2 concen-trations. As stated earlier, gas mixture of 5% CO_2 plus 12 or 20% O_2 (remainder nitrogen) and 10% CO_2 plus 90% N_2 can be used to calibrate both O_2 and CO_2 electrodes.

pH Electrode

The modern pH electrode is an ultramicro Sanz electrode consisting of a pH sensitive glass rolled into a fine capillary tube which draws in a very small quantity of blood to be tested. It maintains anaerobic and thermostatic conditions essential for pH measurement. It is important to know the pH of the buffer solution in the measuring half-cell for purposes of calibration. When the measuring half-cell contains the buffer solution with pH of 7.384 the difference between the two half cells is 0.554 pH units and a 33.5 mv potential difference is predicted. Thus, the voltmeter measures 33.5 mv and a slope potentiometer sets the display at 7.384. Two point calibrations are generally sufficient.

NONINVASIVE BLOOD GAS MONITORING

Blood gas analysis requires repeated arterial punctures or cannulation. Several noninvasive methods have emerged in the last quarter of a century as fairly reliable alternatives to arterial sampling.

Oximetry

Oximetry involves the assessment of arterial oxygen saturation. The concept of pulse oximetry is based on three principles (Fig. 142.1).

1. *Spectrophotometry:* Every substance has a unique absorbance spectrum, and the different types of hemoglobin have different absorption spectra. The currently available pulse oximeters consist of a probe containing two small, high intensity monochromatic light emitting diodes (LEDs) that are activated alternatively and emit light at 660 nm (red) and 940 nm (infrared) wavelengths. These two wavelengths are used because oxyhemoglobin and hemoglobin have different absorption spectra-oxyhemoglobin absorbs less light than deoxyhemoglobin in the ultraviolet region, while the reverse occurs in the infrared region.
2. *Lambert-Beer law:* The absorption of light as it passes through a solution is proportional to the concentra-

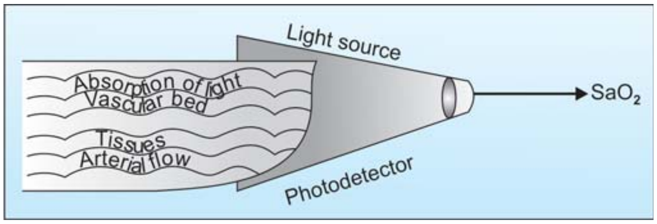

Fig. 142.1: Oximetry-light of known wavelength is passed through the finger tip and measured by the photodetector after absorption by the vascular bed and other tissues (or the finger tip)

tion of those molecules within the solution which have the vibrational frequencies on sympathy with the wavelength of the light.

3. *Optical plethysmography:* The presence of a pulsatile signal generated by the arterial blood that is relatively independent of the nonpulsatile venous and capillary blood and other tissues. Two components of light absorption are associated with pulsatile blood flow; a constant component due to absorption by skin, subcutaneous tissue, venous blood and a pulsatile component due to absorption by the pulsating arterial blood. Comparing the peak and the trough absorbencies, the contribution from nonarterial sources becomes irrelevant. Using changes in absorption during each pulsation the pulse oximeter eliminates the constant component.

CO-oximeter, on the other hand, operates using four different wavelengths and can measure total hemoglobin, oxyhemoglobin, carboxyhemoglobin and methemoglobin, and expresses each as a percentage of the total hemoglobin in a given sample of blood. The value reported by a CO-oximeter is commonly termed "fractional saturation" and is equal to the amount of oxyhemoglobin expressed as a fraction of the amount of total hemoglobin, i.e. the total of all the active and inactive forms of hemoglobin with respect to the oxygen-binding capability (oxyhemoglobin × 100)/(total hemoglobin + oxyhemoglobin + carboxyhemoglobin + methemoglobin).

Pulse oximeters use only two wavelengths and therefore, cannot distinguish between the relative concentrations of each type of hemoglobin derivative present in the blood. A pulse oximeter thus measures the functional saturation, i.e. the relative concentration of oxyhemoglobin expressed as a fraction of the total amount of hemoglobin able to bind oxygen, namely, the ratio of the concentration of oxyhemoglobin and the concentrations of oxyhemoglobin and deoxyhemoglobin. The ratio of absorbencies at these two wavelengths is calibrated empirically against direct measurements of arterial blood oxygen saturation (SaO_2) in volunteers and the resulting calibration algorithm is stored in a digital microprocessor within the pulse oximeter to give the estimated patients' oxygen saturation (SpO_2). At 85% SaO_2, the amount of light absorbed by hemoglobin and oxyhemoglobin is about the same. Hence the normalized amplitudes of the red and infrared signals are equal (i.e. R/LR = 1.0).

In healthy volunteers, oximeters commonly have a mean difference (bias) of less than 2% and a standard deviation (precision) of more than 3% when SaO_2 is 90% or above. Comparable results have also been obtained in critically ill patients with good arterial perfusion. Accuracy of pulse oximeters deteriorates when SaO_2 falls to 80% or less. Most manufacturers report accuracy to within ± 2% for SpO_2 70% to 100 percent, and ± 3 percent for SpO_2 50 to 70%, with no reported accuracy below 50% saturation. There can also be a delay between a change in SpO_2 and the display of that change, and this depends on the signal averaging time, circulation time and the site of the oximeter probe. In general, finger probes are slower (24–35 sec) than earlobe probes (10–20 sec).

Limitations

Pulse oximeters have several limitations, which need to be considered while interpreting SpO_2.

1. They estimate the arterial oxygen saturation (SaO_2) and not the arterial oxygen tension (PaO_2). Pulse oximeters measure SaO_2 that is physiologically related to arterial oxygen tension PaO_2 according to the oxygen-hemoglobin dissociation curve. It is known that because of the sigmoid shape of the oxygen dissociation curve, large changes in PaO_2 may occur in the upper and lower horizontal portions of the curve with minimal changes in the SaO_2. The oxygen-hemoglobin dissociation curve is flattened at saturation values less than 90 to 95% and errors of only a few % in SaO_2 measurements could easily represent a large and significant error in the oxygen tension values. Therefore, pulse oximeters are not accurate enough to safeguard against hyperoxia in neonates at risk of retrolental fibroplasia. Factors that affect the oxygen hemoglobin dissociation curve such as pH, temperature, $PaCO_2$ affect the relationship between oxygen saturation and PaO_2. Pulse oximeters also give us no information regarding the acid-base or the ventilatory status of the patient and hence should not be used as an alternative to blood gas monitoring.

2. Low perfusion states such as hypotension, vasoconstriction, hypothermia or cardiopulmonary bypass and cardiac arrest, produce a signal that is too small to be processed and may make it difficult for the sensor to distinguish a true signal from background noise. Increased venous pulsations as seen in right heart failure can lead to artificially lower SpO_2 readings.
3. The presence of abnormal hemoglobins can lead to erroneous pulse oximetry measurements. At 940 nm, carboxyhemoglobin has minimal light absorption, while at 660 nm, its absorption coefficient is similar to oxyhemoglobin thus in the presence of elevated carboxyhemoglobin levels, oximetry overestimates the SpO_2. Methemoglobin contributes to light absorption at both 660 nm and 940 nm. As the concentration of methemoglobin increases, red and infrared light absorptions increase driving the ratio towards unity which correlates with a saturation of 85%. The difference in the optical absorbance of adult and fetal hemoglobins is too small (<3%) to affect the clinical accuracy of pulse oximetry measurements.
4. Nail polishes, specifically blue, green or black colors have light absorbance near 660 nm and affect the measured SpO_2 leading to falsely low readings. Most studies indicate that the concentration of hemoglobin does not affect the pulse oximeter reading until the hematocrit reaches values less than 10%. Polycythemia, on the other hand, does not affect SpO_2. A number of dyes and pigments can interfere with the accuracy of pulse oximetry. Hyperbilirubinemia has not been shown to affect SpO_2 and in one study, bilirubin levels up to 30.6 mg/dl did not affect the accuracy of pulse oximeter.
5. The readings of pulse oximeters may be affected by high frequency radio interference from electrocautery units and high-intensity light sources such as infrared, xenon and fluorescent lamps. Motion artifact continues to be a significant source of error and false alarms.

Clinical Applications

Pulse oximetry is a noninvasive, relatively inexpensive way to measure and continuously monitor oxygen saturation (Fig. 142.2). Pulse oximetry is widely used during anesthesia, surgery, critical care, hypoxemia screening, exercise and transport from the operating room to the recovery room and in the emergency room. The availability of small, lightweight optical sensors makes SpO_2 monitoring, especially applicable for preterm neonates, pediatric and ambulatory patients. Easy application and fast response time of pulse oximeter helps in monitoring patients during procedures like bronchoscopy, endoscopy, cardiac catheterization, exercise testing and sleep studies. They are commonly used during labor and delivery for both the mother and infant. In critically ill patients, noninvasive monitoring can decrease the distress caused by repeated arterial punctures and assist in titrating the FiO_2 and ventilatory settings. Continuous monitoring also provides information on trends in the patient's condition, to assist the clinician in assessing the response to therapeutic procedures. Hypoxemia is detected more frequently and early during anesthesia and in the recovery rooms with the use of pulse oximetry. Bronchospasm, atelectasis, and bradycardia can be detected more frequently in the group monitored by pulse oximeters. It is also a valuable tool in palliative and supportive care for patients with end stage diseases to determine the need to prescribe or to withhold oxygen therapy.

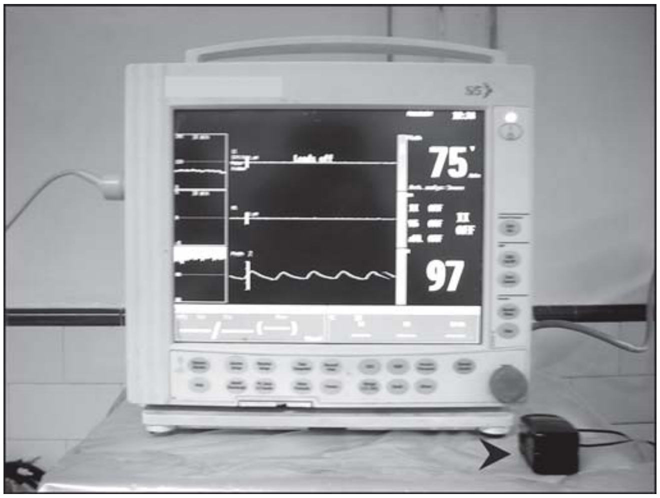

Fig. 142.2: A commonly used pulse oximeter used to continuously monitor SaO_2. The arrow depicts a portable pube oximeter, which can be easily carried around

Generally, the accuracy of most noninvasive pulse oximeters is acceptable for a wide range of clinical applications. Pulse oximetry has replaced transcutaneous oxygen tension monitoring in neonatal intensive care. Intrapartum fetal oximetry is also shown to compare well with fetal scalp blood gas assessment in neonatal management.

Recognizing the above-mentioned limitations and applying appropriate corrective interventions are essential to optimize the clinical use of pulse oximeters. To overcome some of the limitations of pulse oximetry from finger, ear or toe where the pulsatile flow is more easily compromised, esophagus has emerged as another alternative site for continuous monitoring in cases of poor peripheral circulation.

Transcutaneous Oxygen Measurement

Partial pressure of oxygen in blood perfusing the skin ($PtcO_2$) has been used as an estimate of arterial PO_2. This can be done using a modified Clarke electrode which uses a platinum cathode and a silver anode in a potassium chloride solution. Oxygen diffuses from the skin across the membrane to the electrode and reacts with the electrons provided by the anode. The resulting current generated is proportional to the PaO_2. Gas exchange at the skin surface is dependent on the cutaneous blood flow and metabolism. Application of local heat (40–45°C) increases the local blood flow and decreases the influence of cutaneous blood flow on $PtcO_2$ measurement. Actual PaO_2 rather than SpO_2 is measured and hence can be used to monitor hyperoxemia and prevent its complications especially in neonates. Values are not affected by abnormal hemoglobins. $PtcO_2$ can be used to assess shunt in a patient on supplemental oxygen, detect onset of hemodynamic instability and limb ischemia. Oxygen reaches the surface after traversing the epidermis. Skin also consumes oxygen, so there is always a gradient between $PtcO_2$ and PaO_2. Response of $PtcO_2$ electrode to a rapidly changing PaO_2 is slow. These problems are minimized in neonates and infants in view of the thin skin with lower metabolism. Local heating may lead to thermal injury to the skin and the site of the electrodes may need to be changed frequently. Accuracy is affected by low perfusion states, hemoglobin concentration, capillary density, and hydration of the epidermis. It has a potential role in monitoring in neonates and infants in critical care, but in adults the use of $PtcO_2$ measurement is limited. Unpredictable correlation of $PtcO_2$ with PaO_2, slow response characteristics and the need for 3 to 4 hourly site changes, limit its use for monitoring during anesthesia, exercise and sleep studies.

Transcutaneous PCO_2 Measurement

Transcutaneous CO_2 ($PtcCO_2$) measurement reflects $PaCO_2$ in the arterial blood in a similar fashion as the $PtcO_2$ which reflects PaO_2. The electrode senses the PCO_2 by monitoring changes in either the pH of bicarbonate containing electrolyte solution or the infrared absorption from a sample chamber. In view of a much higher solubility of CO_2 in the tissues, $PtcO_2$ estimation is less dependent upon cutaneous perfusion than $PtcCO_2$. Therefore heating the skin to 40°C suffices. The electrode can be left in place for up to 48 hours without the risk of thermal injury. Heating causes a temperature dependent rise in the PCO_2 and an overestimation of $PaCO_2$.

Transcutaneous PCO_2 measurement has been also employed for apnea test. In brain dead patients, a $PtcO_2$ of 60 mm Hg accurately predicts a $PaCO_2$ of 60 mm Hg allowing a reduction in the duration of apnea test. Combined O_2-CO_2 electrodes are also available. Since the OH– ions produced by O_2 reduction accumulate in these electrodes, there is a problem of change in the pH of the electrolyte solution for PCO_2 sensing. Some of the electrodes are designed to consume the accumulated OH– ions preventing the pH shift.

Capnography

Continuous waveform display of the changes in the concentration of carbon dioxide throughout the ventilatory cycle is called capnography. Capnography was developed in 1943 and introduced to clinical practice in the early 1950s. Commonly, capnography uses the principle of infrared light absorption (infrared spectro-metry) or mass spectrometry. The first method depends on the concept that CO_2 strongly absorbs infrared light at a wavelength of 4280 nm. This infrared radiation passes through the sample chamber where it is absorbed by CO_2 and the remaining unabsorbed radiation is focused onto a detector with a semiconductor that creates an electrical signal. The concentration of CO_2 is directly proportional to the amount of infrared light absorbed and higher the CO_2 concentration in the gas mixture the more infrared radiation is absorbed and less arrives at the detector. This method allows for real time, continuous measurement, and display of PCO_2 with a delay time of approximately 0.25 second.

The end-tidal ($PetCO_2$) CO_2 monitors can be categorized as mainstream or sidestream variety depending upon the gas sampling technique. Mainstream analyzers are placed in the airway circuit usually between the end of the endotracheal tube and the Y connection. They provide continuous monitoring and the response is rapid. They are heavy, may cause kinking or dislodgement of the endotracheal tube and increase the dead space. The sensors can be disrupted by humidity and secretions and heating is required to prevent condensation. The second method is the sidestream analyzer, in which the gas sample is aspirated from the breathing circuit through a small bore tube to a remote analyzer. Time delay, loss of expired tidal volume and clogging by pulmonary

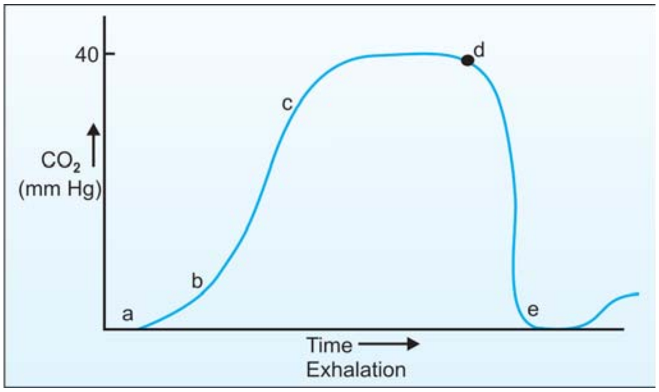

Fig. 142.3: A normal capnogram (see text for details)

secretions are the main disadvantages. It may also be contaminated by ambient air.

The capnogram during expiration is normally divided into three phases (Fig. 142.3). The first phase: (a) represents the gas from the anatomical dead space (trachea) that is free of CO_2. In the second phase (b) the curve rises sharply as the alveolar gas that contains CO_2 mixes with the dead space. This represents emptying of rapidly emptying alveolar spaces. As expiration continues (c) more and more of the alveoli empty and CO_2 concentration rises rapidly until a plateau (d) that essentially represents alveolar gas, is reached (phase 3). When inspiration starts the CO_2 level drops sharply and there is a rapid down-stroke of the curve to zero (e). The highest CO_2 tension measured during the plateau phase (i.e. the point at which the plateau ends just before inspiration) is referred to as the end tidal CO_2 concentration ($PetCO_2$).

$PetCO_2$ is commonly used to estimate $PaCO_2$ quantitatively; however the $PetCO_2$ is less than the $PaCO_2$, and in normal individuals P (a-et) CO_2 gradient ranges between 2 and 5 mm Hg. This is because of the normal physiological dead space. The $PetCO_2$ can be affected by changes in alveolar ventilation, CO_2 production (metabolism) and transport (perfusion). Capnography is helpful in ensuring adequacy of pulmonary ventilation, assessing changes in pulmonary blood flow and physiological dead space, and detecting the addition of CO_2 to the systemic circulation. $PetCO_2$ can increase in conditions with increased production of CO_2 (fever, sepsis), decreased ventilation or equipment malfunction. Decrease in $PetCO_2$ with increase in the gradient can occur secondary to increased dead space (as during hypotension, pulmonary emboli, and cardiac shunts), incomplete alveolar emptying, decreased CO_2 production or equipment malfunction.

$PetCO_2$ can be used for continuous noninvasive monitoring of $PaCO_2$ as long as the capnogram waveform remains unchanged, the temperature remains constant and the ventilatory and cardiovascular functions are stable. A normal capnogram with a large difference between $PetCO_2$ and $PaCO_2$ indicates substantial physiologic dead space.

Capnography has been shown to be useful during intubation to ensure tracheal rather than esophageal intubation. CO_2 is primarily eliminated from the lung and the concentration of CO_2 in the stomach is negligible, so with tracheal intubation the $PetCO_2$ is high (20-45 mm Hg) and remains so, whereas with esophageal intubation the $PetCO_2$ is usually zero and the waveform disappears. Capnography is also helpful in recognizing disconnection from ventilation system, accidental extubation and airway obstruction. Capnography provides a simple, noninvasive, rapid continuous monitor and can be helpful in patients undergoing elective surgery under general anesthesia, patients receiving hyperventilation to decrease intracerebral edema, and those requiring apnea monitoring. It has also been helpful as a prognostic tool during cardiopulmonary resuscitation (CPR). Sudden increase in $PetCO_2$ indicates successful (CPR) with return of spontaneous circulation. Falsely low $PetCO_2$ can occur due to leaks in the sampling system or circuit.

Capnographic waveform changes are also important and may be characteristic of certain clinical situations; hence it is essential to monitor the waveform tracing in addition to the numerical value of $PetCO_2$. An elevation of baseline indicates clinically important rebreathing of exhaled air secondary to malfunction of expiratory value or exhaustion of CO_2 absorbent. Delayed up-stroke with flattening of phase 2 and blurring of the distinction between phase 2 and 3 is seen in obstructive pulmonary diseases. Restrictive lung diseases cause irregularity in the plateau due to uneven alveolar emptying.

Capnography in the intensive care unit (Fig. 142.4) during mechanical ventilation can help in detecting the development of pulmonary emboli (rapid fall in $PetCO_2$) or a pneumothorax (inability to maintain a plateau). Capnography can also be used to measure the physiological dead space using mixed expired CO_2 tension ($PetCO_2$). It can help in determining the best positive end-expiratory pressure (PEEP) during mechanical ventilation. The hypothesis is that PEEP decreases the dead space by recruiting alveoli, whereas higher PEEP leads to over distention of the alveoli that can increase the dead space. The smallest Pa-etCO_2 gradient coincides with the maximal recruitment of the alveoli without over distention and the least shunt, and hence the PEEP level can be adjusted while monitoring the Pa-etCO_2 gradient in addition to other parameters.

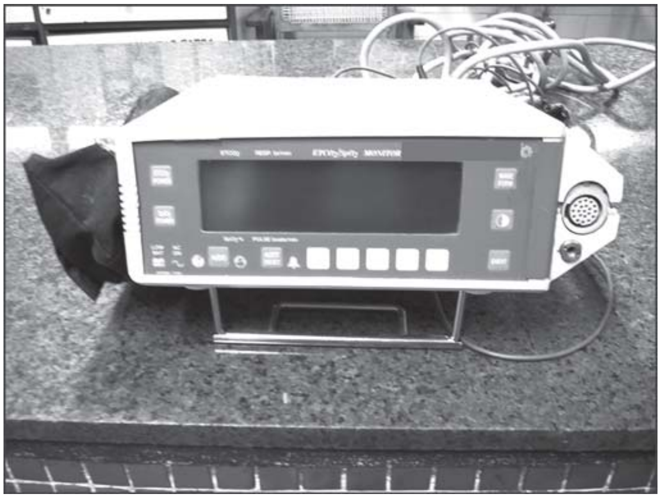

Fig. 142.4: Capnography instrument used in ICU

Capnography, however, cannot be reliably used for patients wearing face masks and nasal cannulae. The readings should be interpreted with caution in critically ill patients and should be periodically confirmed by an arterial blood gas analysis.

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Cutaneous Capnography

Ankur Mehta, Prashant Chhajed

INTRODUCTION

Cutaneous carbon dioxide tension ($PcCO_2$) measurement is used as a noninvasive surrogate measure of $PaCO_2$, which is used either to estimate $PaCO_2$ or to determine trend changes in $PaCO_2$. Although $PcCO_2$ monitoring has been available since the 1970s, it is not used as commonly as one might expect, this has been mainly attributed to technical factors. The special features of $PcCO_2$ monitoring are that it and averages out breath-by-breath variations and has almost no inherent "noise" or variability so that it is often found to be the best trend monitor for detecting small changes in $PaCO_2$.[1] Arterial blood gas analysis is the "gold standard" method to measure the arterial partial pressure of carbon dioxide ($PaCO_2$). However, arterial sampling including arterial catheterization is invasive and expensive. Intermittent arterial puncture is also associated with pain and discomfort for the patient.

To evaluate the accuracy of transcutaneous PCO_2 ($PtcCO_2$) as a surrogate for $PaCO_2$, in a cohort of adult critically ill patients in a medical Intensive Care Unit (ICU). Prospective observational study comparing paired measures of transcutaneous and arterial PCO_2. A total of 189 paired PCO_2 measures were obtained. Twenty-one were excluded from analysis, because profound skin vasoconstriction was present. Finally, 168 were analysed, including 137 obtained during mechanical ventilation and 82 under catecholamine treatment. Body temperature was below 36°C for 27 measurements. Mean duration of monitoring was 17+/-17 h. The mean difference between $PaCO_2$ and $PtcCO_2$ was -0.2+/-4.6 mm Hg with a tight correlation (R(2) = 0.92, p > 0.01). PCO_2 bias did not significantly change among three successive measurements. Changes in $PaCO_2$ and in $PtcCO_2$ between two blood samples were well correlated (R(2) = 0.78, p > 0.01). Variations of more than 8 mm Hg in $PtcCO_2$ had 86% sensitivity and 80% specificity to correctly predict similar changes in $PaCO_2$ in the same direction. Catecholamine dose or respiratory support did not affect $PtcCO_2$ accuracy. Hypothermia had only a small effect on accuracy. No complication related to the prolonged use of the sensor was observed. Transcutaneous PCO_2 provided a safe and reliable trend-monitoring tool, provided there was no major vaso-constriction.[2]

When first introduced, $PcCO_2$ measurement was combined with the measurement of PcO_2. Cutaneous oxygen (PcO_2) and $PcCO_2$ monitoring were introduced to provide noninvasive measures of the arterial partial pressure of oxygen (PaO_2) and $PaCO_2$.[3,4]

Pulse oximetry came to use in the mid eighties and quickly replaced transcutaneous blood gas analysis. Oxygen saturation measured with a pulse oximeter (SpO_2) provides a surrogate measure of arterial oxygen saturation. However, measurement of SpO_2 does not completely reflect ventilation. Due to the S-shape of the oxygen dissociation curve, hypoventilation with a decrease in the PaO_2 may remain unnoticed over a period of time. Furthermore, with the administration of supplemental oxygen during various medical procedures carried out under sedation, although the patient would have adequate arterial saturation, one would nevertheless remain unaware of the adverse physiological trend that may be reflected by changes in the $PaCO_2$. Therefore, taking this limitation of pulse oximetry into consideration, some new generation monitors have now come up with combining cutaneous $PcCO_2$ measurement along with pulse oximetry in one sensor.[5,7] With evolution in technology, there has been considerable progress in the technical aspects of $PcCO_2$ monitoring in the last few years.

Comparison with Arterial Blood Gas

Arterial blood gas analysis is the gold standard for measuring the arterial partial pressure of carbon dioxide ($PaCO_2$). As this measurement is intermittent, an arterial catheterization is often performed to allow repeated sampling. Arterial blood gas analysis or arterial catheterization can be time consuming, painful for the patient and bears the risk of catheter-related infection, hemorrhage, ischemia, arteriovenous fistula and pseudoaneurysm formation.[8] In addition, there is a risk of preanalytical errors when venous blood is sampled air bubbles are trapped in the syringe, or the specimens are transported via pneumatic tube delivery systems which can potentially lead to false measurements results.[9-11] In patients with endotracheal intubation, the measurement of end-tidal carbon dioxide tension ($EtCO_2$) is routinely performed and this has shown to correlate with arterial partial pressure of carbon dioxide. $PaCO_2$.[12,13] However, $EtCO_2$ may inaccurately estimate $PaCO_2$ in case of ventilation/perfusion mismatch found in patients with obstructive lung disease and acute respiratory distress syndrome.[14,15]

Measurement of $EtCO_2$ using side-stream capnography in nonintubated sedated patients has the risk of oral leakage when patients alternate between oral and nasal breathing and can yield incorrect measurements.[16] Pulse oximetry provides a continuous and an accurate measurement of hemoglobin saturation with oxygen.[17] However, it is a good surrogate only for oxygenation, and does not adequately reflect ventilation due to lack of carbon dioxide measurement.[18] Cutaneous carbon dioxide tension monitoring has been available for several years, but has not found common usage in several fields of clinical practice due to perceptions of being time and work intensive, difficult calibration procedures, long equilibration time and the necessity to frequently change the skin site of the sensor to avoid thermal injury to the skin.[19,20] Recently developed devices have features like automatic calibration, shorter response and equilibration times.

Development of $PcCO_2$ Monitoring Devices

The frequent change in sensor membranes and long calibration procedures have given $PcCO_2$ monitoring a reputation of being more labor intensive.[21] Some authors have attributed slow response time of the electrodes and the reflex vasoconstriction of the skin vessels related to hyperventilation as factors making transcutaneous measurements unreliable for monitoring blood gas changes.[22] With evolution in technology, considerable progress has been made in shortening the response times, calibration and equilibration times, reducing the temperature of the sensor to 42°C and analog to digital conversion of the signal in the sensor itself.[5] Until recently, the $PcCO_2$ sensors were heated between 43 and 45°C. Skin injuries have not been uncommon at these temperatures.[23] The newer generation $PcCO_2$ sensors, which are heated to 42°C, can be safely kept continuously for periods of up to 8 hours with minimal risk of thermal skin injury and the sensor sites do not need to be changed frequently.[24]

Measurement of $PcCO_2$ is possible because carbon dioxide has high tissue solubility and diffuses through the skin. It can be performed using monitors which employ the Severinghaus electrode or infrared sensors.[20] Most $PcCO_2$ monitors are based on Severinghaus principle. $PcCO_2$ is performed by placing a heated surface electrode on the skin. Application of heat to the skin surface increases blood flow in the arteriovenous anastomoses and the venous plexus. When this occurs, capillary blood is arterialized (Table 143.1).[21] Adapted from the article: The Design, Use, and Results of

TABLE 143.1: Typical characteristics of a transcutaneous PCO_2 ($tcPCO_2$) sensor

Size	
Diameter	15 mm
Height	8 mm
Weight	3 g
PCO_2 range	1–200 mm Hg (0.1–27 kPa)
In vitro response time (10–90%)	50 s
Arterialization time after application	3-10 min, depending on the site of the sensor on the skin

Transcutaneous Carbon Dioxide Analysis: Current and Future Directions.[25]

Site for Measurement

The ear lobe sensor has been reported to detect the SpO_2 change, 5 to 37 seconds faster than a finger sensor and the $PcCO_2$ change 9 to 48 seconds faster than a cutaneous sensor fixed at the upper arm.[6] The heated sensor increases the blood flow at the measurement site. The arterialization time of the ear lobe (i.e. the time until the cutaneous value reflects the arterial value) is significantly shorter at the earlobe (2.5 ± 1 min) than at the inner arm (7 ± 2 min).[26,27] Warming the ear lobe with the sensor not only increases the blood flow which is required for $PcCO_2$ measurement but also improves the quality of the SpO_2 signal, which has been questioned at the ear lobe.[21,26,28,29] Digital ear pulse oximetry (part of combined SpO_2 and $PcCO_2$ sensor) has been reported to have shorter SpO_2 response times than conventional, analog ear pulse oximetry. Due to these factors, the delay to the detection of hypoxemia may be shortened. *Other measurement sites: forehead – check papers or abstracts. This becomes particularly important while measurements are sought in infants and neonates as they typically will not have ear lobe to place the sensor.*

Factors Influencing $PcCO_2$ Monitoring

The success of $PcCO_2$ monitoring depends on technical and patient factors. The technical factors which may affect the accuracy of the measurement include an improper application of the sensor membrane, trapped air bubbles in the electrolyte solution under the membrane, damaged sensor membranes, delayed changing of sensor membrane, calibration gas leaks leading to an improper calibration and excessive force on the ear lobule in case of ear clips. The patient factors which may influence $PcCO_2$ values include hypoperfusion at the site of measurement, shock, edema, skin thickness the thickness of the ear lobule for ear clips and the use of vasoconstricting drugs.[4,30] A cardiac index below 1.5 L/min can dramatically increase the $PcCO_2$–$PaCO_2$ gradient.[31] There is also a distinct possibility of occasional errant $PcCO_2$ values, e.g. difference of 8 to 12 mm Hg compared to arterial blood gas analysis.[20]

MEDICAL APPLICATIONS OF $PcCO_2$ MONITORING

End Tidal Carbon Dioxide Monitoring

Measurement of $PetCO_2$ is a noninvasive method of estimating $PaCO_2$. For the estimation of pulmonary dead space, there is an excellent correlation between (1) the difference (gradient) between $PaCO_2$ and the $PetCO_2$, and (2) the ratio between dead space and tidal volume (VD/VT). Its use to confirm correct placement of endotracheal tube in the airway has a sensitivity and specificity of up to 100%. This method cannot be used to detect bronchial or hypopharyngeal misplacements. With the relationship between $PaCO_2$ – $PetCO_2$ and VDS/VT well established, the research in the detection of pulmonary embolism is promising but incomplete.[32]

Advantages of End Tidal Carbon Dioxide Measurements

One of the most common causes of intubation failure is inadvertent esophageal intubation, which can have catastrophic consequences.[32] Direct visualization of the endotracheal tube passing through the vocal cords, endotracheal tube condensation, observation of chest wall movement and auscultation of breath sounds are commonly used clinical signs to aid confirmation of correct endotracheal tube placement. However, as none of these are infallible, the addition of CO_2 detection using the colorimetric device is a very useful adjunct to clinical assessment. The disposable $ETCO_2$ detector significantly decreases the time for clinical determination of endotracheal tube position. The detector also has prognostic value for return of spontaneous circulation and short-term survival in adults and children.[35,36] In adults, none of the patients with colorimetric $ETCO_2$, 2% were successfully resuscitated after cardiopulmonary resuscitation.[33]

Limitation of End Tidal Carbon Dioxide Measurements

Colorimetric $ETCO_2$ detectors cannot detect hypocarbia or hypercarbia, right main stem bronchus intubation or oropharyngeal intubation in spontaneously breathing patients.[33] If the colorimetric detector is contaminated with acidic gastric contents or drugs, such as adrenaline (epinephrine), there is a fixed yellow discoloration and results are unreliable. Humidity decreases the clinical lifespan of the detector from a maximum of two hours (Portex) or 24 hours (Smiths). CO_2 is a product of cellular metabolism and is removed through the circulation and the lungs. Therefore, $ETCO_2$ reflects ventilation, metabolism and circulation.[33] During cardiopulmonary resuscitation, a positive test confirms placement of the endotracheal tube within airway, whereas a negative test indicates either esophageal placement or airway intubation with poor or absent pulmonary blood flow.[34] In this situation, an alternative means of assessing endotracheal tube placement is required.

Neonates requiring venoarterial Extracorporeal Membrane Oxygenation (ECMO) may also potentially show a false negative result with the $ETCO_2$ detector. In this scenario, the membrane oxygenator, bypassing the pulmonary circulation, removes CO_2, resulting in significantly reduced $ETCO_2$. The reliability of end tidal CO_2 measurement, however, is limited, particularly in the presence of parenchymal lung disease or air leakage at the face mask.[35]

Clinical Settings for the Use of Cutaneous Capnography

There are several conditions where $PcCO_2$ monitoring can be useful (Table 143.2). There is an overlap of the clinical indications where both $PcCO_2$ and $PetCO_2$ monitoring may be used. Both these methods have independent indications, sometimes complimentary to each other in patient care.

Use in Emergency Room

Transcutaneous Carbon Dioxide Tension ($TcPCO_2$) monitors offer a noninvasive method of continuous measurement of arterial carbon dioxide tensions. The concordance between the $TcPCO_2$ measurement and the value obtained from arterial blood gas sampling was measured in patients attending the emergency department. A prospective observational cohort study was performed in 49 adult patients who underwent arterial blood gas sampling as a part of their assessment. Blood gas sampling and recording of the $TcPCO_2$ level from the monitor was done simultaneously. Concordance between the two values ($PaCO_2$ and $TcPCO_2$) which was demonstrated using the method described by Bland and Altman with the mean difference of 0.02 kPa (95% CI, 0.11–0.15). The Pearson's correlation coefficient was 0.94 ($p<0.001$) and the Bland-Altman limits of agreement were +/-0.9 kPa. In adult patients, concordance between carbon dioxide measurements by transcutaneous monitor and arterial blood sampling is good. Using the transcutaneous method, patients may be monitored noninvasively which may reduce the need for repeated blood gas sampling.[36]

TABLE 143.2: Clinical applications of $PcCO_2$ monitoring

Operating room – patient monitoring during and after anesthesia

- Intensive care unit
  Neonatal
  Adult critical care
  Monitoring patients receiving noninvasive ventilation
  Guiding mechanical ventilation
  Monitoring of patients after extubation
- Endoscopy under conscious sedation
  Bronchoscopy
  Thoracoscopy
  Gastroscopy/colonoscopy
- Sleep laboratory
  Assessment of alveolar hypoventilation
  Titration of noninvasive ventilation
- Lung function laboratory
  Oxygen titration in patients with severe chronic obstructive pulmonary disease
  Diagnosis of hyperventilation
- Cardiopulmonary exercise testing
- Assessment of hyperventilation response in patients with hypercapnia

Adapted from: Chhajed PN, Heuss LT and Tamm M. Cutaneous carbon dioxide monitoring in adults Current Opinion in Anaesthesiology. 2004; 17:521-5.

Operation Room

$PcCO_2$ monitoring has been shown to provide better estimates of $PaCO_2$ values in patients undergoing various surgical procedures.[30,37-39] Although, $PetCO_2$ may be inaccurate because of ventilation/perfusion mismatch, it has become a standard for monitoring carbon dioxide concentrations during general anesthesia. $PcCO_2$ has been suggested to be a valuable addition to capnography in patients with an increased $PetCO_2/PaCO_2$ difference and in situations in which the continuous, noninvasive and precise control of carbon dioxide level is required (e.g. one lung ventilation). We believe that $PcCO_2$ and $PetCO_2$ monitoring are complementary in many situations. It is unlikely that $PcCO_2$ monitoring will replace $PetCO_2$ monitoring, as $PetCO_2$ allows for detection of life-threatening situations such as accidental esophageal intubation, ventilator disconnection or pulmonary embolism.[37]

The pulse oximetry is widely used to monitor patients postoperatively. Although it accurately measures arterial oxygen saturation, it provides no information on ventilator status. When patients are receiving high concentrations of supplemental oxygen, oxygenation can be maintained with inadequate alveolar ventilation because of the diffusion of oxygen molecules from the airways into the alveoli. In this setting, severe hypercapnia and respiratory acidosis may result in this setting. This phenomenon of apneic oxygenation illustrates a major limitation in monitoring patients postoperatively with the pulse oximetry.[40]

If alveolar ventilation ceases, the PCO_2 increases at a rate of 2.7–4.9 mm Hg per minute.[41] In the absence of supplemental oxygen, the maximal carbon dioxide pressure compatible with life is approximately 100 mm Hg. Beyond this value, there is excessive displacement of alveolar oxygen, leading to lethal hypoxia and death. Oxygenation may be maintained during insufficient or absent ventilation if high concentrations of oxygen are administered. Because of the extraction of oxygen by erythrocyte hemoglobin in the pulmonary capillaries, an oxygen concentration gradient develops between the upper airways and the alveoli. This leads to mass diffusion of oxygen molecules down the airways and into the alveoli, even in the absence of ventilation, however, this process is inadequate to remove carbon dioxide which is thus retained until the buffering capacity of blood and tissues is exceeded and profound respiratory acidosis results. This process is known as diffusion respiration or apneic oxygenation.[40]

Intensive Care Unit

The potential applications of $PcCO_2$ measurement in the ICU include the monitoring of patients receiving mechanical ventilation, noninvasive ventilation and postextubation. The aim in these situations is mainly to monitor the trends of change in $PaCO_2$ by monitoring $PcCO_2$. End tidal CO_2 ($PetCO_2$) is commonly used in patients receiving mechanical ventilation. However, $PetCO_2$ cannot be applied to patients receiving non invasive ventilation because of air flow through the mask. The response time of $PcCO_2$ values to a change in non-invasive ventilation has been shown to be compatible with the aim of clinical monitoring.[20]

Patients with respiratory failure are at risk for worse hypercapnia when off ventilator. Assessment of hypercapnia and changes in arterial PCO_2 are often used to determine whether patient receiving a high level of ventilatory support can be considered for a spontaneous breathing trial (SBT). Transcutaneous PCO_2 measurement is helpful to assess and manage patients during spontaneous breathing trials.[42] Whereas arterial oxygen saturation (SaO_2) is commonly estimated by pulse oximetry, $PaCO_2$ may be estimated from end-tidal carbon dioxide tension[2] or transcutaneous carbon dioxide tension ($PtcCO_2$). Since alterations in ventilation/perfusion matching and the use of noninvasive mask ventilation may reduce the correlation of end-tidal carbon dioxide tension with $PaCO_2$, transcutaneous monitoring of $PtcCO_2$ is increasingly used if the rapid tracking of transient fluctuations of $PaCO_2$ is not essential.

Neonatal Intensive Care Unit

Arterial Oxygen Saturation (SaO_2) and arterial carbon dioxide partial pressure $PaCO_2$ are two of the most important respiratory parameters in the treatment of critically ill neonates. Noninvasive monitoring of these parameters is desirable for continuous estimation of the respiratory status and to reduce blood loss because of repeated blood gas analyses. Transcutaneous measurement of PCO_2 represents a simple and noninvasive technique for continuous monitoring of ventilation.[43]

Pulse oximetry and carbon dioxide pressure measured by capillary arterialized blood gases and a combined transcutaneous carbon dioxide and pulse oximetry ($PtcCO_2$/ SpO_2) monitor were compared in 65 patients (asthma, n = 16, recurrent bronchitis, n = 8, lung infection, n = 8, cystic fibrosis, n = 15, interstitial lung disease, n = 6, neuromuscular disease, n = 12). Daytime capillary arterialized blood gases and nocturnal recording of pulse oximetry and carbon dioxide by means of a combined $PtcCO_2/SpO_2$ monitor were performed in 50 other patients receiving nocturnal noninvasive respiratory support at home. Nocturnal hypercapnia may occur in children receiving nocturnal noninvasive respiratory support at home. Nocturnal pulse oximetry and daytime arterial blood gases are not sufficiently accurate to diagnose nocturnal hypercapnia, underlying the importance of a systematic carbon dioxide monitoring in children receiving noninvasive respiratory support. In the study undertaken shows first, that the values for SpO_2 and $PtcCO_2$ measured by a combined $PtcCO_2/SpO_2$ monitor are reliable in children, and second, that nocturnal hypercapnia is observed in a significant number of children treated at home with nocturnal long-term noninvasive respiratory support. This nocturnal hypoventilation is not associated with clinical symptoms of sleep disordered breathing, nocturnal desaturation, or daytime hypercapnia on capillary arterialized blood gases, underscoring the value of a systematic nocturnal PCO_2 monitoring in children treated by noninvasive respiratory support at home.[44]

Although, the direct measurement of $PaCO_2$ remains the gold standard, it provides only a single measurement of what is often a rapidly changing and evolving clinical picture. Given these concerns, there remains a clinical need for a means to continuously monitor $PaCO_2$ without the need for repeated blood gas analysis. Although, initially introduced into the neonatal intensive care unit; with improvements in the technology, transcutaneous CO_2 monitoring can now be used in infants, children and even adults. When compared with end-tidal carbon dioxide ($ET\text{-}CO_2$) monitoring techniques, transcutaneous CO_2

monitoring has been shown to be equally as accurate in patients with normal respiratory function and more accurate in patients with shunt or ventilation-perfusion inequalities. Transcutaneous CO_2 monitoring can be applied in situations that generally preclude end-tidal CO_2 monitoring such as high frequency ventilation, apnea testing, and noninvasive ventilation. Transcutaneous CO_2 monitoring has also been used in spontaneously breathing children with airway and respiratory issues such as croup and status asthmaticus as well as to monitor metabolic status during treatment of acidosis related to diabetic ketoacidosis. Transcutaneous carbon dioxide monitoring may be a useful adjunct in various clinical scenarios in infants and children. It should be viewed as a complimentary technology and may be used in combination with end-tidal CO_2 monitoring.[45]

Endoscopy Room

Diagnostic and therapeutic endoscopic procedures are now increasingly performed under sedation with supplemental oxygen.[46-48] As discussed earlier, pulse oximetry does not completely reflect the ventilatory status. Respiratory depression often occurs following administration of sedative medication and this may have to be treated with sedation reversal and/or mask ventilation.[49,50]

The British Thoracic Society Guidelines suggest that $PcCO_2$ monitoring may be useful in patients with COPD having hypercapnic respiratory failure.[51] Evans et al. have reported in a study of 22 patients that hypoventilation with significant elevation of $PcCO_2$ occurs during bronchoscopy and provides an earlier indication of respiratory depression during flexible bronchoscopy compared with pulse oximetry.[52] However, they also concluded that $PcCO_2$ analysis was complex. In a recent study, the mean baseline and peak $PcCO_2$ levels were 38 mm Hg and 49 mm Hg, respectively. The mean duration from baseline to peak $PcCO_2$ level was 14 minutes. SpO_2 dropped to ≤ 90% in 15 patients and the mean increase in $PcCO_2$ was 14 mm Hg.[53] Similarly, significant hypoventilation has been reported for the first time in patients undergoing medical thoracoscopy performed under local anesthesia and sedation.[54] The baseline $PcCO_2$ measurement was 39 mm Hg and the peak measurement during the procedure was 50 mm Hg.[54] In a prospective randomized study in patients undergoing colonoscopy, the mean increase in $PcCO_2$ with midazolam was 8.2 mm Hg as compared to 6.6 mm Hg with propofol. The mean difference from initial $PcCO_2$ to that, five minutes after the end of the procedure, was 4 mm Hg with midazolam and 0.9 mm Hg with propofol.[55] The findings of these studies supported that combined $PcCO_2$ and SpO_2 measurements during endoscopy performed under sedation might improve patient safety.

The combined POX/$PcCO_2$ monitoring at the earlobe is a novel approach to detect hypoventilation and therefore might improve patient safety during sedation. It may be used to titrate the administration of sedative drugs to prevent an unintentional slide into deep sedation or anesthesia with the risk of development of apnea. Larger studies, especially with short-acting sedative drugs like propofol, are needed to confirm the clinical benefit of this novel technique.[56] In the study of 33 patients (48% female; mean age B SD 59 B 12.9 years) undergoing colonoscopy under sedation and analgesia with midazolam combined with alfentanil or without any sedation or analgesia shows (1) that values recorded with the combined POX/$PcCO_2$ sensor correlate excellently with blood gas analysis; (2) that in sedated patients undergoing colonoscopy hypoventilation reflected by retention of PCO_2 can easily be detected by the use of a combined POX/$PcCO_2$ ear sensor, and (3) that monitoring with the combined POX/$PcCO_2$ sensor is more specific in the detection of hypoventilation than standard POX alone.[56]

Flexible Bronchoscopy

Flexible bronchoscopy under local anesthesia and sedation is widely performed to diagnose and manage a variety of lung diseases. The purpose of sedation is to facilitate examination of tracheobronchial tree, carry out necessary diagnostic and interventional procedures and provide patient comfort. Oximetry measures the oxygenation of blood and can detect hypoxemia, but it can not detect hypercarbia and hence the adequacy of ventilation.[52] When bronchoscopy is performed under conscious sedation without supplemental oxygen, oxygen desaturation will occur rapidly giving a good indication of ventilator status. However, most centers routinely offers oxygen supplementation during flexible bronchoscopy. Due to the S-shaped curve of the oxygen dissociation curve, in such situation alveolar carbon dioxide tension will have to increase further before significant hypoxemia is manifested.[57] Therefore, a reliable substitute of carbon dioxide arterial tension ($PaCO_2$) measured noninvasively is required as it enhance patient safety during flexible bronchoscopy. Ventilation can be effectively monitored using combined oximetry and cutaneous capnometry.[58]

Patients with chronic obstructive pulmonary disease (COPD) which were defined using the American

Thoracic Society/European Respiratory Society guidelines demonstrates the feasibility of measuring combined oximetry and cutaneous capnography effectively to monitor ventilation during flexible bronchoscopy. Patients with COPD who are not in hypercapnic respiratory failure have a similar risk of hypoxemia and hypercapnia compared with those without COPD during bronchoscopy. The peak $PcCO_2$ is higher in patients with a higher baseline $PcCO_2$ and is associated with lowest SpO_2 during bronchoscopy. Significant hypoxemia is associated with the peak $PcCO_2$ and baseline SpO_2. With the current study results, it is not possible to predict and accurately select a group of patients who should undergo capnography during bronchoscopy. Patients with elevated baseline $PaCO_2$ or a low baseline SpO_2 will have the benefit of better monitoring of ventilation using such a device. Specifically, patients with a longer duration of procedure did not show a different rise in $PcCO_2$ compared with the others. Furthermore, the current authors expected an association of the sedative dose with rise in cutaneous carbon dioxide tension, but that was also not the case. Therefore, future studies need to analyse the different patient groups with regards to the baseline cutaneous carbon dioxide tension to potentially limit the application of cutaneous capnography to only a specific group of patients.[58]

Assessment of Long-Term Oxygen Therapy

Long-term oxygen therapy (LTOT) is used in patients with hypoxemia due to severe obstructive and restrictive pulmonary diseases, interstitial lung diseases or pulmonary hypertension. Assessment of patients on home oxygen therapy is usually done with arterial blood gas analysis.

Arterial blood gas sampling is invasive and can be painful. Cutaneous carbon dioxide is a non-invasive surrogate of $PaCO_2$. It is used both to estimate $PaCO_2$ and to determine trend changes.[59]

Long-term oxygen therapy is routinely used in patients with hypoxemia due to severe obstructive and restrictive pulmonary diseases, interstitial lung diseases, or pulmonary hypertension.[60-62] Oxygen therapy has been shown to improve survival and reduce hospitalization in patients with COPD and severe hypoxemia at rest.[63-65] Widely accepted indications for long-term oxygen therapy include a PaO_2 of –55 mm Hg (–7.3 kPa) while breathing room air.[60-62,66] In patients with complications such as polycythemia or evidence of pulmonary hypertension and/or episodes of right heart failure that reflect the systemic effects of chronic hypoxemia, continuous oxygen therapy should be prescribed even if the stable PaO_2 while breathing room air is 56 to 59 mm Hg (7.3 to 7.8 kPa).[60,61] The therapeutic goal is to maintain a pulse oximetric saturation (SpO_2) of –90% during rest, sleep, and exertion.[60-62,66] The guidelines for the assessment of home oxygen therapy vary depending on the country.[60-62] In Switzerland, oxygen titration consists of repeated arterial blood gas analyses, which includes the measurement of PaO_2 and $PaCO_2$ with and without supplemental oxygen. Arterial blood gas sampling is invasive and can be painful. Hence, there is a need for a noninvasive method. Since uncontrolled oxygen supplementation in hypercapnic patients can lead to the suppression of hypoxic respiratory drive, pulse oximetry alone is not adequate for the estimation of oxygen requirements, and the assessment of carbon dioxide (measured invasively or noninvasively) is also essential. Transcutaneous carbon dioxide tension ($PtcCO_2$) is a noninvasive surrogate of $PaCO_2$.[57] It is used both to estimate $PaCO_2$ and to determine trend changes. The measurement of $PtcCO_2$ is possible because carbon dioxide has high tissue solubility, diffuses through the skin, and can be detected by a sensor at the skin surface.[7] Combined cutaneous capnography and oximetry (SpO_2) is now possible with a single earlobe sensor.[5,7] This sensor is based on the Severinghaus principle, and $PtcCO_2$ is measured by placing a heated surface electrode on the skin. The application of heat to the skin surface increases blood flow into the arteriovenous anastomoses and the venous plexus, and capillary blood is arterialized. Patient factors that may influence $PtcCO_2$ values include hypoperfusion at the site of measurement, shock, edema, skin thickness, and vasoconstricting drugs.[57] Combining oximetry and cutaneous capnography may potentially reduce the need of arterial blood gas sampling.

Sleep Laboratory

The application of continuous $PcCO_2$ monitoring to overnight studies has been limited due to changing of the skin site of the probe after 4 hours and recalibrating to prevent thermal injuries to the skin. This is a time consuming procedure and the acquisition of the $PcCO_2$ values is delayed further by the equilibration time of up to 20 minutes. As discussed earlier, continuous $PcCO_2$ monitoring between 5 to 8 hours has been shown to be reliable in adults at a probe temperature of 43°.[67,68] However, the authors also reported that the time lag of $PcCO_2$ values was 5 ± 3 minutes and this was attributed to the lowering of the probe temperature to 43°C. The possibility to perform continuous eight hour $PcCO_2$ monitoring (with validation studies) would allow to study better the ventilation patterns during polysomnography and also be a tool for optimal titration of nocturnal noninvasive ventilation pressures in patients with chronic respiratory failure.

Lung Function Laboratory

This in another area where we feel that $PcCO_2$ monitoring has several potential applications (see Table 143.2). A suspected diagnosis of hyperventilation can be confirmed or excluded by the use of $PcCO_2$ monitoring.[69] $PcCO_2$ monitoring might be helpful for oxygen titration especially in patient with severe chronic obstructive pulmonary disease. Therefore, multiple arterial blood gas sampling can be avoided.

Cardiopulmonary Exercise Testing

Cutaneous estimations of PCO_2 and SPO_2 can be used in cardiopulmonary exercise testing, circumvening need for arterial canulation.[70]

Summary

Summary of applications and potential future use in clinical practice.

With evolution in technology $PcCO_2$ monitoring is now less cumbersome than before. Combined $PcCo_2$ and SpO_2 measurement has great potential to improve patient safety by better monitoring of ventilation during conscious sedation and general anesthesia, including postoperative surveillance. In clinical practice, instead of doing arterial blood gas repeatedly on patients receiving mechanical ventilation, non invasive ventilation and post-extubation, cutaneous capnography may offer a lesser invasive approach for decision making and patient management. In endoscopy room where pulse oximetry does not completely reflect the ventilation status, $PcCO_2$ combined with oximetry can help to detect hypoventilation. With more data coming from sleep laboratory, lung function laboratory and cardiopulmonary exercise testing the potential benefit of $PcCO_2$ measurement will help in oxygen titration, ventilation patterns during polysomnography and also be a tool for optimal titration of nocturnal non invasive ventilation pressures in patients.

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Role of Ultrasonography in Critical Care Medicine

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INTRODUCTION

Over the last two decades, ultrasonography has found a major application in the practice of critical care medicine. In the future, ultrasonography will have a major impact in advancing the quality of care in critically ill patients. The advantages of Critical Care Ultrasonography (CCUS) are evident; the intensivists personally perform the ultrasonography examination, so, they are in a position to immediately interpret the results in order to answer the clinical question under consideration. Thus, ultrasonography allows rapid diagnosis and therapeutic interventions at the bedside. Standard radiology or cardiology department based ultrasonography service inevitably introduces a time delay between the need for the examination, which is immediate and the performance of the examination, which is delayed, often by many hours. In addition, radiologists or cardiologists have minimal knowledge of the clinical situation. The time delay and clinical dissociation of the offline reader prevent their results from being integrated into the clinical plan quickly and efficiently as can be done by the intensivists. Performance of ultrasonography by intensivists also avoids the risk associated with transport of critically ill patients out of the Intensive Care Unit (ICU) for imaging studies.

By definition, the intensivist performs all aspects of the critical care ultrasonography examination at bedside like image acquisition, image interpretation and clinical application. The field of critical care ultrasonography has therefore been developed by critical care clinicians and is separate conceptually from the ultrasonography as practiced by the radiology and cardiology community. For this reason, the risks associated with the inexperienced intensivist ultrasonographer misinterpreting ultrasound results, misdiagnosing and mistreating their patients cannot be overstated.[1] Therein lies the importance of fellowship training programs incorporating a formal ultrasonography curriculum for their fellows including supervised, hands-on training.[1] Incorporation of ultrasonography into routine frontline critical care practice will require that professional societies develop high quality educational programs in order to ensure that attending level intensivists are fully trained in the discipline.

Healthcare quality has been usefully defined around six fundamental domains.[2] The usefulness and limitations of ultrasonography in improving care of critically ill patients can be described in reference to these quality care domains as summarized in Table 144.1.[3]

This chapter will review important applications of ultrasonography in critical care medicine. For more comprehensive review of the field, the reader is referred to standard texts (See reference).

TRAINING IN CRITICAL CARE ULTRASONOGRAPHY

The intensivist who seeks to develop competence in critical care ultrasonography needs to follow an organized approach to training. A key question that needs to be answered is what constitutes the subject matter of the field. With the knowledge of this, the learner has a roadmap to follow. The American College of Chest Physicians (ACCP) in partnership with La Société de Réanimation de Langue Française (SRLF) has written a consensus statement that defines competence in critical

TABLE 144.1: Benefits and limitations of ultrasound in impacting quality of care in critical care

Quality of Care Domain	*Definition*	*Advantages of US*	*Limitations of US*
Safety	Reducing/eliminating errors that happen during healthcare experience	1. Safe, noninvasive 2. Available 24/7 at bedside with immediate interpretations 3. Eliminates risks associated with moving patients off ICU monitoring for diagnostic tests 4. Improves safety for procedures	1. Expertise variable 2. Inaccurate interpretation by an inexperienced operator may lead to serious errors. 3. Potential of excess use because of easy availability, often at expense of meticulous physical examination 4. May fail to use, more difficult to obtain, but better diagnostic tests.
Effectiveness	Using well established, evidence-based principles, provider experience and patient values in achieving the desired care.	Guidelines for clear indications of ultrasound use in critical care are emerging	Requires adequate operator training/experience. Requires adequate acoustic window/imaging condition for satisfactory data gathering.
Efficiency	Using finite resources in the best possible way to optimize the value of resources	Being performed by the ICU physicians themselves, focused evaluation in a given clinical context can lead to efficient care without delay	Enough operator experience should be there for efficient data gathering and utilization of data in the care of the patient, being operated and interpreted by the clinician, lack of objectivity and confirmatory bias remain
Equity	Equal access to healthcare resources by all patients	Ultrasound is cheaper than many other imaging modalities	Costs of initial investment for equipments and personnel training mean that it will remain inaccessible in many ICUs in near future
Timeliness	Providing diagnostic and therapeutic services to patients in timely fashion when they need them	Critical care ultrasound is largely performed by intensivists themselves, being available readily when trained personnel are there.	24/7 intensivists proficient in using ultrasound may not be available.
Patient centeredness	Providing care and services to patients where they need it in a way that lead to a satisfactory healthcare experience	Use of a safe, fast modality reduces the burden on the related to unnecessary transport and pain. Immediate information can be communicated to the patient and family. Immediate implementation of actions based on results can improve patient satisfaction	Not available in all ICUs round the clock

care ultrasonography[4] (Table 144.2). This statement outlines in simple format the elements of the field that define competence.

Training in critical care ultrasonography requires mastery of the cognitive elements of the field; this is available in the standard textbooks and medical literature and in well designed e-learning format (http://www.iccuelearning.com). Image acquisition is the second mandatory component of competence and can only be learned by repeated practice, initially with normal subjects followed by practice on patients. Image acquisition is a key element of competence because the intensivist personally performs the ultrasonography examination at the bedside. Mastery of image acquisition requires knowledge of machine control, transducer manipulation and scanning protocol. It requires that the learner should be trained by a knowledgeable supervisor. There is also a major auto-didactic component to acquiring skill at image acquisition, so, the trainee should devote many hours of hands-on practice. The third component of training is for image interpretation. This requires review of

TABLE 144.2: ACCP Expert Consensus Statement on competence in critical care ultrasound[4]

Basic Principles

- Understanding of fundamental principles of ultrasound physics
- Knowledge of machine and transducer controls
- Knowledge of normal and abnormal ultrasound anatomy
- Knowledge of the pathophysiologic consequence of the imaged abnormality
- Knowledge of image interpretation, clinical applications, and specific limitations of ultrasonography.
- Ability to understand the goal directed nature of ultrasound examination in a critical care setting, in search of a specific clinical question.

Pleural Ultrasonography

- Identification of presence of pleural effusion as a relatively hypoechoic or echo-free space surrounded by typical anatomic boundaries like diaphragm, chest wall, ribs, normal/abnormal lung
- Identification of other important structures in the neighborhood like liver, spleen, kidney, heart, pericardium, spinal column, aorta, inferior vena cava
- Identification of characteristic dynamic findings of pleural fluid
- Characterization of fluid
- Identification of miscellaneous findings such as pleural-based masses or thickening
- Performance of semi quantitative assessment of fluid volume
- Recognition of specific limitations of ultrasonography to identify pleural fluid due to inadequate image acquisition conditions or nature of pleural fluid/other pleural pathology.

Lung Ultrasonography

- Identification and characterization of the normal aeration pattern
- Identification and characterization of consolidated lung with or without air bronchograms
- Identification and characterization of alveolar interstitial pattern
- Identification and characterization of air artifacts to rule out pneumothorax
- Identification and characterization of findings that rule in pneumothorax, e.g. presence of lung point (both by 2D imaging and M-mode).

Abdominal Ultrasonography

- Identification and characterization of intraperitoneal fluid by static and dynamic image characteristics. Qualitative assessment of intraperitoneal fluid volume
- Identification of all the relevant abdominal structures like abdominal wall, diaphragm, liver, gallbladder, spleen, kidney, bladder, bowel, uterus, spinal column, aorta, IVC
- Assessment of the urinary tract which includes identification of bladder, identification of urinary catheter, identification of abnormal bladder contents; differentiation of distended bladder from ascites
- Identification of both kidneys, presence or absence of hydronephrosis, measurement of kidney in longitudinal axis
- Identification of abdominal aorta, assessment of the aorta, identification of abdominal aortic aneurysm.

Vascular Ultrasonography: Guidance of Vascular Access

- Identification of relevant central and peripheral veins and arteries: internal jugular/carotid, subclavian vein/artery, axillary vein/artery, brachial vein/artery, radial artery, femoral vein/artery vein, peripheral veins such as basilic, cephalic, external jugular vein
- Differentiation of vein from artery based on anatomic position, compressibility, phasic changes during respiration
- Identification of adjacent nonvenous structures such as muscle, mass, lymph node
- Identification of normal anatomic variability in structure and position
- Identification of vascular thrombosis.

Vascular Ultrasonography: Diagnosis of Venous Thrombosis

- Identification of relevant veins and their associated artery: internal jugular, subclavian, axillary, brachial, basilic, common femoral, proximal saphenous, superficial femoral, popliteal
- Identification of venous thrombosis by visualization of endoluminal thrombus
- Knowledge of correct performance of compression study with identification of normal and abnormal results
- Identification of adjacent structures, e.g. lymph node, mass, hematoma, ruptured Baker cyst, etc.

both normal and abnormal images, not only for purposes of identification of disease, but also for integrating the knowledge into clinical management. Like image acquisition, image interpretation requires many hours of review of relevant images. It is not clear at the present time that how many scans must be performed or images reviewed to achieve competence. An international consensus group is working to develop guidelines for training and it is an area of active research. The ACCP-SRLF statement will be the foundation document for the development of training guidelines. Presently, there is no mechanism available in Europe, America or Asia for a formal certification process in critical care ultrasonography. This will be a future challenge.

TECHNICAL CONSIDERATIONS

In critical care ultrasonography, the intensivist is responsible for all aspects of image acquisition. This requires a knowledge of basic ultrasound physics, an understanding of common artifacts of ultrasound imaging and knowledge of machine function.

The Physics of Ultrasound

Sound is created when a moving/vibrating object creates alternate pressure or density changes in sequential layers of surrounding media. The media can be conceptualized to be comprised of columns/layers within each layer, the matter undergoes alternate compression and rarefaction or alternate high and low points of pressure change (Fig. 144.1). One layer, during the pressure change, transmits some energy to the next layer and thereby the sound propagates.

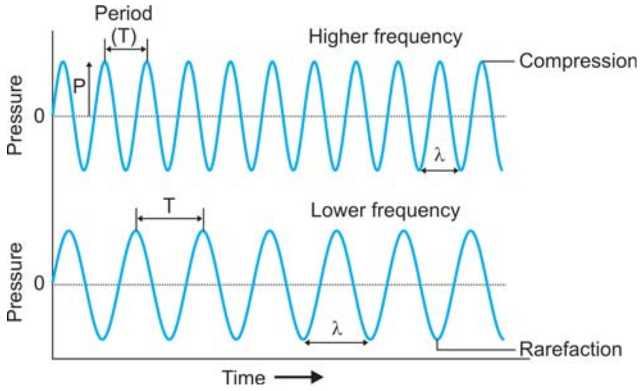


Fig. 144.1: Characteristics of sound. Sound propagation can be represented in a sinusoidal waveform. As sound propagates, each layer of medium undergoes compression and rarefaction and pressure changes. Note the inverse relationship between frequency and wavelength of sound. (*Source:* With permission from www.usra.ca)

Several parameters are described as follows which are used to define the properties of sound (Fig. 144.1):

Cycle and period: A cycle is one complete vibration of the medium with change of pressure/density of the medium from baseline to a high point through a low point back to the resting position. The time necessary for the sound wave to complete one cycle is known as its period (T). Period is measured in units of time, usually µsec.

Wavelength: The length of a single cycle measured in units of length is called a wavelength (λ). The wavelength of sound in a particular medium is inversely proportional to the frequency of the sound and is defined by the formula:

Wavelength = Speed of the sound in the medium/Frequency

The wavelength of diagnostic ultrasound is 0.1–0.6 mm.

Frequency (f): The number of cycles completed in one second is known as frequency. A standard measure of frequency is Hertz (Hz); one Hertz is one cycle per second (cps) (1 Hz = 1 cps). Ultrasound, by definition, is sound with frequency of more than 20 KHz (1 kHz = 1000 Hz). Typical frequencies used in diagnostic ultrasound range from 2–10 MHz (1 MHz = 1 million Hz). Most emitted and reflected sounds contain a lowest frequency, known as the fundamental frequency, and multiples of the fundamental frequency, known as harmonic frequencies or simply harmonics.

Amplitude: With the propagation of sound, the particles in the medium move from their resting position, leading to change in pressure and density. The particles come back to their resting positions, and pressure and density also return to the baseline. The difference between the peak and resting values of any of these parameters, pressure and density, is called the amplitude (P) of the sound. Amplitude is a reflection of the "loudness" and the energy of the sound. The amplitude of the sound is described on a logarithmic scale; the units of this scale are "bells". A decibel (dB) is 0.1 of bells.

Power: The amount of energy delivered per second is defined as power. Power = k x $(\text{amplitude})^2$ [k is the coefficient]. The unit of power is "watts".

Intensity: Intensity is the amount of energy delivered per second to the surface of the medium and is defined as power per unit area (expressed in the unit watts/cm^2). It is directly proportional to the power (amplitude) and inversely proportional to the area. Intensity of ultrasound determines the biological effects of ultrasound such as tissue heating. Diagnostic ultrasound typically uses an intensity of 0.001 to 100 watts/cm^2.

Speed: Propagation speed of sound in a particular medium is determined by the density of the medium. Speed of sound is 1540 m/s in soft tissue, 1450 m/s in fat, 300–1200 m/s in lungs and 2000–4000 m/s in bone.

Generation of Ultrasound and the Ultrasound Image

Generation of ultrasound is based on the "principle of piezoelectricity". Piezoelectricity is the ability of some natural and artificially made materials to generate an electrical potential when a mechanical stress is applied to them. The induction of a voltage across the material on application of mechanical stress is known as direct piezoelectric effect. The same materials also exhibit the reverse piezoelectric effect: the production of stress and/or strain when an electric field is applied. The piezoelectric material used in the ultrasound transducer is usually lead zirconate titanate (PZT) crystals.

An ultrasound probe contains multiple elements of a piezoelectric material. These elements act as acoustic transducers. Under an electric voltage, these elements undergo mechanical distortion. When the applied voltage is turned off, the crystals come back to their original shape. During this change of shape, some of the mechanical energy is converted into sound energy which is emitted by the transducer towards the target organ. Whenever the ultrasound waves encounter a surface or an interface with a different density, part of the sound wave is reflected back to the probe and is detected as an echo (see below). The energy of the reflected sound wave deforms the crystals. This generates an electrical current that the machine processes and displays as a pixel (Fig. 144.2). The stronger the reflection, the greater is the strength of the returning echo and the greater is the strength of the electrical current it generates. An ultrasound beam contains multiple wavelets, each one after reflection contributing a pixel in the image. Thus, multiple wavelets within an ultrasound beam, after reflection from multiple adjacent points within a target organ, create a collection of pixels, the image of the organ. Ultrasonography machines perform all the time calculations assuming that speed of travel of ultrasound waves in human tissues is 1540 meters/sec. The distance from the transducer of the object causing the echo is calculated from the time delay between generation of the ultrasound from the transducer and reception of the reflected sound. The longer the delay, the deeper the structure will be represented within the image.

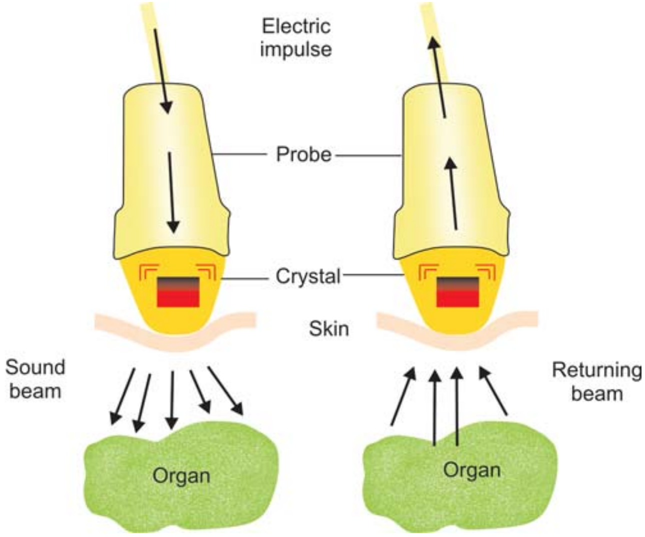
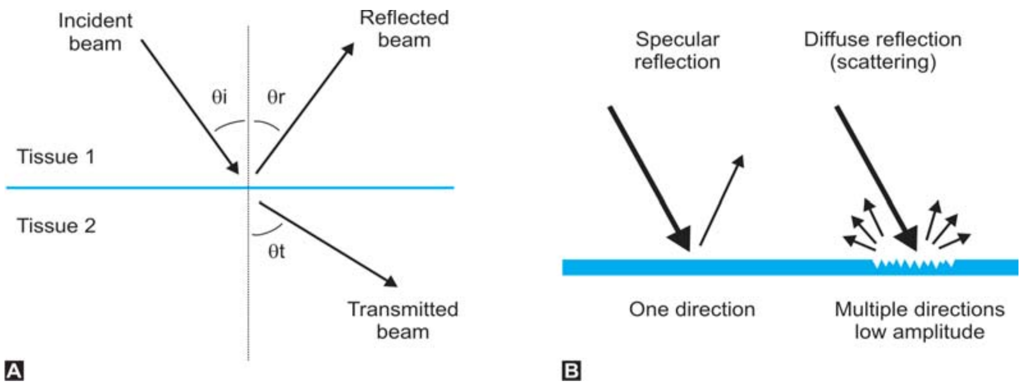


Fig. 144.2: Generation of ultrasound. Application of a voltage to PZT crystals lead to their mechanical distortion and generation of ultrasound waves. Reflected ultrasound waves deform the crystals leading to the generation of electrical impulse. (*Source:* With permission from www.usra.ca)

Interaction of Ultrasound with the Medium and at Interfaces

As ultrasound travels from its source through a medium (tissue), it undergoes progressive loss of energy (i.e. reduction in amplitude) and this process is known as attenuation. Ultrasound is absorbed by the medium causing attenuation and in the process generates heat. Attenuation depends on the frequency of ultrasound and the nature of the medium. In any given medium, the higher is the frequency of the ultrasound (i.e. shorter wavelength), the greater will be the attenuation.

At the interface between two mediums (or two different tissue layers), a part of the ultrasound beam undergoes reflection and the other part is transmitted forward (Fig. 144.3A). The reflected part of the ultrasound (echo) forms the basis of all diagnostic imaging. The amount of reflection at any interface depends on the difference in the acoustic impedance of the two media and the wavelength of the ultrasound. Most soft tissues have similar impedance typically at the boundary of two soft tissues (i.e. kidney/fat), only 1% of the ultrasound is reflected. On the other hand, ultrasound is intensely reflected at the surface of bones; as no ultrasound can penetrate the bone, no structure can be seen beyond a bony structure. Ultrasound also undergoes scattering (i.e. intense multidirectional reflection) in air (Fig. 144.3B). If air is interposed between the ultrasound beam and the target object, the energy in



Figs 144.3A and B: Interaction of ultrasound with the medium and at interfaces. (A) Shows refraction and reflection of ultrasound at the interface between two media. (B) Shows specular reflection and scattering. (*Source:* With permission from www.usra.ca)

the ultrasound beam is lost by scattering; the returned echo is minimal and a satisfactory image cannot be obtained.

Reflection is also determined by the wavelength of the ultrasound. The smaller is the wavelength, the smaller will be the size of object capable of reflecting it. If the boundary between two media is imagined as made up of multiple small reflectors, it follows that the finer details of the boundary can be seen if the wavelength of the ultrasound is smaller than the size of those small components of the boundary. In other words, resolution (i.e. ability to see two close-by objects separately) improves. Similarly, if two components of the boundary or two objects are separated by a distance greater than the wavelength of the emitted ultrasound, they are clearly seen as separate objects.

The intensivist ultrasonographer needs to have a clear understanding of the relationship between penetration, resolution and the frequency of ultrasound. Ultrasound waves of higher frequency (i.e. shorter wavelength) are reflected easily by smaller objects, thereby improving resolution. However, as more energy is reflected by superficial structures and through attenuation, the ability of higher frequency ultrasound to penetrate deeper structures is limited. Higher frequency ultrasound images superficial structures in greater detail but cannot penetrate to image deeper structures. Higher frequency ultrasound is therefore used for vascular studies and studies of superficial structures. Conversely, lower frequency ultrasound is used to image deeper structures although with a predictable loss of resolution (e.g. in abdominal ultrasonography).

Important Terminologies Related to Ultrasound

Attenuation

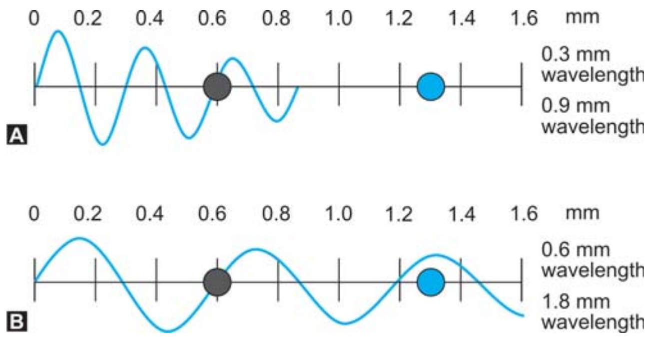
The progressive decline in amplitude or strength of ultrasound, as it passes deeper through the tissues, is known as attenuation. While attenuation is the result of absorption of sound energy as it passes through the tissue, reflection of ultrasound at each level also weakens the strength of the beam that penetrates further.

Echogenicity

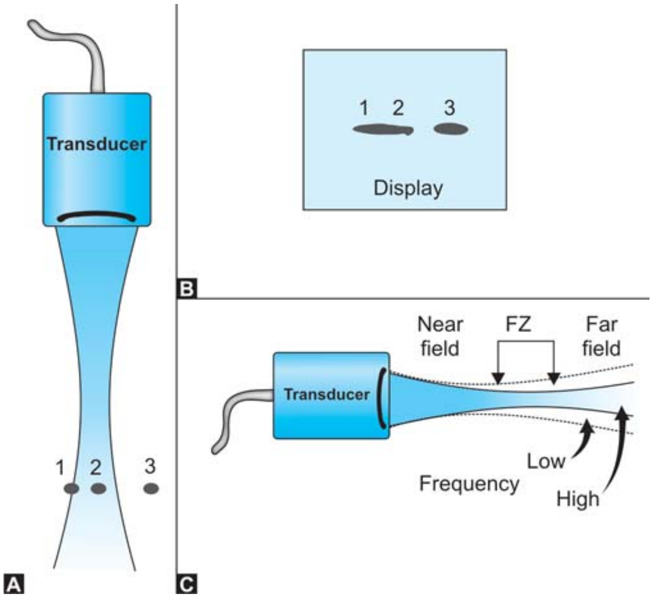
The term echogenicity refers to the brightness of an element in an ultrasound image. Echogenicity depends on the strength (amplitude) of the reflected ultrasound. A hypoechoic structure appears less echogenic than the surrounding anatomical structures. A hyperechoic structure appears more echogenic than the surrounding anatomical structures. An isoechoic structure has the same echogenicity as the surrounding anatomical structures. An anechoic structure has absent echogenicity and it appears black. Fluid filled structures are often anechoic. Some ultrasonographers use the liver as the reference standard to judge echogenicity for other structures.

Resolution

Resolution, specifically spatial resolution, refers to the ability of the machine to show two closely spaced objects as separate entities with distinct outline. Resolution determines the details of a structure. Axial resolution refers to the minimum distance between two objects placed along the axis of the beam, where the two structures are identified as separate. Axial resolution depends on the frequency of the ultrasound (Fig. 144.4). Lateral resolution is defined as the minimum distance between two objects placed along a line perpendicular to beam axis, where the two structures are identified as separate. Lateral resolution is largely dependent on the width of the ultrasound beam and may be improved to some extent by altering the focal zone of the transducer (Figs 144.5A to C). Line density contributes to lateral



Figs 144.4A and B: Axial resolution depends on pulse length. An ultrasound pulse commonly consists of 2 or 3 sound cycles of the same frequency. A higher frequency ultrasound has shorter cycle length and therefore provides better axial resolution. In Fig. 144.5 A, the axial resolution is sufficient to distinguish the 2 target objects as separate because the incident wave hits target # 1 (black) before hitting target # 2 (blue). In Figure 144.5B, both target # 1(black) and target # 2 (blue) are hit by the same wave and both target objects are seen as one. (*Source:* With permission from www.usra.ca)



Figs 144.5A to C: Lateral resolution depends on the ultrasound beam width, which in turn is inversely related to the ultrasound frequency. Lateral resolution is poor when the two structures lie at the same depth within the same beam width. Because the returning echoes overlap with each other side by side, the two structures (1 and 2 in figure) will appear as one on the display (A and B). Lateral resolution is best at the focal zone where the width of the beam is also narrowest (C). Keeping the target object at the focal zone helps to obtain the best resolution. (*Source:* With permission from www.usra.ca)

resolution, a factor that can be modified by a machine with sophisticated controls.

Artifacts

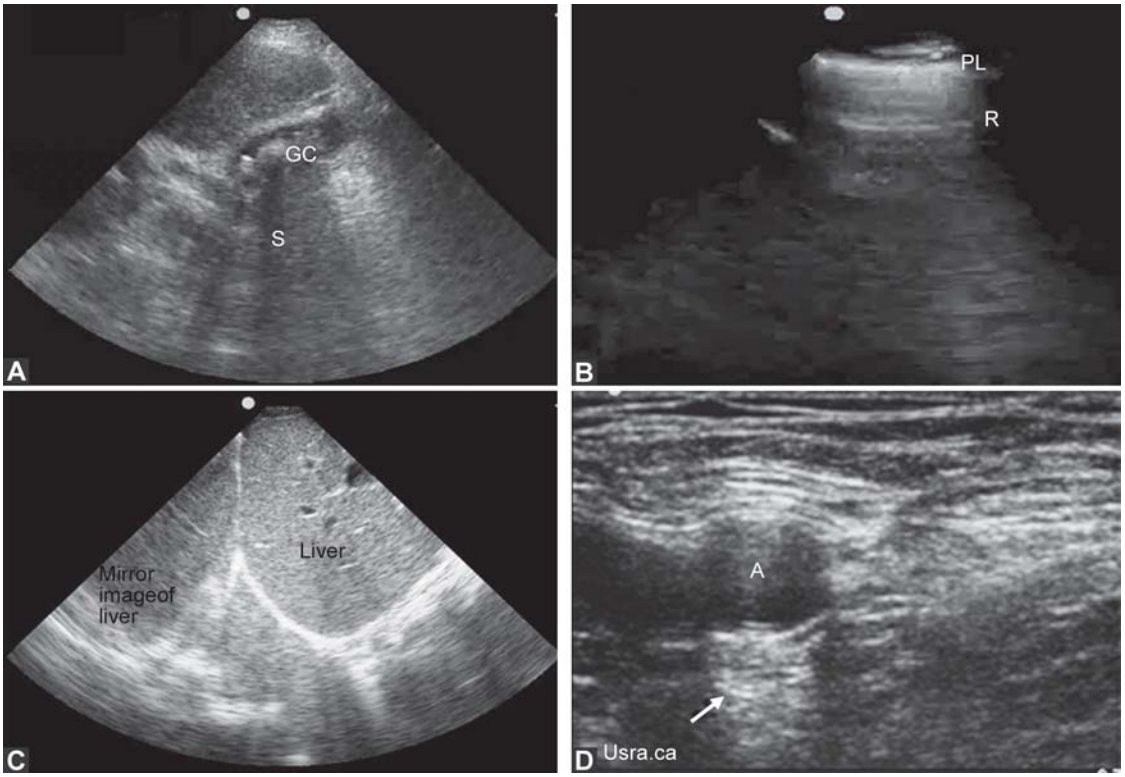
Artifacts are features of the image that do not originate from the object being imaged.[5] The intensivist ultrasonographer needs to be able to identify different types of artifacts in order to avoid errors related to their misinterpretation. Artifacts may arise because of equipment problems, patient related factors (e.g. obesity), unsatisfactory operator technique (e.g. due to inappropriate gain setting), movement of the target organ (e.g. due to translational respiratory artifacts) or because of sound-tissue interactions. This last category of artifacts (sound-tissue artifacts) results from the physical characteristics of ultrasound and the way it reacts with tissue. Common types of sound-tissue artifacts are discussed below.

Acoustic Shadow Artifact: This artifact occurs when a structure which is near, totally reflects the incident ultrasound beam and the ultrasound beam penetration is severely impeded. No structure beyond the reflector is visible, as the deep structures are shadowed by the reflector. Examples of acoustic shadow artifact include a gall bladder stone with a shadowing deep to it (Fig. 144.6A) or rib shadows.

Reverberation Artifact: This artifact occurs when the ultrasound beam is reflected back and forth between two surfaces. The depth of an image is calculated by the ultrasound machine by the time delay between sending the ultrasound beam and receiving the reflected echo. With each reflection in the closed space between two surfaces, part of the reflected beam escapes and reaches the transducer after a delay that is exact multiplicative of the time that the first reflection needed to reach the transducer. For each such reflection, the machine has no way to differentiate from the first reflection. Each reflection is therefore interpreted by the machine as an object that resembles the original reflective surface, at a depth that is multiplicative of the distance between the two reflective surfaces (Fig. 144.6B). Some of the important findings in lung ultrasound are based on the principle of reverberation artifacts.

Mirror Image Artifact: This artifact occurs if a reflector in the path of the beam has a curved structure (e.g. diaphragm) and reflects sound like a mirror (Fig. 144.6C).

Posterior Acoustic Enhancement Artifact: This artifact is typically seen as a hyperechoic area deep to a fluid-filled (anechoic) structure. The beam passes through the



Figs 144.6A to D: Common ultrasound imaging artifacts: (A) Gallbladder stone (GC) with acoustic shadow artifact (S). (B:)Reverberation artifact (R) from reverberation of ultrasound from pleural line (PL). In lung ultrasonography, these artifacts are known as A-lines. (C) Mirror image artifact. Strong reflection of ultrasound from a specular reflector like diaphragm creates a mirror image of liver. (D) Posterior acoustic enhancement artifact, appearing as a hyperechoic region (arrow) deep to a fluid filled structure (e.g. a vessel, **A** = artery). (*Source:* Right lower panel www.usra.ca with permission)

area of very low attenuation coefficient and enters an area deep to the structure with more energy than the ultrasound beam that has not passed through the fluid filled structure. As the beam enters an area of higher attenuation with more energy, there is much stronger reflection, making that area appear hyperechoic (Fig. 144.6D).

Different Ultrasound Modalities

Two-Dimensional (2-D) Imaging

Most critical care ultrasonography is performed with 2-D imaging technique, also known as B-mode ultrasonography. The most common transducer is either of a phased array or linear array design. The ultrasound beam is rapidly cycled across the transducer head, typically at 30 or more times per second. At this frame rate, the operator observes an uninterrupted pattern of organ motion on the 2-D image.

M-Mode (Motion Mode)

A M-mode image displays the movement of all structures against time along a single beam line (Fig. 144.7). The single beam line is displayed against a time axis. Each reflecting structure in the path of the beam is represented by a line; the undulation of the line along the Y-axis of the image reflects the movement of the structure while time is represented along the X-axis. If a structure in the path of the beam has no movement over time, it will be reflected as a straight line. M-mode is useful for measuring rapidly moving cardiac structures as the sampling frequency is much higher than the 2-D imaging, on the order of 1200 sampling cycles per second.

Doppler Imaging

Doppler is particularly useful for measurement of blood flow velocity. It has an extensive utility in advanced critical care echocardiography, but is seldom used in other aspects of critical care ultrasonography. The physics

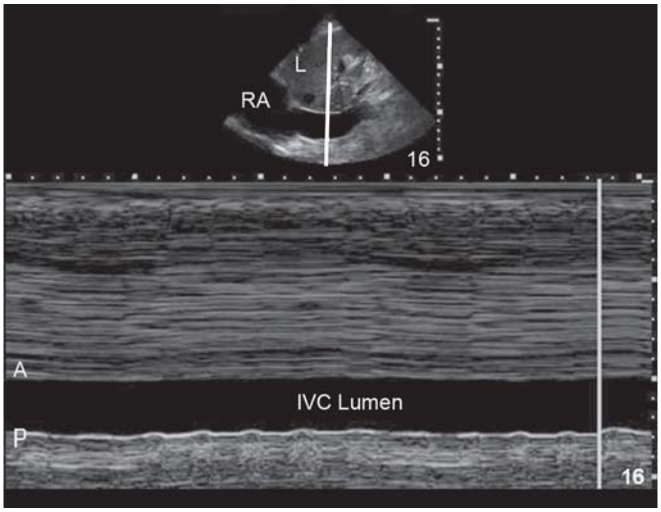


Fig. 144.7: M-mode examination of IVC. The upper panel of the figure shows the level (longitudinal section at right paramedian location) where the M-mode examination was performed. ***A*** represents anterior wall of IVC and ***P*** represents posterior wall of IVC. In this case, minimal respiratory variation of IVC lumen size is indicated by minimal undulation of the lines **A** and **P**. RA= Right atrium; L= Liver

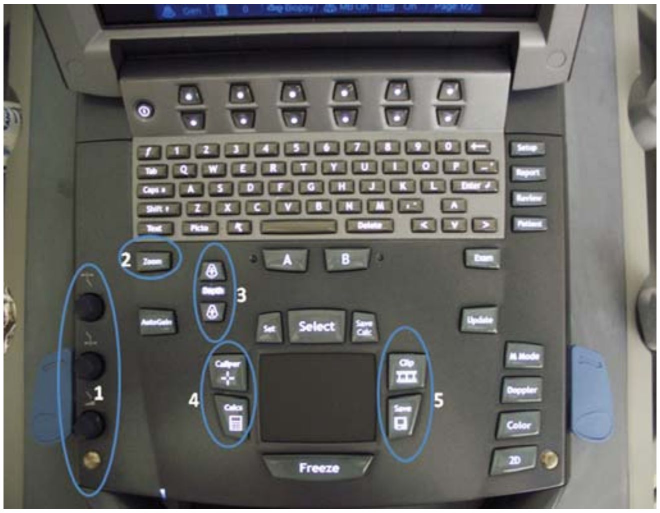


Fig. 144.8: User interface showing common control buttons in a portable ultrasonography machine. 1. Gain 2. Zoom 3. Depth 4. Caliper and calculation function 5. Memory functions for saving still and video clips. (See text for description)

and imaging strategy of Doppler ultrasonography is beyond the scope of this text. The reader is referred to definitive resources.[6]

Machine Controls

The intensivist ultrasonographer is responsible for all aspects of image acquisition. This requires knowledge of the machine controls (Fig. 144.8). Machines of different manufactures have control surfaces of radically different designs. It is not possible to describe here the details of the machine controls that are specific to a wide variety of machines. Some full capability ultrasonography machines have very complex controls that require a well aquainted ultrasonography technician for their proper operation. In general, portable machines are designed for the ease of operation and the control surfaces are relatively simple. A well designed portable machine with straight forward controls can be mastered easily by the intensivist. In a generic sense, the operator must be able to locate and learn to manipulate the following basic controls.

Depth: All modern ultrasonography machines of use in ICU allow for depth control. The operator can choose to examine superficial or deep structures by altering the depth of penetration of the ultrasound beam. As a general rule, the depth is set so, that the target structure is located at the middle of the screen.

Projection Indicator: All machines have an indicator on the screen that is referenced to a marker on the transducer. In any given ultrasound image, the structures which are on the side of the transducer marker are projected to the indicator side of the screen image. By international convention, abdominal, thoracic and vascular ultrasonography is performed with the screen image indicator, set to the left of the screen; whereas echocardiography is performed with the screen indicator on the right of the screen.

Gain: All modern ultrasound machines have a gain control. The gain control is adjusted to optimize the brightness of the image. The gain is a feature of image processing, that amplifies the returned echo. The effect of increasing gain is to increase the brightness of the image. The strength of the echo returning from deeper structures is often weak. Increasing the gain may improve image quality and the structures will be better seen on the screen. If the gain is set too high, nonspecific brightness will be seen throughout the image. Image quality will be degraded with the details and discriminations among different structures being lost. Brightness of different parts of the image can be adjusted individually to obtain an optimum image quality. This allows the ultrasonographer to adjust the gain individually for different objects at different depths from the surface. Echoes from the objects from near field are stronger and can be reduced in amplitude (gain reduced). The echoes from objects in far field (farther from the transducer) are weaker and can be increased in amplitude.

Zoom: Most machines allow the operator to magnify a specific part of the image for more detailed analysis.

Focus: Some machines have a focus control. This allows the operator to alter the width of the ultrasound beam at a specific point in the image, thereby improving lateral resolution in the area of interest. Other machines have automated this function such that the optimal focus point is at the center of the ultrasound image without need for machine adjustment.

Doppler Control: Control of Doppler ultrasound function requires knowledge of Doppler physics and is beyond the scope of this chapter.

Calipers and Freeze Function: Most ultrasound machines allow the operator to freeze the image, to replay the image in slow motion for review, and to make accurate measurements of distance and area from the frozen image.

Memory Function: Most modern ultrasound machines are designed with the ability to store both frozen images and video clips. Older generation machines may require a video or DVD recorder to be attached to the machine. Image and video capture is an essential component of good ultrasonography practice, as it permits documentation, off-line analysis, education and quality review.

THORACIC ULTRASONOGRAPHY

Thoracic ultrasonography that includes examination of lung and pleura is a key skill for the intensivist. It is easy to learn and has useful application at the bedside in day to day practice of critical care medicine. For example, it has utility for rapid diagnosis of patients with respiratory failure or for evaluation of acute dyspnea. Standard supine chest radiographs are difficult to interpret frequently due to nonspecific opacification pattern; whereas thoracic ultrasonography allows for accurate identification of pleural effusion, consolidation, atelectatic lung, alveolar interstitial syndrome and pneumothorax.[7] Ultrasonography has the potential to reduce the need for chest radiographs and chest computerized tomography with its high radiation exposure.[8,9]

Dr Daniel Lichtenstein is responsible for the development of lung ultrasonography. His original work in 1990s defined the field and has been validated by many other groups. Basic principles of thoracic ultrasonography have been defined by Lichtenstein:[10]

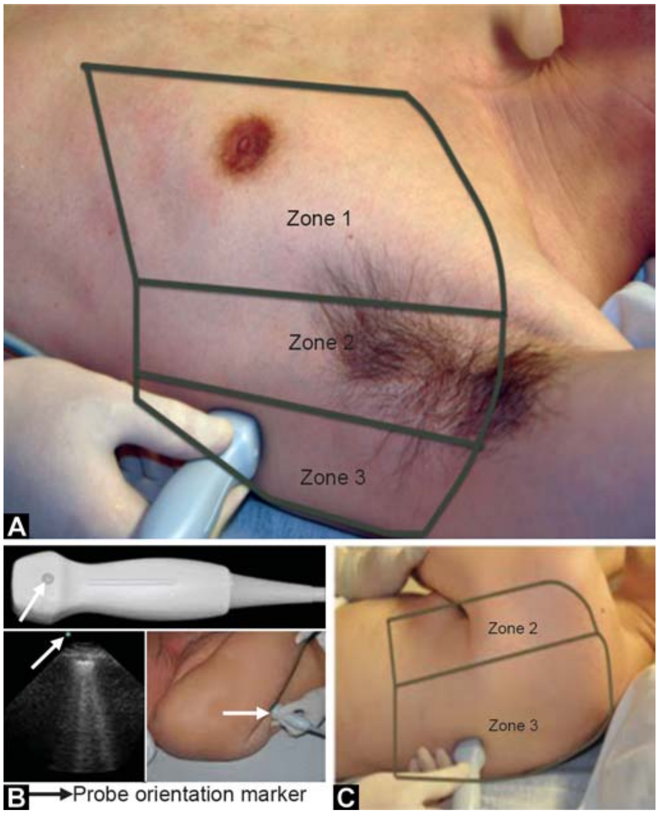
1. In the thorax, air and fluid have opposite gravitational dynamics, so, by inference, in the supine patient, pleural effusion will be seen posteriorly and pneumothorax will be seen anteriorly.
2. The lung is the most voluminous organ.
3. All lung signs arise at the level of the pleural line.
4. Lung ultrasonography is based on the analysis of artifacts.
5. Lung patterns are dynamic; serial examinations are valuable.
6. Most acute lung disorders abut the lung surface.

Equipment

Any ultrasound machine that is capable of abdominal or cardiac imaging can be used for thoracic ultrasonography. Most general ultrasonography is performed with transducers with the frequency of 3.5–5 MHz. A probe of this frequency and of convex-sector design can be conveniently used for longitudinal scanning through the intercostal spaces. Transducers of 3.5–5.0 MHz frequency range do not have sufficient resolution for a detailed analysis of pleural surface pathology. However, they offer better penetration so that deeper structures can be visualized. High frequency probes (7.5–10 MHz), designed for vascular examination, can be used for detailed pleural examination. These transducers allow excellent resolution of the pleural surface, but at the expense of limited penetration and visibility of deeper structures. Most standard ultrasound machines are adequate for thoracic ultrasonography, however some modern handheld units may lack adequate near-field resolution. When there is a pleural effusion, the inside of the chest wall may not be clearly visualized; this might lead to error in estimating the depth of needle penetration when performing thoracentesis. Some recent generation ultrasonography machines use extensive image processing for image smoothing. This may mask standard lung ultrasound findings such as lung sliding.

Examination Protocol

Lung ultrasonography in the critically ill patient is generally performed with the patient in supine position. It is useful to follow an organized protocol that divides the chest into anterior and lateral compartments (zones) (Fig. 144.9A). The former is the area between the sternum and the anterior axillary line, and the latter is defined as the area between the anterior and posterior axillary lines. With the transducer held perpendicular to the skin surface in a longitudinal scanning axis (Fig. 144.9B), the clinician examines the underlying pleural surface and lung through the rib interspaces. By moving the transducer over adjacent interspaces, the examiner can lay down a series of scan lines and develop a three-dimensional model of the thorax



Figs 144.9A to C: Technique of thoracic ultrasonography: (A) The lung can be divided into compartments for imaging. (B) Probe is placed longitudinally across the intercostals space with the orientation mark pointing upwards. (C) Probe placement in a supine patient to look for posterior effusion. (*Courtesy:* Dr Pierre Kory, Attending Physician, Department of Pulmonary and Critical Care Medicine, Beth Israel Medical Center, New York, USA and Assistant Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA)

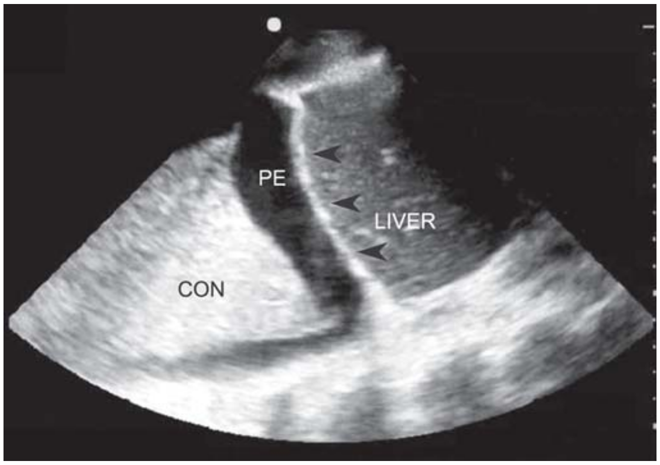


Fig. 144.10: In the longitudinal scanning axis, diaphragm appears as a bright curvilinear structure (arrowheads). Also seen in the image are liver, consolidated lung (CON) and small amount of pleural effusion (PE). The dense area of airless consolidated lung appears to have the same echodensity as liver, known as sonographic hepatization (see text).

by using a multiple tomographic plane approach. The posterior compartment, which lies between the posterior axillary line and the spine, cannot be imaged with the patient in the supine position. If there is a requirement to examine the posterior compartment, the patient can be rolled into a lateral decubitus position, alternatively, the transducer can be pressed into the mattress and angled towards the central body mass to obtain a partial view of the posterior structures (Fig. 144.9C). The probe should always be orientated to the marker on the probe points cephalad (Fig. 144.9), the machine should be set to project the screen marker to the left. Maintaining this rule in probe position and machine set-up helps the operator to remain orientated to the anatomic axis of scanning, as the cephalad structures of the image are always projected to the left of the screen.[11] The gain and depth setting should be optimized to achieve adequate magnification, resolution and brightness of the structures being examined. For example, for examining the pleural surface, the depth setting should be adjusted for near field examination. As lung ultrasonography is often performed to address a specific question, complete scanning of all lung zones may not always be required. Supine examination of the anterior and lateral chest wall can answer many clinically important questions. Examination of the anterior chest wall rapidly rules out pneumothorax and interstitial syndrome. Examination of the lateral chest wall is useful for the identification of free flowing pleural effusion and alveolar consolidation. Small pleural effusion and posterior consolidation can be detected by examining the posterior compartment.[11]

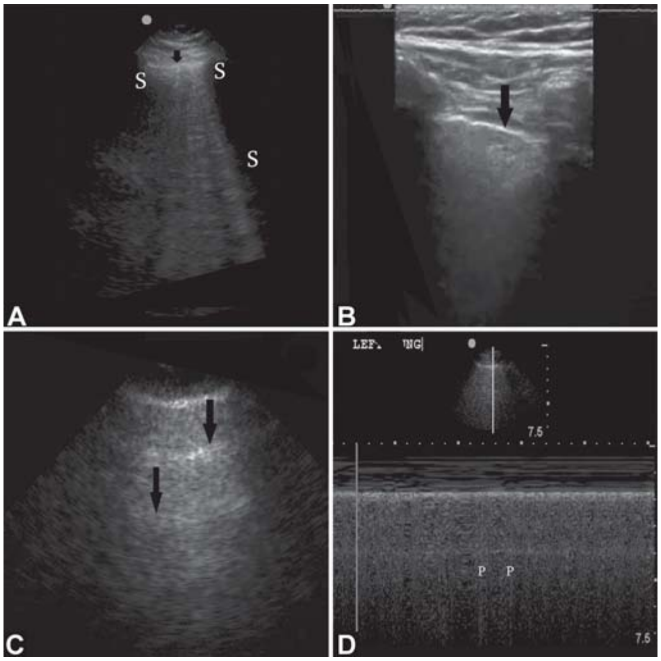
As standard protocol, the clinician should routinely visualize both the hemidiaphragms. In longitudinal scanning axis, the diaphragm appears as a bright curvilinear structure (Fig. 144.10) that moves in synchrony with respiration.

As an organizing principle, the large difference in acoustic impedance of ultrasound between air and tissue leads to intense reflection at any air-tissue interface. When parenchymal air is replaced by fluid or an infiltrative process, depending on the ratio of air to fluid, ultrasound findings progress from normal aeration pattern to alveolar/interstitial edema pattern to tissue density pattern.

Normal Findings

In a longitudinal scan through an intercostal space, the rib shadows are seen on both the sides of the image and serve as a basic landmark (Fig. 144.11A). Related to the major difference in the acoustic impedance between the chest wall and underlying air filled lung tissue, the ultrasound beam is strongly reflected from the surface of the lung. This point of reflection of ultrasound from the lung surface corresponds to the pleural surface. It appears as a bright, highly echogenic line between two adjacent ribs, approximately 0.5 cm below the periosteal origin of the rib shadow (Figs 144.11A and B). The normal pleura is 0.2–0.4 mm thick.[12] A 3.5–5.0 MHz probe does not allow sufficient resolution to visualize the parietal and visceral pleural surfaces separately so, that the pleural line represents a single summation interface. Aerated lung is not seen as an anatomically distinct entity because of strong reflection of the ultrasound beam at the pleural interface. However, aerated lung has a distinctive ultrasound pattern that results from reverberation artifact. Aerated lung is characterized by the presence of "A" lines which are horizontally orientated curvilinear hyperechoic lines, observed deeper to and parallel to the pleural line (Fig. 144.11 C). "A" lines may occur in single or multiple numbers and result from the reverberation of the ultrasound beam between the pleural surface and skin. If there is more than one A line in the ultrasound image, the distance between A lines will be a multiplicative of the distance between the pleural surface and the skin. Several A lines are often visible. The actual number of A lines has no significance as long as there is at least one.[13] A lines are strongly correlated with a normal aeration pattern on chest CT scan at the site of the transducer application to the chest wall.[7] Examination of the pleural interface is characterized by two dynamic findings: Lung sliding and lung pulse.

Lung Sliding: Lung sliding occurs due to the movement of the visceral pleura against parietal pleura in phase with respiration. Lung sliding appears as "twinkling" at the level of the pleural line, in rhythm with respiration.[13] An M-mode examination of the pleural line reveals a pattern known as the "sea shore" pattern and allows the examiner to document the presence of lung sliding with a single frozen image that can be easily printed out for documentation (Fig. 144.11D). Lung sliding is minimal at the apex and maximal at the lung bases. The presence of lung sliding indicates apposition of parietal and visceral pleural surfaces at the site of transducer placement. The presence of lung sliding rules out pneumothorax at the site of transducer placement on the chest wall. The examiner may quickly examine multiple interspaces over the anterior lung zones, thereby excluding pneumothorax with a high level of certainty.



Figs 144.11A to D: Normal findings in lung ultrasonography. (A) In longitudinal scanning through an intercostals space, the rib shadows (S) serve as the basic landmark. Pleura is seen as a bright echogenic line (arrow); (B) A high frequency probe (7.5 MHz in this image) shows the pleural line (arrow) in greater resolution; (C) A-lines (arrows) are generated by reverberation of ultrasound, a normal finding; (D) M-mode record lung sliding generates "sea-shore" pattern. Lung pulse (P) is also shown in the image

Lung Pulse: Lung pulse occurs due to the movement of the visceral pleura against parietal pleura in phase with cardiac contractions.[14] Lung pulse is best seen at pleural surfaces adjacent to the heart, but may be observed over the right chest as well. Lung pulse can be recorded with M-mode for purposes of easy documentation (Fig. 144.11D). The presence of lung pulse indicates apposition of the parietal and the visceral pleural surfaces at the site of transducer placement. The presence of lung pulse rules out the presence of pneumothorax at the site of transducer placement on the chest wall. The examiner may quickly examine multiple interspaces over the anterior lung zones, thereby excluding pneumothorax with a high level of certainty.

Abnormal Findings in Thoracic Ultrasound

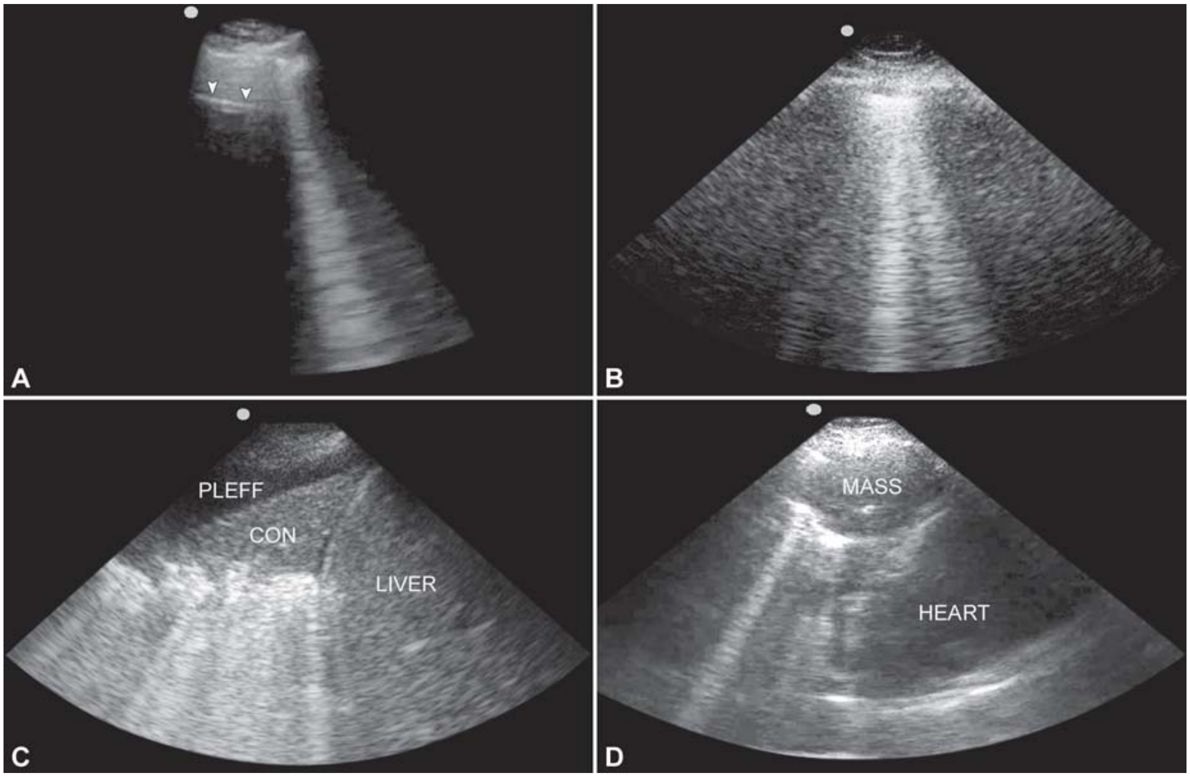
B Line(s)

B line(s) are an important finding of lung ultrasonography and often reflect the presence of pulmonary pathology. They have characteristic features which are as follows[13] (Figs 144.12A to D):

1. They are vertical in orientation.
2. They rise from the pleural line and move with the movement of the pleural line (in synchrony with lung sliding and lung pulse).
3. They spread to the bottom edge of the image.
4. They efface A lines at the point of intersection.
5. They are narrow at their point of origin at the pleural surface and spread out as they approach the edge of the image.

It is very important that the clinician ensures whether these criteria are fulfilled for definitive identification of B lines. B lines may reflect significant lung abnormality and can be mistaken for mimickers (Z line and I line).[13] The location and number of B lines determine their significance. A few B lines are often found in the lower lateral intercostal spaces in normal subjects.[15-17] Multiple B lines in the nondependent areas of lungs are usually of pathological significance, particularly if they appear as multiple comet tail artifacts. Multiple B lines evoke a pattern similar to a rocket at lift-off and the term "lung rockets" have been used to describe the pattern (Fig. 144.12 B). A pattern that is definitively pathologic occurs when at least three B lines are detected in a single scanning position over the anterior chest (Fig. 144.12 B).[16,17]

B lines or comet tail artifacts result from successive reverberation at the interface between air and pathologically thickened interlobular septa, at the lung visceral pleural interface.[16] This occurs most frequently when interlobular septae are distended with fluid or other infiltrative or inflammatory process. These include interstitial lung disease, e.g. idiopathic pulmonary fibrosis or sarcoidosis,[18] acute cardiogenic pulmonary edema, lung contusion, acute lung injury and acute respiratory distress syndrome,



Figs 144.12A to D: A. Line(s) arises from the pleural line and effaces A-line (arrowheads) at the intersection. B. Three or more B-lines in a single longitudinal scan plane is considered pathological. C. Shows multiple B lines (lung rocket) arising from the margin of an area of consolidation (CON). A small pleural effusion (PLEFF) is also seen. D. Shows a single B-line arising from the margin of subpleural lung mass. Of note, the lung mass provided an acoustic window to visualize the heart in this scan plane. Consolidated lung can also provide a suitable acoustic window to visualize a deeper intrathoracic structure

lymphangitic carcinomatosis and early/resolving lung consolidation.[15,16,19,20] B lines, when focal in location, suggest a localized process such as pneumonia. The presence of diffuse B lines suggests a generalized process such as cardiogenic pulmonary edema. Comet-tail artifacts have been associated with alveolar-interstitial shadows seen on chest radiograph and they can be considered equivalent to Kerley B lines seen on a plain radiograph. Lichtenstein et al. demonstrated tomodensitometric correlations of the thickened subpleural interlobular septa as well as ground-glass areas, two lesions present in acute pulmonary edema, with the presence of the comet-tail artifact.[16] Lichtenstein et al. have compared chest Computed Tomography (CT) findings with ultrasound and found 95% accuracy of ultrasonography in the diagnosis of alveolar-interstitial syndrome in comparison to CT scan.[7]

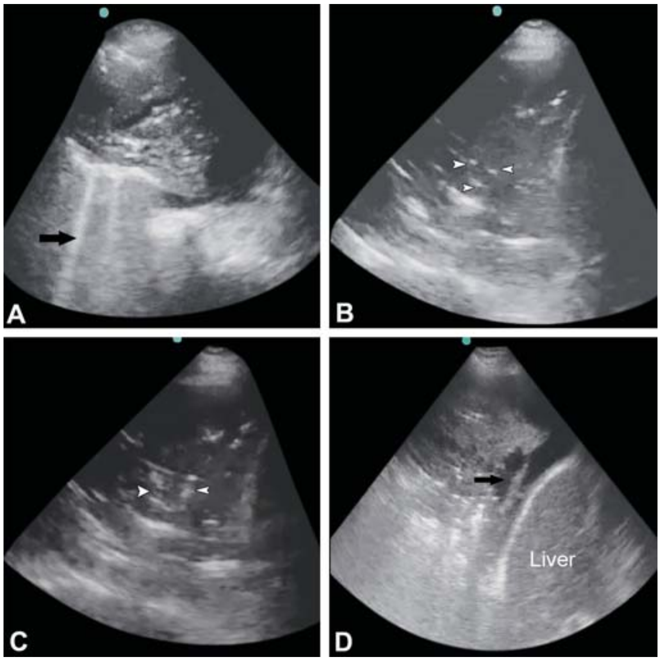
Acute cardiogenic pulmonary edema results in B lines. An elevation of left-sided cardiac pressures causes distension of interlobular septa in the nondependent lung zones. This distension of interlobular septa causes multiple B lines or comet tail artifacts in the nondependent lung zones. The findings of multiple B lines are therefore sensitive, but nonspecific means of detecting cardiogenic, i.e. hydrostatic edema. The presence of A lines in the nondependent lung zones is strong evidence that left-sided cardiac pressures are not elevated. Lichtenstein et al. have demonstrated that the presence of A lines in the anterior lung zones with the patient in the supine position indicates that the pulmonary artery occlusion pressure (PAOP) is always ≤18 mm Hg and usually ≤13 mm Hg.[21] Presence of A lines therefore excludes cardiogenic pulmonary edema as the cause for respiratory dysfunction. This fact has important clinical application as will be discussed later.

Alveolar Consolidation

Alveolar consolidation can be diagnosed by thoracic ultrasonography. Consolidated lung has tissue density without change in dimension with respiration. It has similar echodensity as liver; hence the term sonographic hepatization of lung has been used for descriptive purposes (Fig. 144.13A and D). The border between the tissue density of alveolar consolidation and aerated lung may be shredded or irregular and may exhibit B lines or comet tail artifact (Fig. 144.13A). Punctate echogenic foci may be visible within an area of alveolar consolidation. These represent air-filled bronchi and are termed as "sonographic air bronchogram".[22] Depending on the plane of scanning, they may appear as nonpulsatile, linear echoes converging towards the root of the lung or scattered echoes of variable lengths (Fig. 144.13A). Posterior reverberation artifacts or acoustic shadowing may also be produced by echoes related to large proximal bronchi.[23] The sonographic air bronchogram may be mobile and may exhibit movement that is independent of the surrounding movement of the lung related to respiratory cycle (Fig. 144.13B and C). The mobile air bronchogram (also known as dynamic air bronchogram) indicates that the bronchus supplying that area of alveolar consolidation is patent and not blocked by endobronchial pathology. In some cases, multiple, branching, nonpulsatile, anechoic, tubular structures can be seen within the area of consolidation representing fluid-filled bronchi; these are known as sonographic "fluid bronchogram".[24] Alternatively, they may represent pulmonary vascular structures, the distinction between the two may be made by color Doppler. Sonographic alveolar consolidation can be observed only if the process abuts the pleura allowing ultrasound to penetrate through the abnormality should the process be deep within the lung, it cannot be visualized through created lung due to the ultrasound blocking characteristics of air. In the majority of cases, alveolar consolidation abuts the pleura, making it easily accessible to ultrasound analysis.[25] Where a pleural effusion is present, it provides an acoustic window to visualize the underlying consolidation. Likewise, the presence of consolidation provides an acoustic window to visualize underlying structures that will not normally be visible such as heart or great vessels.

The finding of sonographic alveolar consolidation pattern is descriptive and does not imply a specific diagnosis such as pneumonia. Similar to plain radiography and CT scan, a sonographic consolidation pattern may result from a wide variety of pathological processes. Any disease process that results in airless alveolar structures can give rise to sonographic consolidation pattern like atelectasis (compressive or resorptive), infiltrative processes (tumor, purulent material as in pneumonia), severe pulmonary edema with flooding of alveoli, etc.

Alveolar consolidation can be accurately diagnosed by ultrasonography. In a study of critically ill patients, ultrasonography was found to have a sensitivity of 90% and specificity of 98% with high interobserver concordance for the diagnosis of alveolar consolidation using CT scan as the gold standard.[25] Alveolar consolidation may be localized to any part of lung and its identification requires clinical correlation. In a patient present with fever, cough, purulent sputum and dyspnea,



Figs 144.13A to D: Alveolar consolidation. A. An area of consolidation with sonographic air bronchogram (bright echogenic spots within the area of consolidation). Also seen are B lines (arrow) arising from the margin of the consolidation; B. Dynamic air bronchogram. During expiration, within the area of consolidation, air bronchogram appears as punctuate bright spots (arrowheads); C. During inspiration, the echogenic spots expand centrifugally towards the pleural surface into branching, echogenic structures (arrowheads) and represent air movement in the bronchi within the area of consolidation; D. Microabscesses within an area of consolidation (arrow) in a case of necrotizing pneumonia

demonstration of an area of consolidation suggests a diagnosis of pneumonia. In patients with necrotizing pneumonia, ultrasound is sensitive in detecting microabscesses (Fig. 144.13D); in complicated cases, it can be used for needle-aspiration guidance in order to obtain etiologic diagnosis with minor and infrequent complications.[22] Ultrasonography has been used to follow response to treatment of both community acquired pneumonia (CAP) and ventilator associated pneumonia (VAP). A decrease in size/number or disappearance of lesions indicates improvement in CAP.[26] In a recent study on VAP, gradual re-aeration of consolidated areas in response to antibiotic treatment was reflected by a continuum of changing ultrasound patterns. Significant correlations between CT and ultrasonography with higher accuracy than chest radiography have been shown in predicting lung re-aeration in this study.[20]

Areas of sonographic alveolar consolidation may be observed in cases of pulmonary embolism. In patients with clinical suspicion of pulmonary embolism, the diagnosis is supported by the sonographic finding of one or more triangular/rounded/wedge shaped areas of consolidation (consistent with pulmonary infarcts) with or without localized/basal pleural effusion.[27-29] The area of consolidation may show a central hyperechoic reflex corresponding to a bronchiole within the area of consolidation. Fresh reperfusion infarcts are homogenous and hypoechoic; older infarcts are less homogenous and well demarcated. Two or more triangular or rounded pleural-based sonographic ultrasound consolidations have been shown to have high specificity for the diagnosis of pulmonary embolism in patients with high pretest probability.[30]

The presence of dynamic air bronchogram is useful in differentiating pneumonia from postobstructive resorptive atelectasis. A pleural effusion commonly causes compressive atelectasis of the adjacent lung that will then have sonographic alveolar consolidation pattern as it is airless. In this case of compressive atelectasis, the bright echoes, representing air bronchogram, appear crowded towards the root of the lung.[23] Dynamic air bronchogram has been described as a helpful feature in differentiating pneumonia from post obstructive (resorptive) atelectasis[31] (Figs 144.13B and C). When present, it is considered good evidence against resorptive atelectasis. Lung sliding also suggests absence of resorptive atelectasis.[14]

Pleural Effusion

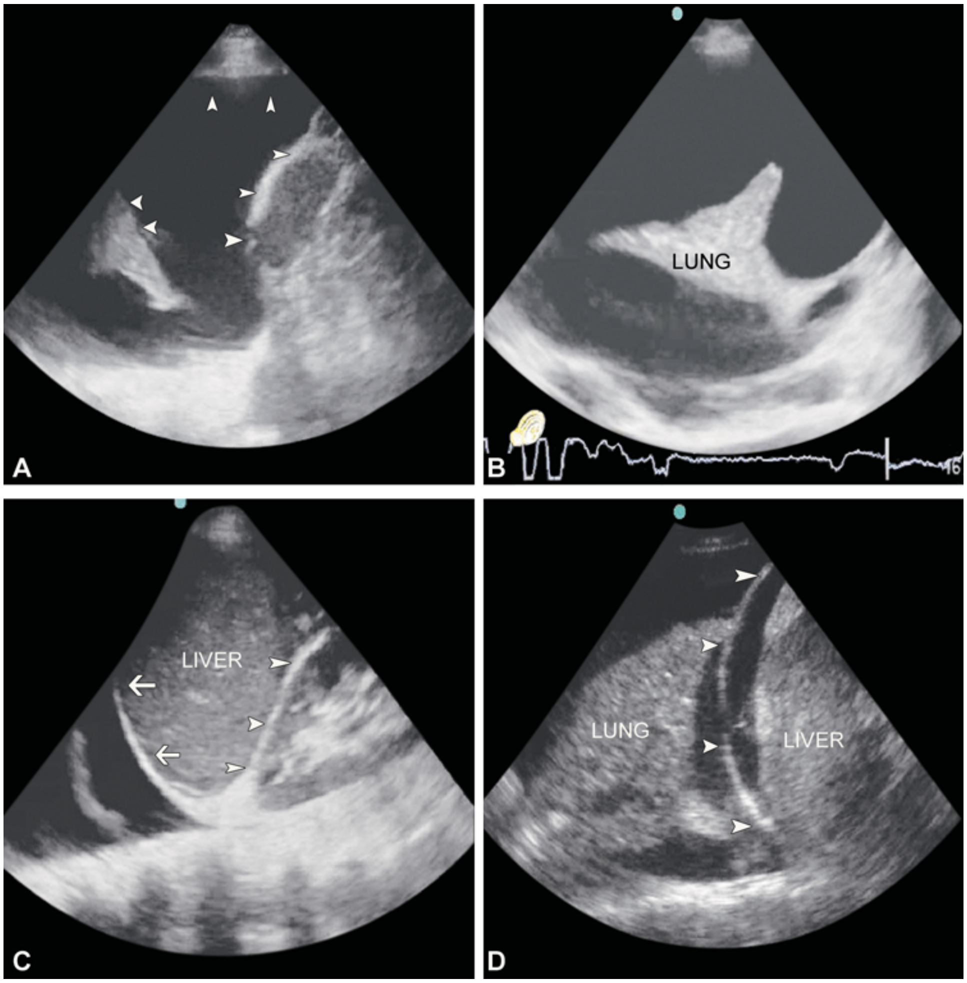
Ultrasonography is useful in the identification of pleural effusion. When the ultrasound detection of pleural effusion has been compared to chest CT scan or clinical confirmation by aspiration of fluid, its sensitivity and specificity of more than 90% has been recorded.[7,32] Ultrasonography is the imaging modality of choice in diagnosing pleural effusion in a supine critically ill patient.

The three cardinal features of ultrasonographic identification of pleural effusion are as follows:[11]

1. Presence of a relatively echo-free space
2. Typical anatomic boundaries that surround this space: the chest wall, the diaphragm and the visceral pleural surface of the lung (Fig. 144.14A)
3. Typical dynamic findings like movement of compressed lung during respiration

Pleural fluid, depending on its composition, may be anechoic or hypoechoic. A simple transudate may appear black (Fig. 144.14B) whereas a complicated pleural effusion may be more echoic (Fig. 144.15A).

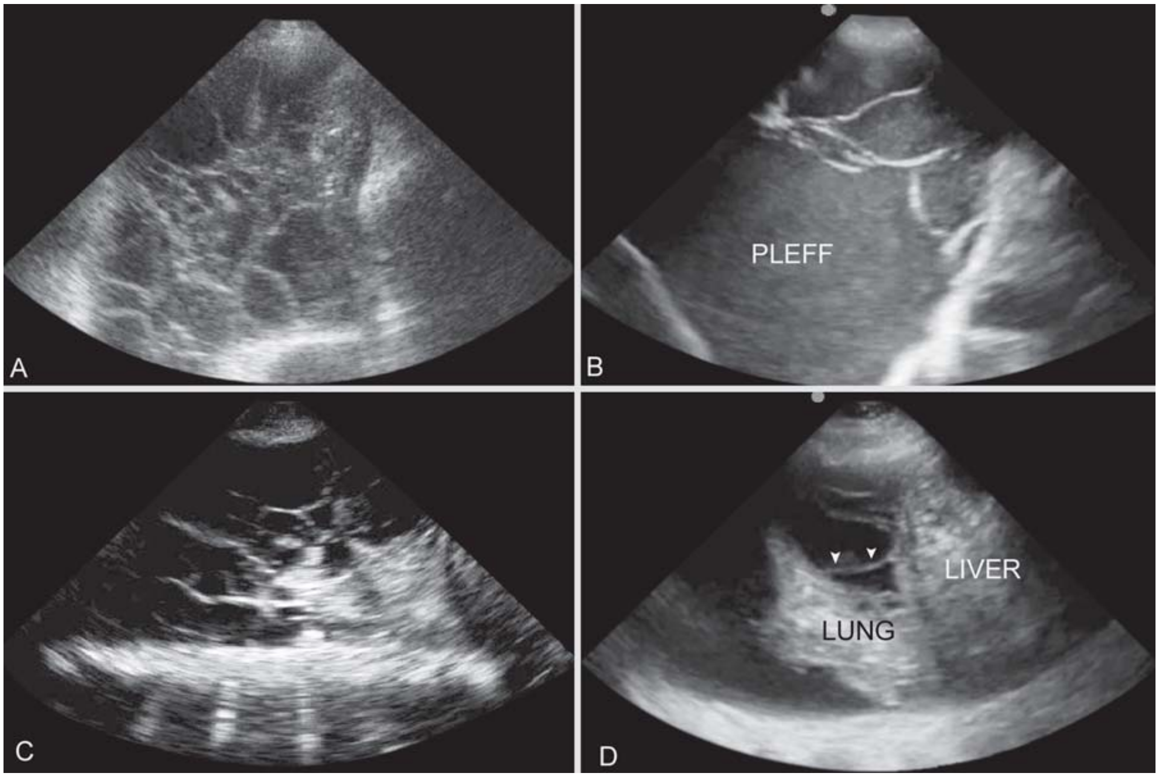
The typical anatomic boundaries are the inside of chest wall, the diaphragm and the visceral pleural surface of the lung. The inside of the chest wall may be difficult



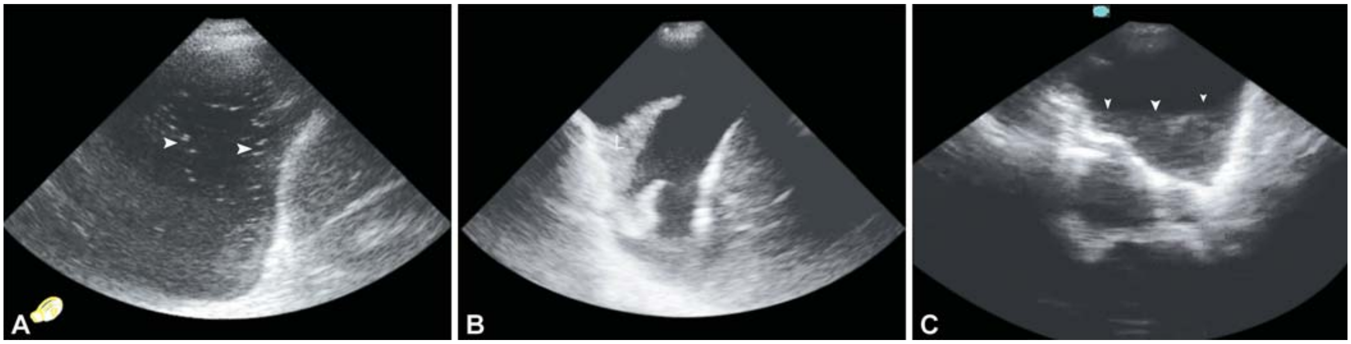
Figs 144.14A to D: Pleural effusion. A. Pleural effusion is identified by the typical anatomical boundaries (arrows): chest wall (above), diaphragm (right) and visceral pleural surface (left); B. Large pleural effusion. A typical transudative effusion is completely anechoic; C. Identifying the diaphragm (arrows) and liver/spleen below the diaphragm is critically important. The hepatorenal recess (arrowheads) may be erroneously identified as diaphragm and the liver as a complex pleural effusion, by an inexperienced operator. An attempted thoracentesis, in such a case, will lead to liver injury. D. Small pleural effusion. The patient also has ascites, seen as hypoechoic area below the diaphragm (arrowheads). Compressed lung shows an alveolar consolidation pattern

to visualize if there is near field clutter artifact. Its identification is important in order to estimate the depth of needle penetration needed to enter the pleural space. The diaphragm is identified as a curvilinear hyperechoic structure that moves with respiratory cycle. The liver or spleen is identified below the diaphragm (Fig. 144.14C). The visceral pleural surface of the lung demarcates the lung adjacent to the pleural effusion. The lung that is adjacent to a pleural effusion will have features of ultrasonographic alveolar consolidation pattern due to compressive atelectasis (Fig. 144.14D).

The dynamic findings characteristic of pleural effusion include lung flapping or jelly fish sign (Figs 144.16A to C) which is the undulating movement of compressed lung within the pleural effusion. A "curtain sign" occurs when aerated lung enters the scanning field during respiratory cycle and obscures visualization of the effusion. Cellular components within an effusion may have respirophasic or cardiophasic movement known as plankton sign (Figs 144.16A to C). Complex effusion may have undulating septations or fronds (Fig. 144.15D). M-mode ultrasound examination of the visceral pleural surface at the interface of the effusion often shows a "sinusoidal pattern", reflecting movement of the pleural surface within the fluid-filled space (Fig. 144.17).



Figs 144.15A to D: Complex pleural effusion. A. Echogenicity within the pleural fluid indicates complex pleural effusion. Also note the developing septations and loculations; B. Echogenic pleural fluid (PLEFF) in a case of hemothorax; C. Complex pleural effusion with multiple loculi; D. Septations (arrowheads) within a pleural fluid collection



Figs 144.16A to C: Other signs in pleural effusion. A. Complex pleural effusion within multiple echogenic foci (arrowheads). In real-time scanning, slow swirling motion of this echogenic material is known as 'plankton sign'; B. In real time scanning, the compressed lung shows an undulating movement, known as lung flapping or jellyfish sign; C. Hematocrit sign: In a richly cellular effusion, the cellular components can sediment forming a bilayer effect (arrowheads)

Free flowing fluid within the pleural cavity assumes a dependent position within the thorax due to gravitational forces. A loculated pleural effusion may be located in nondependent areas of the thorax. In supine patients, a moderate to large pleural effusion can generally be identified by scanning in the mid or posterior axillary line. Small pleural effusion may be difficult to identify due to a posterior location. The operator may need to press the transducer on the mattress and angle the ultrasound beam towards the central body mass. Alternatively, the patient needs to be placed in lateral decubitus position to scan the posterior areas.

Estimation of Pleural Fluid Volume (PEV): Several methods have been described for accurate estimation of pleural fluid volume based on ultrasonography

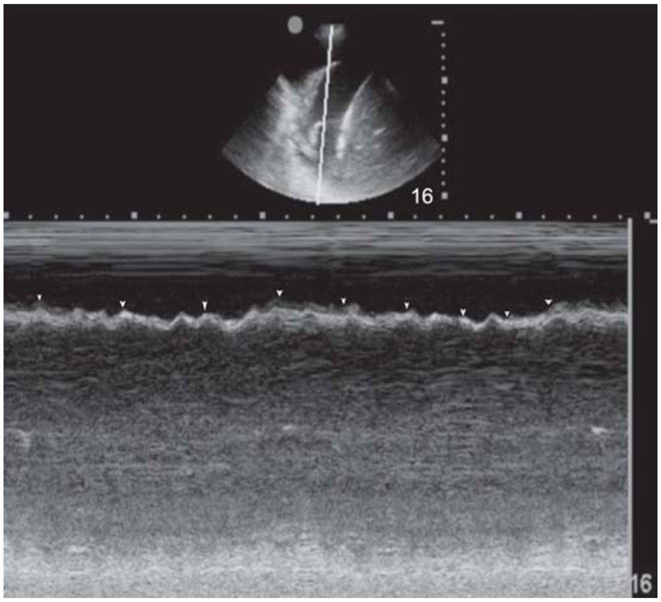


Fig. 144.17: Sinusoid sign: M-mode examination of the visceral pleural surface shows a sinusoidal pattern (arrowheads) reflecting movement of the visceral pleural surface within the effusion

findings.[33,34] Remérand et al. described a multiplanar approach to measure PEV.[35] In their study, contiguous paravertebral intercostal spaces were scanned to detect the upper and the lower limits of the effusion. They showed good correlation of ultrasound PEV with either the volume of the drained pleural effusion or with CT based estimation of PEV.[35] The advantage of very accurate estimation of PEV remains to be established. In frontline critical care practice, it may suffice to identify the volume in qualitative terms, like small, moderate or large, to guide the intensivist in the management of the effusion.

Characterization of Pleural Fluid: Pleural fluid echogenicity, in combination with a patient's clinical history, gives important clues regarding its etiology. Transudates are generally anechoic. Exudative effusions have a variable amount of echogenicity. However, exudative effusions may occasionally be anechoic. Exudative effusions may demonstrate the plankton sign (see above) or swirling echoes and strands that give them a heterogeneously echogenic appearance. Highly cellular exudates like empyema or hemothorax can have a homogeneously echogenic appearance (Fig. 144.15B). Such richly cellular effusions can form a bilayer effect where the cellular components sediment in a dependent area within the effusion under gravitational effect (hematocrit sign, Fig. 144.15D). A complex parapneumonic effusion or empyema can be suspected by finding septations, loculations or stranding within the effusion (Figs 144.15A to C). Pleural ultrasonography is superior in identifying septations within pleural fluid compared to CT scan.[36]

Important Clinical Applications of Thoracic Ultrasonography

The knowledge of thoracic ultrasonography gives the intensivist the ability to immediately assess the critically ill patient at point of care. The clinician can immediately and repeatedly gather information or identify major problems more rapidly and accurately than can be obtained by the standard supine chest radiography. The reader is strongly encouraged to develop skill in thoracic ultrasonography and become proficient in its clinical application in the bedside management of their ICU patient.

Evaluation for Pneumothorax

Pneumothorax may occur in following procedures; may be an underlying cause for cardiopulmonary failure, and when it occurs in a patient on mechanical ventilatory support, it may be immediately life threatening due to tension physiology. Standard chest radiography is unreliable in diagnosing pneumothorax.[37,38-40] Thoracic ultrasonography is a reliable method to exclude pneumothorax with diagnostic performance that is comparable to the reference standard, CT scan[40,41] and superior to chest radiography. It may decrease the need for computed tomography.[42] The presence of sliding lung rules out pneumothorax at the site of examination with 100% negative predictive value.[43] The presence of lung pulse[14] or B lines rules out pneumothorax as the generation of these ultrasound signs depends on apposition of the two pleural surfaces.[10,16] In the supine position, free air in a pneumothorax space accumulates anteriorly (with the rare exception of loculated pneumothorax),[44] so, that rapid scanning at several points over the anterior lung zones rules out pneumothorax if lung sliding is present.

While the presence of lung sliding rules out pneumothorax in an absolute sense, its absence does not rule in pneumothorax. The absence of lung sliding or lung pulse is only suggestive of a pneumothorax. A pneumothorax interposes air between the visceral and parietal pleura so that lung sliding and lung pulse are lost. However, there are other causes of loss of lung sliding:

1. Pleural symphysis
2. Inadequate respirophasic expansion of lung: Dense consolidation, severe ARDS, advanced fibrosis, atelectasis from endobronchial occlusion, may all

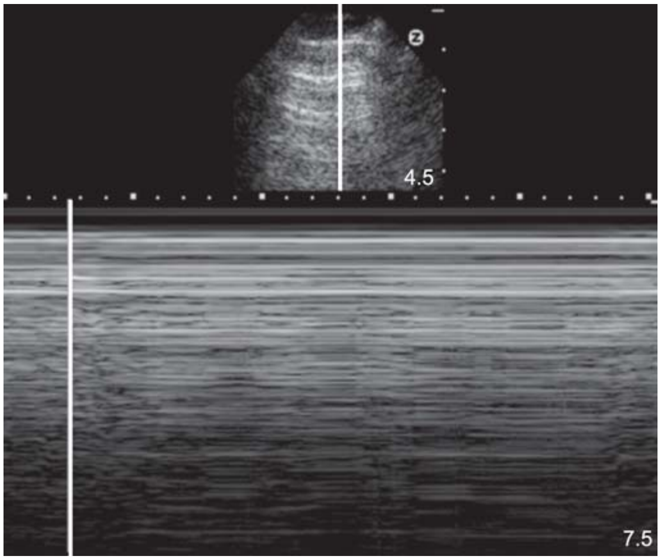


Fig. 144.18: M-mode examination of the lung in a case of pneumothorax. The absence of lung sliding is reflected by a straight pleural line (compare with image 144.11D to understand the difference). Also note the exclusive A-line pattern in the upper panel image

cause loss of lung sliding due to the fact that the underlying disease process restricts air entry during respiration. Lung pulse and B lines may still be present in these cases which is helpful. Apnea will result in loss of lung sliding although lung pulse continues until cardiac arrest supervenes.

When the intensivist checks for lung sliding immediately before central venous access or thoracentesis, the finding of loss of lung sliding immediately following the procedure is strong evidence of procedure related pneumothorax.[45,46] The absence of lung sliding can easily be documented on an M-mode examination of lung (Fig. 144.18).

While the absence of lung sliding can only suggest the presence of pneumothorax, thoracic ultrasonography may be used to diagnose pneumothorax if the intensivist can identify a “lung point”. In a pneumothorax space, the partially collapsed lung will still be apposed to the inside of the chest wall. If the ultrasound transducer is placed at the border of apposition, the partially collapsed lung will enter the scanning plane on an intermittent basis coincident with respiratory cycle. The operator will observe intermittent lung sliding or B lines, as the partially collapsed lung enters the scanning plane during the respiratory activity.[47] This sign is demonstrable at the border of the pneumothorax. The lung point can identify a small pneumothorax and can diagnose pneumothorax when a chest radiograph is nondiagnostic. The more lateral the lung point, the larger is the volume of the pneumothorax.[42] Lung point may be absent in a large pneumothorax with complete collapse of the lung. Identification of the lung point requires advanced scanning skills as it is a subtle finding, making it a specific, but not a sensitive finding.

A pneumothorax space is air filled and therefore has an exclusive A line pattern. The combination of absence of lung sliding with exclusive A line pattern has a high specificity for diagnosis of pneumothorax.[47,48]

Guidance for Thoracentesis

A major application of ultrasonography is for guidance of safe thoracentesis (see procedure section).

Clarification of Supine Chest Radiograph

Standard supine chest radiographs in the ICU are often difficult to interpret. The image is a two dimensional representation of a complex three-dimensional structure. Combined with the problems related to penetration and rotation artifacts, the resultant image gives a nonspecific summation radiodensity of the lung fields. Using ultrasonography, the examiner can rapidly and repeatedly develop a three-dimensional construct of the thoracic compartment that is superior to that derived from supine chest radiograph. By using an organized scan line protocol, thoracic ultrasonography can diagnose pneumothorax, normal aeration pattern, alveolar interstitial pattern, consolidation pattern and/or pleural effusion.

Ultrasound Assessment of Respiratory Decompensation

Acute respiratory failure is a common problem in the ICU. It may present in a patient who is breathing spontaneously or who is decompensating while already on mechanical ventilatory support. In either case, thoracic ultrasonography, when combined with basic Goal Directed Echocardiography (GDE) and lower extremity venous examination, helps the clinician to reach a diagnosis and decide upon an immediate management strategy. Lichtenstein et al. have demonstrated the excellent performance of thoracic ultrasonography for assessment of acute respiratory failure.[49] The authors proposed an algorithm for evaluation of patients with acute respiratory distress termed as “Bedside Lung Ultrasound in Emergency or the BLUE protocol”. Studying a cohort of 260 patients, thoracic ultrasound alone yielded correct diagnoses in 90.5% of cases. Integration of ultrasonography data with clinical assessment is likely to yield even better results.

Thoracic ultrasonography permits the intensivist to rapidly categorize the cause of acute respiratory failure. Pneumothorax, normal aeration pattern, alveolar-interstitial pattern, consolidation and/or pleural effusion are readily identified at the bedside of the decompensated patient. A very specific application of thoracic ultrasonography is in the management of the acutely dyspneic patient who may have respiratory failure due to cardiogenic pulmonary edema. Cardiogenic pulmonary edema results from elevation of hydrostatic pressure within the pulmonary capillary system due to elevation of left heart filling pressures. Lichtenstein et al. have demonstrated that presence of anterior A lines indicates that PAOP is ≤18 mm Hg and usually ≤13 mm Hg. Therefore, in an acutely dyspneic patient, presence of A lines, rules out cardiogenic pulmonary edema in an absolute sense. In an acutely dyspneic patient, anterior A line suggests airway disease, metabolic dysfunction, pulmonary embolism or neurological causes for the dyspnea. However, the presence of multiple anterior B lines is a nonspecific finding. Multiple anterior B lines may result from hydrostatic pulmonary edema, but may have many other potential causes.

Limitations of Thoracic Ultrasonography

Thoracic ultrasonography has some specific limitations:[11]

1. Obesity, edema, subcutaneous emphysema, chest wall dressings, wounds and body position all may prevent adequate image acquisition.
2. Some modern machines with extensive post acquisition image processing have near field clutter which degrades image quality.
3. Difficulty may arise in differentiating a complex pleural effusion from a consolidation. A hemothorax or empyema may be hyperechoic and lack dynamic findings. Air within a pleural effusion may further confuse the interpretation. With this complexity, chest CT may be required in this type of difficult cases. An air or fluid bronchogram supports a diagnosis of consolidation whereas a sinusoidal pattern on M-mode examination is typical of pleural effusion.[25]
4. Thoracic ultrasonography requires that the clinician is adequately trained in the field. For example, in identifying B lines, the examiner must have knowledge of their mimics: I and Z lines.[13] Sliding lung and lung point may be subtle findings.
5. Identification of a pleural effusion is straight forward if it is a large anechoic collection. On the other hand, an empyema or hemothorax may have dense homogenous echogenic pattern, similar to liver and spleen, without any visible septation. They may lack dynamic changes due to their density.
6. Application of lung ultrasonography results requires that the intensivist is able to integrate the findings into their overall analysis of pathophysiology and clinical circumstances.

CRITICAL CARE ECHOCARDIOGRAPHY

Introduction

Hemodynamic failure is a common feature of critical illness as is respiratory failure that derives from cardiac dysfunction. Echocardiographic assessment of hemodynamics is a key component of assessment and management of the critically ill patient. Mastery of Critical Care Echocardiography (CCE) is therefore an important component of Critical Care Ultrasonography (CCUS).

Basic CCE versus Advanced CCE

CCE may be divided into two levels of competence, basic and advanced. Basic CCE is a skill that can be acquired with a short period of training and should be considered as a standard part of competence in CCUS. Competence in advanced CCE requires a long period of training similar in scope to that required for cardiology echocardiographers. For the purpose of frontline critical care applications, we feel that most intensivists do not need advanced level competence in echocardiography. Most important clinical problems may be identified and managed by the intensivist with the basic level training.

Basic CCE uses rapid, real-time, visual two-dimensional assessment of cardiac structure and function with specific focused objectives.[50,51] It includes assessment of cardiac anatomy, global wall motion, biventricular function, gross valvular pathology, pericardium and IVC size (Table 144.3)[4]

Advanced CCE includes all elements of the basic examination with the comprehensive assessment of segmental wall function, valvular function and all elements of standard cardiology type Doppler examination (color and spectral). Advanced CCE also includes assessment of preload sensitivity and hemodynamic function, applications specific to critical care practice. Consensus competency guidelines for intensivists in advanced CCE has been published.[4]

Both basic and advanced CCE are performed within the context of the clinician being competent in the other aspects of CCUS. The value of the cardiac evaluation is amplified if the intensivist uses a whole body approach to CCUS.

TABLE 144.3: Competence in basic critical care echocardiography[4]

- Ability to recognize common echocardiographic patterns
- Ability to assess LV size and global systolic function
- Ability to recognize homogeneous and heterogeneous LV contraction pattern
- Ability to assess global RV size and contraction
- Assessment for pericardial fluid and diagnosis of tamponade
- IVC size and respiratory variation
- Basic color Doppler assessment for (severe) valvular regurgitation.

Equipment

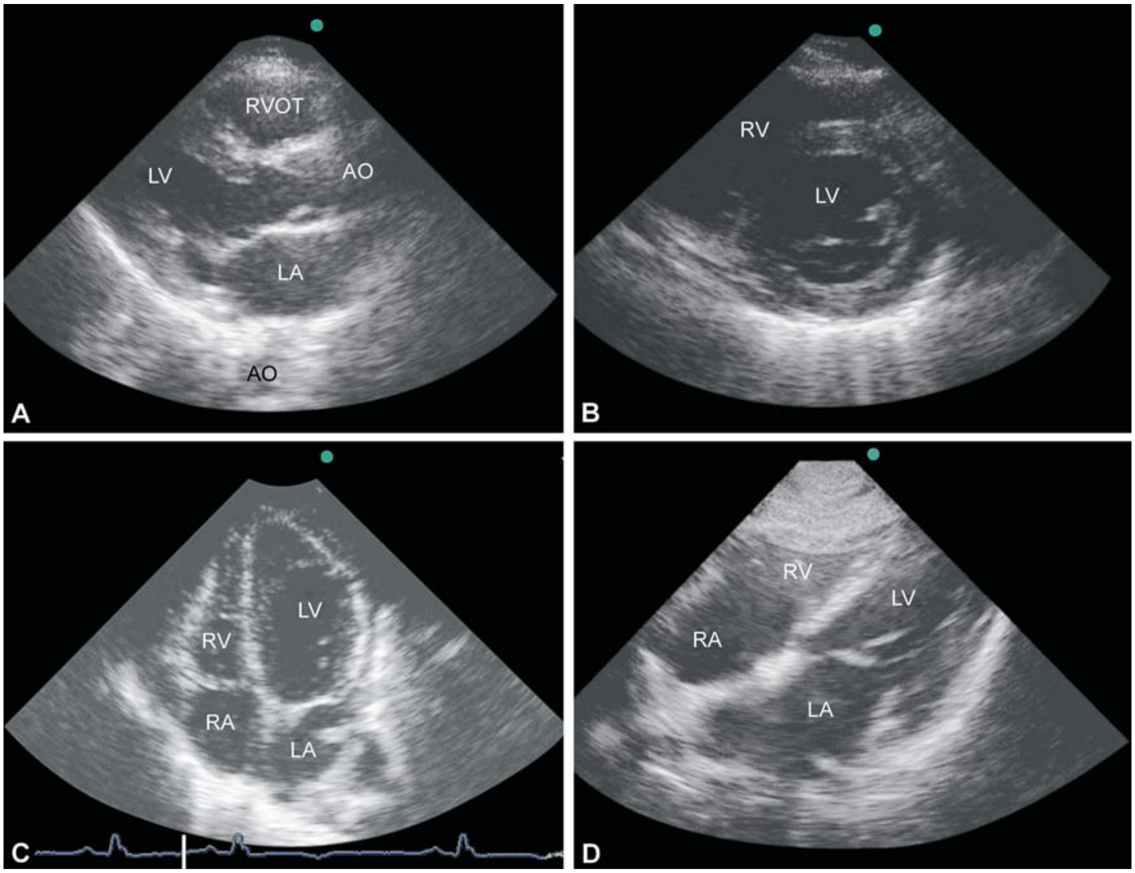
Both basic and advanced CCE require an ultrasonography machine capable of cardiac imaging, with a phased array transducer with the frequency range of 3.5–5.0 MHz. Phased array transducers used for cardiac ultrasonography have a small footprint, so, that they can scan between rib interspaces. Transducers used for cardiac ultrasonography are capable of performing other aspects of CCUS. Full Doppler capability is essential for performing advanced CCE. Basic CCE may be performed without Doppler capability.

Basic CCE

Image Acquisition

Basic CCE relies on five views that are used to answer limited number of clinical questions.

1. *Parasternal Longitudinal-axis View (PSL):* The transducer is placed in the left parasternal area, in the fourth intercostal space, with the index marker oriented towards the right shoulder. By gentle adjustment of probe angle and position, the examiner seeks a tomographic plane such that the image includes Right Ventricular Outflow Tract (RVOT), interventricular septum, left atrium, left ventricular outflow tract (LVOT), the Aortic Valve (AV) and the mitral valve (MV) (Fig. 144.19 A). An adequate PSL view bisects the aortic and mitral valves and includes the LV cavity in its longest axis. The PSL view allows



Figs 144.19A to D: Standard view in basic CCE. A. Parasternal long axis view; B. Parasternal short axis view; C. Apical four chamber view; D. Subcostal (four chamber) view

evaluation of Left Ventricular (LV) size and function, (RVOT), septal kinetics, valvular morphology and pericardial effusion

2. *Parasternal Short-Axis View (PSS):* Once an adequate PSL has been obtained, the transducer is rotated 90º clockwise without any angulation or tilting. This yields the PSS view. By gentle movement and angulation of the transducer, the examiner seeks to establish a cross sectional view of LV at the papillary muscle level, RV and interventricular septum (Fig. 144.19B). An adequate view positions the LV cavity at the center of the screen. The PSS view allows evaluation for pericardial effusion, global and segmental LV function and septal kinetics.
3. *Apical Four-Chamber View (A4C):* The transducer is placed at the LV apex with the index marker oriented towards left shoulder. By gentle movement and angulation of the transducer, the examiner seeks to establish a view from the apex of the RV, the LV, the Right Atrium (RA) and the left atrium (LA) that bisects the mitral orifice. In this view, both ventricles, both atria, interatrial and interventricular septa, the mitral valve and the Tricuspid Valve (TV) and pericardium can be visualized (Fig. 144.19C). The A4C view allows evaluation of RV/LV size and function, septal kinetics and pericardial effusion. This view has major utility in advanced CCE for Doppler based examination of mitral and tricuspid valves and segmental analysis. These are not within the scope of basic CCE.
4. *Subcostal View*: The transducer is placed below the xiphoid process with the index marker oriented towards the left flank. The transducer is held on its top surface in near horizontal position with the bottom surface contacting the patient. The subcostal view allows evaluation for RV/LV size and function, interatrial septal anatomy and function and pericardial effusion (Fig. 144.19D).
5. *Inferior Vena Cava (IVC) View:* The transducer is placed in the right paramedian subcostal position in order to scan the IVC in longitudinal axis. If air within the transverse colon blocks this view, the examiner may attempt a transcostal right paramedian longitudinal axis view or a right lower midaxillary longitudinal axis view. This view visualizes the IVC in longitudinal axis and is useful in assessing preload sensitivity.

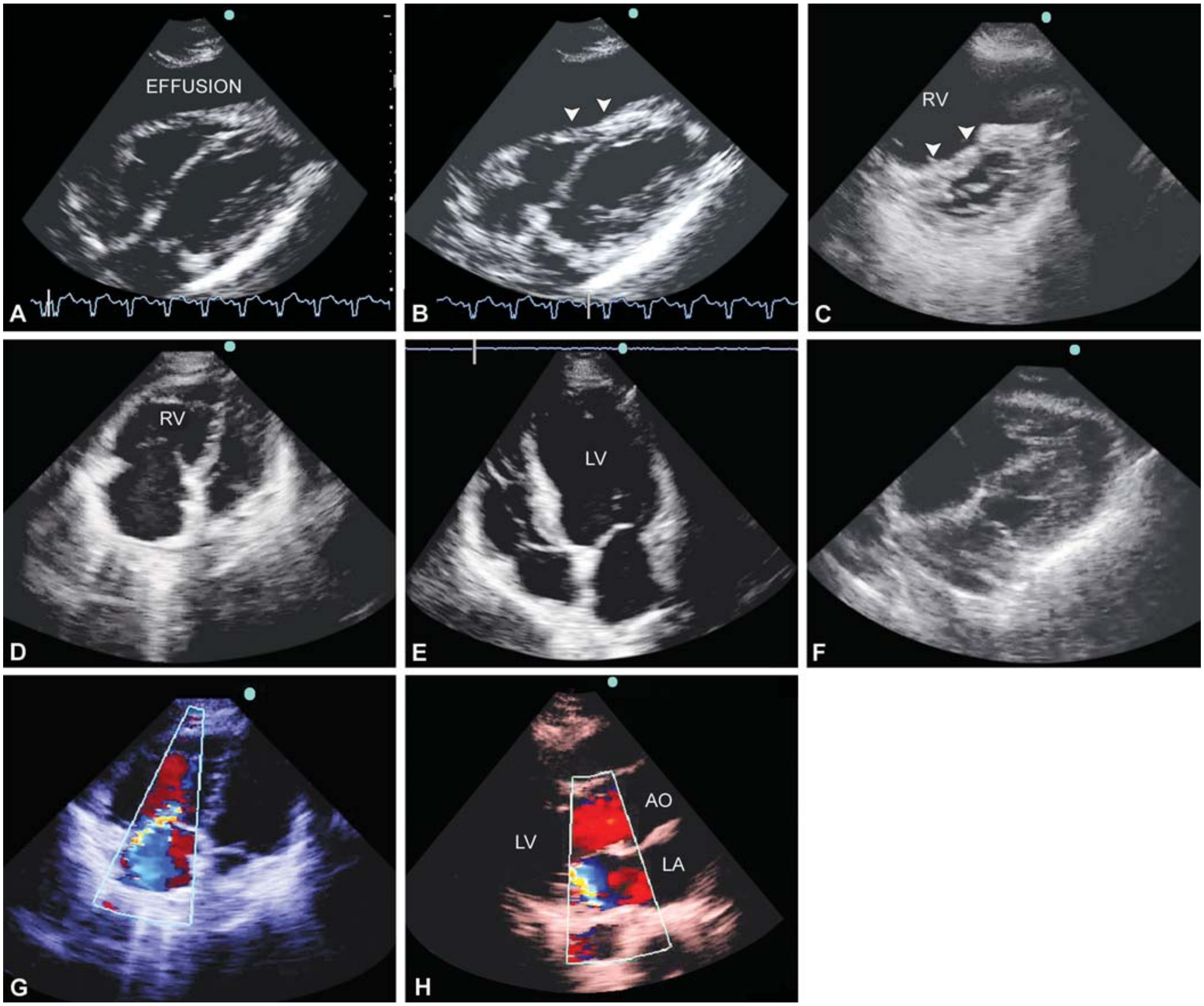
Competence in basic CCE may include qualitative assessment of valve function using color Doppler to assess for severe valvular regurgitation. Comprehensive assessment of valvular function is beyond the scope of basic CCE.

Challenges in image acquisition: Compared to other aspects of CCUS, image acquisition for CCE is more difficult. Ribs block transmission of ultrasound and so represent a barrier to easy examination. The air-filled lung blocks adequate examination and is often interposed between the transducer and the heart. Hyperinflation due to COPD or Positive End Expiratory Pressure (PEEP) may block all image acquisition from anterior chest and the examiner may have to rely on the subcostal image alone. In patients with obesity, heavy musculature, wounds or chest dressings, adequate examination may be blocked. Positioning the patient in lateral decubitus frequently improves image quality, but may be a major challenge in the ICU. Translational artifacts happen when the heart moves with respiratory movement. Patients who are dyspneic and who are on mechanical ventilation, have considerable movement of the heart during examination. The examiner may interpret changes as deriving from intrinsic cardiac contraction when they may represent movement of heart across tomographic planes related to respiratory translation. The position of the heart in the chest may result in suboptimal image acquisition. For instance, diaphragmatic elevation shifts the heart to a more vertically oriented position in the supine patient. Adequate PSL and PSS views are not possible in these circumstances.

In addition to the physical impediments, poor techniques may yield factitious information. For example, in an off-axis image of the LV in a PSL view, the small size of the LV cavity may cause the examiner to conclude that the patient has a hyperdynamic LV with endsystolic effacement suggesting severe hypovolemia. In the AP4, the size of the RV may appear to be very small if the transducer is rotated too far in the counterclockwise position.

Clinical Applications

Basic CCE is used for rapid assessment of cardiopulmonary failure. In approaching a patient in shock, the intensivist seeks to categorize the cause of the shock and to develop an initial management strategy. The frontline intensivist generally uses a simple differential diagnosis for the shock state; obstructive, cardiogenic, hypovolemic or distributive, with the understanding that these causes may frequently coexist. Basic CCE allows the intensivist to identify the primary cause of shock. The examination may be repeated in order to track the effect of the intervention. A few examples will highlight the use of basic CCE in assessment of shock. Obstructive shock may be caused by pericardial tamponade, or acute cor pulmonale due to massive



Figs 144.20A to H: Basic CCE in the differential diagnosis of shock. A. Large pericardial effusion; B. RV diastolic collapse in subcostal view (arrowheads). The ECG tracing and open position of the mitral valve show that the ventricles are in diastole; C. Large RV in parasternal short axis view. Note the leftward displacement of interventricular septum (arrowhead), giving the LV a 'D' shaped appearance and indicating RV pressure overload; D. Apical four chamber view showing RV dilatation. In this view, a normal RV is usually smaller than the LV; E. Large LV in a patient with poor LV function and hypotension; F. Small hypercontractile LV in a patient with hypovolemic shock. Note the complete effacement of LV cavity in systole; G. Color Doppler examination of tricuspid valve showing massive TR (A4C view); H. Color Doppler interrogation of mitral valve showing MR (PSL view).

pulmonary embolism (PE). In the former, the examiner identifies a pericardial effusion of consequential size (Fig. 144.20A). There may be accompanying signs of tamponade effect, like RV diastolic collapse or RA systolic collapse (Fig. 144.20B). In the right clinical context, the pericardial tamponade is identified and life saving pericariocentesis may proceed forthwith. In case of a patient with shock and a large hypocontractile RV (Figs 144.20C and D), massive PE is a major consideration. Lung ultrasonography with predominant A lines and presence of a DVT may confirm the diagnosis and lead to immediate intervention. Within the category of cardiogenic shock, severely impaired LV function will be identified (Fig. 144.20E). Occasionally, marked mechanical disruption of valve function and gross valvular regurgitation will be identified by the basic echocardiographer in a patient with cardiogenic shock (Figs 144.20G and H). Severe hypovolemic shock results in hyperdynamic LV with end systolic effacement of cavity

TABLE 144.4: Competence in basic CCE: Required cognitive skills in recognition of clinical syndromes

Severe hypovolemia
Small, hyperdynamic ventricles with end systolic cavity obliteration
Small (virtual) IVC, IVC with marked respiratory variation in caliber
LV pump failure
Global hypocontractility of LV suggests pump failure
Segmental hypocontractility suggests myocardial ischemia
LV cavity dilatation indicates chronic cardiac disease
RV failure
Acute cor pulmonale is manifested by RV dilatation and paradoxical septal motion
Isolated RV dilatation suggests RV infarct
Dilated, noncollapsible IVC is a corroborative finding
Cardiac Tamponade
Pericardial effusion (size inconsequential if tamponade is clinically suspected)
RA/RV diastolic collapse
Dilated, noncollapsible IVC supports the diagnosis
Acute massive left-sided valvular regurgitation
Normal LV cavity size (LV has no time to dilate)
Normal/hyperdynamic LV systolic function (LV volume overload)
Massive color Doppler regurgitant flow
Cardiac arrest: Clue to etiology (see text for details)
Tamponade
Acute cor pulmonale
Global LV systolic dysfunction
Heterogeneous contractility pattern

(Fig. 144.20F) and/or IVC that is very small in diameter (see below for detailed discussion of preload sensitivity). Distributive shock may present with relatively normal echocardiographic findings. It is obvious that echocardiographic findings must always be interpreted within the overall clinical situation. Chronic cardiac dysfunction may result in major abnormality on screening examination, but it may not be the primary cause of the shock state. Often, there may be more than one primary cause of hemodynamic failure. The integration of image acquisition, image interpretation and cognitive elements of CCUS are required for full application of echocardiographic findings at the bedside. An intensivist who becomes competent in basic CCE will be able to identify different clinical syndromes as listed in (Table 144.4).[4]

Advanced CCE

Advanced CCE allows for comprehensive assessment of cardiac structure and function. The intensivist with competence in advanced CCE has the same level of capability in image acquisition and interpretation as a cardiologist who is fully trained in echocardiography, with the exception of comprehensive assessment of prosthetic valve function, complex congenital heart disease, cardiac source of systemic embolism and stress echocardiography.[4] Beyond sophisticated image acquisition and interpretation skills, the practice of advanced CCE requires that the intensivist has a broad based knowledge of the pathophysiology of cardiopulmonary failure in order to integrate the findings into the care of the patient. The cognitive aspects of competence in advanced CCE and the key questions that can be addressed with advanced CCE have been defined in the ACCP-SRLF competence statement.[4]

Transesophageal echocardiography (TEE) may be an important component of competence in advanced CCE. In some countries, TEE is used on a routine basis by intensivists with both basic and advanced skill level. While this is a desirable practice pattern, we recognize that many ICUs do not have availability of TEE, particularly in North America. There are certain situations where TEE is superior to TTE. Patients with inadequate TTE image quality may require TEE for definitive evaluation of cardiac function. Obesity, edema, high PEEP levels and thoracic wounds or dressings may prohibit adequate TTE imaging. Especially problematic are patients who have thoracic trauma or are status post open heart surgery. Older studies report that TTE in the ICU leads to a successful examination in 50% of attempts[52,53] in comparison to TEE with success in 90% of attempts.[54] However, evolution of TTE technology in the form of high quality portable machines has greatly improved the yield of TTE in the critically ill patient. In our opinion, most patients in the medical ICU can be imaged adequately with TTE technique. The other indication of TEE is to examine cardiac structure and function that is not well imaged with TTE by virtue of its anatomic position. TEE is particularly suited for the detailed analysis of posterior cardiac structures such as the LA and the pulmonary veins with Doppler analysis. The superior vena cava is also better visualized with TEE.

Advanced CCE differs from basic CCE in that it focuses on quantitative analysis of cardiac function and structure whereas basic CCE gives the intensivist a qualitative assessment. Advanced CCE necessarily includes use of both color and spectral Doppler, whereas basic CCE does not. The use of Doppler requires that the intensivist has full knowledge of the physics of the technique as well as the limitations and pitfalls. Discussion of the physics, limitations and pitfalls of Doppler is beyond the scope of this discussion. Competence in advanced CCE requires many hundred hours of training and image interpretation under direct supervision of an experienced echocardiographer and supervisor.

Specific Components

Assessment of LV Structure and Function

a. *LV Volume:* End diastolic LV area may be measured in multiple axes and used for the identification of hypovolemia. The end diastolic area of the LV at papillary muscle level in the PSS view is a parameter that can be used to identify preload sensitivity (see below).[55] The measurement of LV end diastolic and end systolic areas may be used to measure stroke volume using Simpson's method.

b. *LV Contraction:* A global subjective assessment of LV function can be made and graded as hyperdynamic, normal, mildly reduced, moderately reduced or severely reduced. Visual estimate of Ejection Fraction (EF) may be made very accurately when compared to quantitative measurement of EF. Assessment of LV contractile function includes observation of LV segmental function based on a standard 17-segment model defined by the American Heart Association (AHA).[56] The visual analysis of segmental wall function is based on thickening of the wall segments and the endocardial excursion of the wall segment; excursion of >30% and wall thickening of >50% are considered normal.

c. M-mode analysis of cardiac function is a part of advanced CCE. It is useful for detailed analysis of high frequency cardiac functions such as valve fluttering, premature coaptation of valve leaflets, systolic anterior motion of mitral valve, mitral valve prolapse, septal kinetics and pulmonary valve function. The utility of M-mode examination of ventricular function has major limitations in the assessment of fractional shortening and EF related to the complex three dimensional structure of the heart and the possibility of asymmetric segmental wall function.

d. Stroke volume (SV) may be measured both with TTE and TEE. Typically, it is measured in the LVOT but may be measured at other valve orifices, if the examiner seeks to measure quantitative valve regurgitation/stenosis or for shunt physiology. Once SV is measured, cardiac output is known and multiple hemodynamic indices can be derived using standard formula such as systemic vascular resistance, pulmonary vascular resistance and indices of ventricular work.

   The SV is ascertained by measuring the LVOT diameter from PSL view (Fig. 144.21A). The diameter is used to calculate the area of LVOT. From A4P view, the transducer is angled anteriorly to obtain an apical five chamber view that includes the LVOT (Fig. 144.21B). A pulsed wave Doppler interrogation box is placed in the LVOT and the resultant velocity envelope is integrated to yield the Velocity Time Integral (VTI). SV is calculated as follows (Figs 144.21C and D):

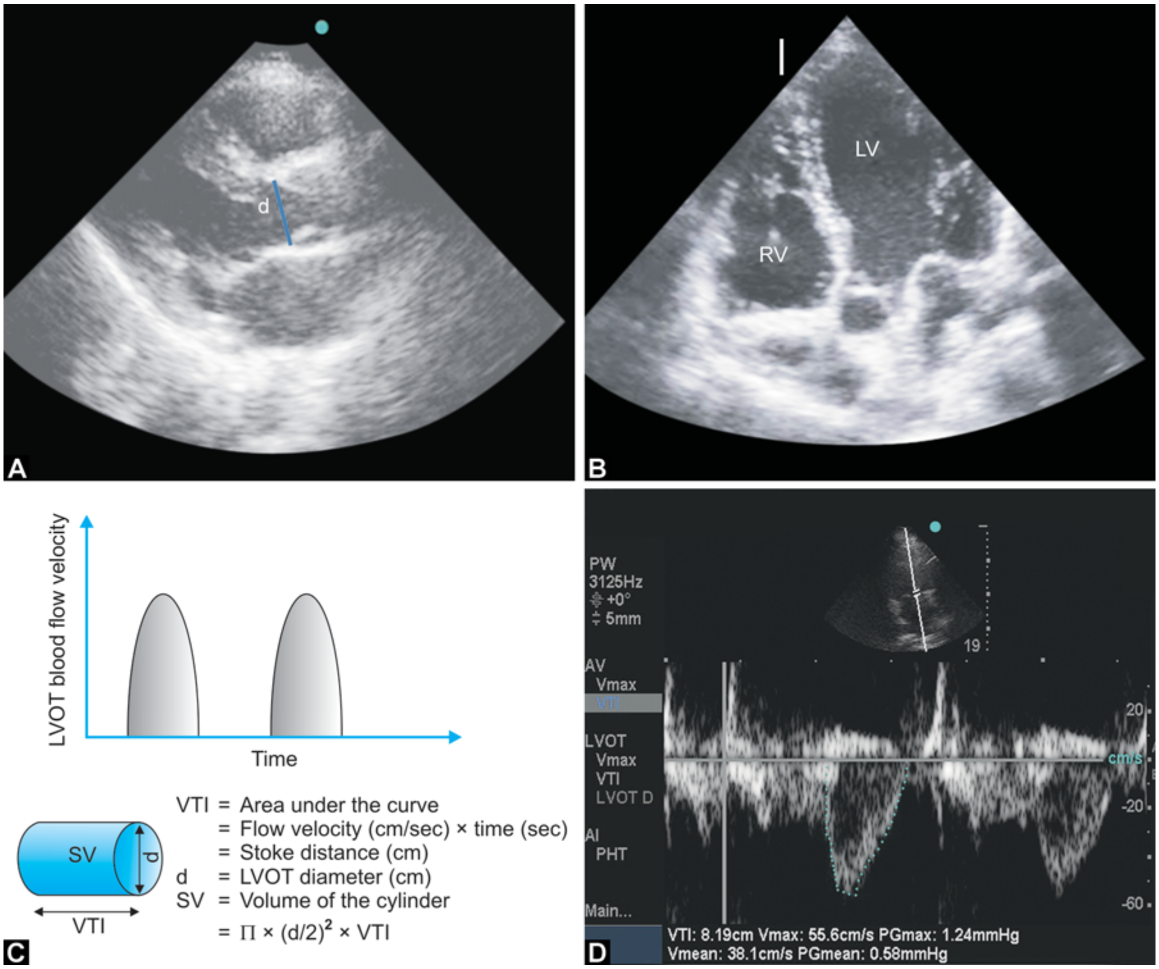
   SV (ml) = LVOT area (cm^2) x VTI area (cm)
   LVOT cross-sectional area=LVOT radius)^2 x 3.14
   (LVOT is assumed as a circle, the area therefore being represented by the formula πr^2)

e. Other measures of LV systolic function may be derived from Doppler assessment. In presence of mitral regurgitation (MR), continuous wave Doppler examination of the MR jet permits calculation of the rate of pressure increase (dP/dt) within the LV during isovolumetric contraction. This dP/dt is sensitive to changes in contractility and is independent of preload or afterload.[57] Systolic mitral annular descent measured by tissue Doppler gives an estimate of global LV function.[58]

f. Assessment of LV diastolic function is based on Doppler assessment of transmitral filling, pulmonary venous flow pattern and lateral mitral annular velocity. These values may be used for quantitative assessment of PAOP. Use of TEE is particularly suited for detailed analysis of pulmonary vein inflow, the results of which may be used to estimate PAOP.

Assessment of RV Structure and Function

RV diastolic overload is manifested as RV dilatation. It can impair LV diastolic function, can contribute to hemodynamic failure, and has implications when assessing a patient for fluid therapy. A visual comparison of LV and RV size and RV cavity shape gives qualitative information about RV diastolic overload. A normal RV is smaller than the LV and crescentric in shape from PSS view (Fig. 144.20B). Both ventricular areas can be measured at end diastole from an A4C view. Other authors have used the subcostal view.[59] The normal RVEDA:LVEDA ratio is between 0.36 and 0.6 (0.48±0.12).[60] Moderate dilatation is defined as ratio 0.7–0.9 and severe dilatation as ratio >1. Some authors have shown that visual analysis of RV dilatation by a trained echocardiographer correlates well


A
d
B
LV
RV
LVOT blood flow velocity
Time
SV
d
VTI
VTI = Area under the curve
= Flow velocity (cm/sec) × time (sec)
= Stoke distance (cm)
d = LVOT diameter (cm)
SV = Volume of the cylinder
= Π × (d/2)² × VTI
C
PW
3125Hz
+0°
5mm
19
AV
Vmax
VTI
LVOT
Vmax
VTI
LVOT D
AI
PHT
Main...
20
cm/s
-20
-60
VTI: 8.19cm Vmax: 55.6cm/s PGmax: 1.24mmHg
Vmean: 38.1cm/s PGmean: 0.58mmHg
D

Figs 144.21A to D: Measurement of aortic VTI and LV stroke volume during TTE. A. LVOT diameter (d) is measured in systole at the level of aortic annulus from a PSL view. The distance is measured between the point where the anterior aortic cusp meets the ventricular septum and the point where the posterior aortic cusp meets the anterior mitral leaflet. The line should be perpendicular to the anterior aortic wall; B. An apical five chamber view visualizes the LVOT and pulse Doppler interrogation box is placed at the aortic annulus or close to it; C. Schematic representation of the principle of stroke volume measurement (see text for details); D. Doppler measurement of flow velocity at LVOT

with quantitative measurement.[61] RV diastolic dysfunction results in a characteristic septal dyskinesia pattern measured with M-mode and that is identified as septal paradox by 2D echocardiography.

Assessment of RV systolic function is based on a qualitative visual analysis of RV free wall and interventricular septum contraction. The contractile function can be graded as normal, mild, moderate or severely reduced. In a patient with abnormal RV systolic function, evidence of RV systolic overload may be present. Septal dyskinesia is the hallmark of RV systolic overload. Septal dyskinesia results when an increase in RV afterload leads to a prolongation in RV contraction beyond the end of LV ejection. This leads to a transient increase in RV pressure over LV pressure when RV is still contracting though LV has started to relax. This leads to a posterior movement of the interventricular septum.[62] This paradoxical septal motion can be observed visually and can be more precisely recorded by M-mode at mid-ventricular level from a PSL view. Septal dyskinesia can also be diagnosed by measuring systolic Eccentricity Index (EI). From a PSS view of the LV at papillary muscle level, measurements are taken at end-systole. D1 is measured as a diameter that bisects the papillary muscles and D2 as an orthogonal diameter to D1. D2/D1 is taken as the EI. A normal systolic EI is 1; EI > 1 indicates septal dyskinesia.[63]

RV free wall thickness is assessed at end diastole on the subcostal view. The normal thickness is 3.3 ± 0.6 mm. In presence of features of RV systolic overload, significant thickening of RV free wall helps to differentiate between acute and subacute/chronic cor pulmonale.

Assessment of Valve Function

Advanced CCE permits comprehensive assessment of valve function. This may be an important component of assessment of a patient with cardiopulmonary failure. In the ICU, major valve failure may be the cause of the problem. Alternatively, presence of significant valve dysfunction may contribute to compromise of hemodynamics in the patient who has another life-threatening disorder. The comprehensive assessment of valvular function requires competence in detailed 2D assessment of the anatomy of the valve apparatus. This includes identification of valve vegetations and their mimics, as well as subtle findings as such as valve thickening and disruption of paravalvular structures. Complete evaluation of prosthetic valve anatomy and function requires a highly competent echocardiographer who has specific training in the subject. The intensivist with competence in advanced CCE may provide screening service but may wish to call for consultation in this situation. Generally speaking TEE is required for full evaluation of prosthetic valve function.

The evaluation of valve function starts with 2D assessment and color Doppler analysis. If significant valvular dysfunction is suspected, spectral Doppler analysis allows for quantification of both stenotic and regurtitation dysfunction. Color Doppler is frequently used in a qualitative fashion to grade the degree of valve regurgitation. Methods of quantitative assessment include use of continuity method, the proximal isovelocity surface area method and/or measurement of vena contracta. Identification of significant stenosis or regurgitation includes determination of the possible etiology such as endocarditis, rheumatic heart disease, subvalvular stenosis, congenital lesion, chordae/papillary muscle dysfunction, etc.

Examination of Cardiac Pressures

Advanced CCE has in common with standard cardiology echo the measurement of a wide variety of cardiac pressures. Using spectral Doppler, the intensivist can accurately measure such pressures as pulmonary artery systolic pressure, pulmonary artery diastolic pressure, left atrial pressure, left ventricular end diastolic pressure, etc. Generally, measurement of cardiac pressures with Doppler requires that there will be some degree of valvular regurgitation or stenosis.

Examination of Pericardial Space

The identification of pericardial effusion and qualitative identification of RV and/or RA compression is part of the skill set for basic CCE. Advanced CCE allows the intensivist to examine other features to identify more precisely findings that favor the presence of cardiac tamponade physiology. The use of M-mode permits accurate timing of wall movement of the RV and RA free wall in the PSS, subcostal, A4C views. Tamponade physiology is suggested by diastolic collapse of the RV free wall and/or systolic collapse of RA free wall. Tamponade physiology causes increased variation in MV and TV inflow velocities during respiratory cycling. Neither chamber compression nor variation of diastolic inflow is highly specific or sensitive for presence of tamponade and multiple confounders may be present in any given patient. The diagnosis of cardiac tamponade cannot be made by echo alone but rather is based on the clinical context.

Clinical Applications

It is beyond the scope of this discussion to review all aspects of advanced CCE that are relevant to critical care practice. What follows is a review of two important components of advanced CCE that are of particular interest to the intensivist but are not often included in the cardiologist performed echocardiography: identification of preload sensitivity and measurement of stroke volume and its derived indices.

When managing a patient with shock, a key question is whether an infusion of volume will result in improved Cardiac Output (CO)/Stroke Volume (SV); in other words, whether the patient is volume responsive (preload sensitive) or not. This is a key question for the clinician, as volume resuscitation may be of great benefit to a patient in shock but dangerous if given in the wrong circumstance. For example, a patient with acute cor pulmonale and massively dilated RV who is in shock should not receive volume resuscitation as further RV dilatation will restrict LV filling and result in worsening hemodynamic function. Inappropriate volume resuscitation has been associated with poor outcome.[64] There are several approaches to identifying whether the patient in shock is volume responsive. From a physiological point of view, the clinician seeks to determine whether the ventricles are on the steep portion of the Frank-Starling curve (where there will be SV augmentation with volume resuscitation) or whether they are on the flat portion (where volume infusion will not increase SV). In some clinical situations, the need for volume is clear from the history (e.g. history of blood loss, vomiting, diarrhea, etc.) and physical examination (e.g. poor skin turgor); in such cases, volume replacement is clearly warranted and can be undertaken without any further study.

A traditional approach to identify volume responsiveness is the static measurement of pressures. Both CVP and PAOP are now known to be poor predictors of volume responsiveness with the exception of the occasional patient who has very low cardiac filling pressures.[65,66] The end diastolic LV diameter and area are criteria that can be used for identification of volume responsiveness; an end-diastolic LV diameter of <25 mm and LV end diastolic area of <55 cm^2 are criteria used for diagnosis of hypovolemia.[55] End-systolic cavity obliteration is also a sensitive sign of hypovolemia and low preload.[67]

Advanced CCE permits the intensivist to make a variety of dynamic measurements that predict volume responsive shock with a high level of accuracy. Dynamic parameters to identify preload sensitivity are based on the premise that a change in preload will change the SV (or its surrogate CO) if the patient in situated on the ascending portion of the Frank-Starling curve. Based upon these parameters, the clinician may identify a patient as being preload sensitive before administering volume resuscitation. This avoids unnecessary and potentially harmful volume infusion.

Michard et al. showed that significant variations in pulse pressure in patients on mechanical ventilatory support identify preload responsiveness.[68] The patients had to be passive on mechanical ventilatory support and in sinus rhythm. An arterial PP variation between inhalation and exhalation of more than 12% is strongly predictive of preload sensitivity and far superior to common static pressure measurements. Pulse pressure in this situation is directly proportional to SV, so, that the observation of significant pulse pressure variation actually represents a significant variation of SV. Using this information, the advanced echocardiographer may examine directly the variation of SV in reference to cyclical variation of intrathoracic pressure in a patient on mechanical ventilation provided the patient is passive and in regular cardiac rhythm. The ventilator, by increasing intrathoracic pressure during inspiration, alters the preload of ventricles. Elevation of intrathoracic pressure during inspiration has the effect of reducing preload of the RV and augmenting the preload of the LV; during exhalation the effect is reversed. Therefore during mechanical ventilation, if SV that is measured by real time echo varies to a significant extent, there is a high probability that the patient will have augmentation of SV following volume infusion. If there is a lack of change in SV, the patient will not have augmentation of SV following volume infusion and therefore should not receive it.

As a surrogate of SV, Feissel et al. has used the VTI or flow velocity measured in the descending aorta.[69] This technique requires a transesophageal Doppler transducer and is less practical than measuring SV directly at LVOT by TTE. A variation of greater than 12% in SV, VTI or the flow velocity in this position indicates that the patient in shock will have improvement in SV and therefore CO following volume resuscitation.

The method of measuring SV variation with respiration has been shown to be useful only in patients who are passive on ventilatory support in normal rhythm and therefore has limited application. An alternative technique, which has been shown to be effective in spontaneously breathing patients, uses passive leg raising (PLR). Raising both legs in the supine patient to 45° results in rapid augmentation of venous return to the heart. With this simple maneuver, about 300 ml blood is delivered to the intrathoracic compartment constituting a major volume challenge which is completely reversible when legs are lowered. In performing the PLR maneuver, the intensivist measures the LVOT VTI, before and one minute after the maneuver. A PLR-induced increase in SV of >12% has been shown to be predictive of central hypovolemia; the same also predicted an increase in stroke volume of >15% in response to volume expansion.[70,71]

Measurement of SV variation during ventilator cycling or with PLR requires advanced CCE skills. It may be limited by poor image quality and takes time. These limitations have encouraged investigators to look for a simpler noninvasive surrogate of aortic VTI and LV SV volume. Brachial artery peak velocity ($Vpeak_{brach}$) is one such parameter that can be measured using Doppler. Monge Garcia et al. have studied respiratory variation of brachial artery peak velocity ($\Delta Vpeak_{brach}$) to predict fluid responsiveness in mechanically ventilated patients.[72] A $\Delta Vpeak_{brach}$ value >10% predicted fluid responsiveness, defined as ≥15% increase in SV index, after volume expansion with a sensitivity of 74% and a specificity of 95% (Fig. 144.22). Préau et al. has shown that PLR combined with measurement of change in femoral artery flow velocity is useful in identifying

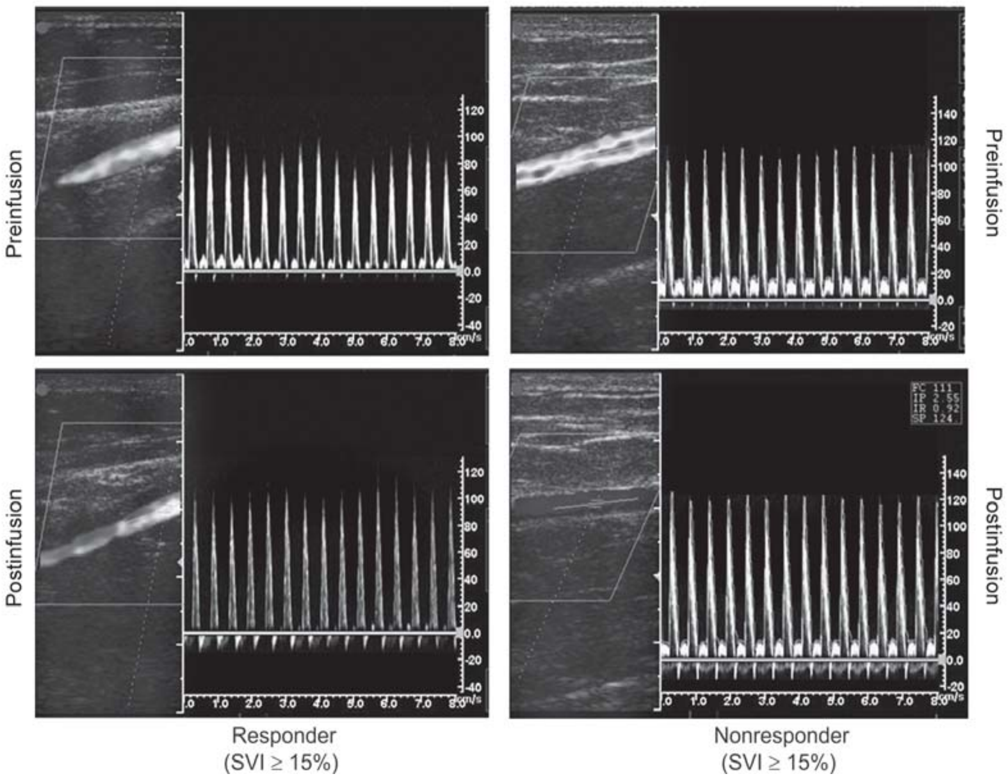


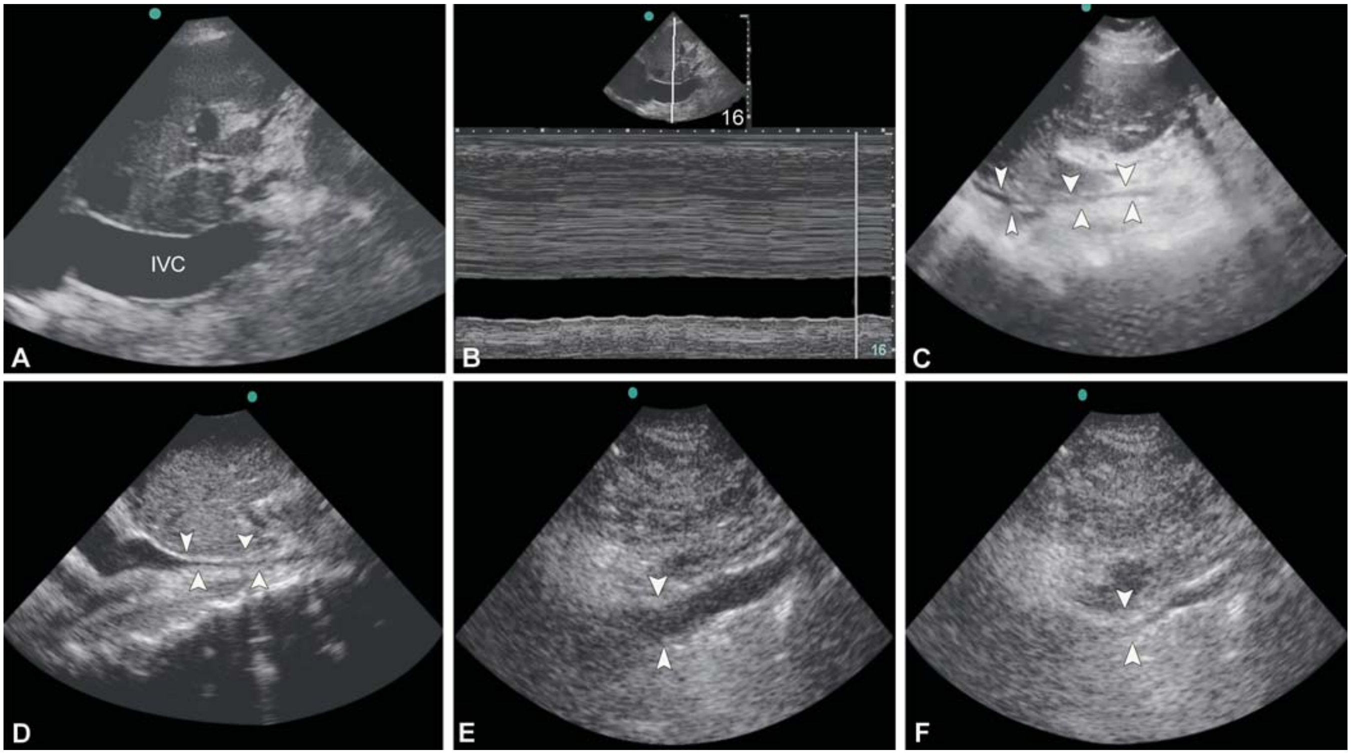
Fig. 144.22: Illustrative example of Doppler evaluation of brachial artery peak velocity variation in a responder patient and nonresponder patient. In the responder patient (left), volume expansion (VE) induced a decrease of brachial artery peak velocity variation ($\Delta Vpeak_{brach}$) by 15% (from 23% at baseline to 8% after VE). Response to volume challenge was evident in 27% increase in stroke volume index in this patient (not shown in the figure). In the nonresponder patient (right), volume expansion did not induce any significant change in $\Delta Vpeak_{brach}$ (from 9% to 9% after VE). Stroke volume index increased only 8% after VE in this patient (*Source*: Reproduced from Monge Garcia MI, Gil Cano A, Diaz Monrove JC. Brachial artery peak velocity variation to predict fluid responsiveness in mechanically ventilated patients. Crit Care. 2009; 13:R142. Original publisher BioMed Central Ltd. Image reproduced within the scope of open access policy of BioMed Central)

preload sensitivity in spontaneously breathing patients.[73] Conceptually, variation in brachial artery or femoral artery flow is similar to measurement of pulse pressure variation with an arterial catheter and has the major advantage that it can be performed easily by clinicians with minimal training in ultrasonography.[74]

Lung ultrasonography has a role in guiding volume resuscitation in critically ill patients with shock. If such a patient has A line predominance in anterior lung zone, Lichtenstein et al. have demonstrated that PAOP is ≤18 mm Hg and in high proportion of cases ≤13 mm Hg.[21] The presence of A line predominance does not indicate the need of volume resuscitation, but indicates that volume resuscitation can be given to the patient without concern that it will cause elevation of left sided filling pressures.

Assessment of IVC size and its variation with respiration have been used to predict fluid responsiveness (Figs 144.23A to F). The exact location used for measurement of IVC diameter varies in different reports.[75,76-78,79-82] IVC diameter can be measured 2–3 cm from the right atrium in a longitudinal view. For accurate measurements, an M-mode tracing, perpendicular to the IVC is used (Fig. 144.23B). An IVC diameter of <10 mm may predict a positive response to fluid infusion.[81] Cut-off values for the difference in IVC diameter between inspiration and expiration of 12% (using max-min/mean) and 18% (using max-min/min) for IVC have been reported to accurately separate responders from nonresponders.[78,81] The above measures have been validated only in patients who are passive on mechanical ventilation, in regular rhythm and who have normal RV function.

Variation of superior vena cava size coincident with ventilator cycling may also be used to predict preload sensitivity.[83] This requires use of TEE.



Figs 144.23A to F: IVC diameter and its variation help to predict fluid responsiveness. A. Large dilated IVC; B. M-mode examination of the IVC shows little respiratory variation of diameter; C and D. Very small or 'virtual' IVC (arrowheads) in a volume depleted patient; E and F: Significant respiratory variation of IVC diameter during mechanical ventilation in a volume depleted patient. E shows IVC diameter in inspiration and F shows IVC diameter in expiration

ABDOMINAL ULTRASOUND: SCOPE IN ICU

Abdominal ultrasonography has important, but limited applications in the ICU. It is neither necessary nor realistic for the intensivist to become fully trained in all aspects of abdominal ultrasonography. Abdominal ultrasonography is used to answer important specific questions; so, the modality is best deployed as a screening tool. As the intensivist uses ultrasonography for screening purposes, they must understand when to refer the patient for more complete study by a fully trained ultrasonographer. Abdominal ultrasonography has specific technical limitations and abdominal CT may be required for definitive imaging. However, abdominal CT requires transport of the unstable patient, has considerable radiation dose, and cannot be preformed repeatedly. Ultrasonography is performed quickly at the bedside and answers certain clinical questions with a high level of accuracy. Schachrer et al. reported the experience of 400 ultrasonography examinations in the ICU.[84] New pathological findings were detected in one third of cases with confirmation of known pathology in another third. In 80% of cases, no other imaging test had to be performed. We will review the aspects of abdominal ultrasonography that are relevant to the intensivist.

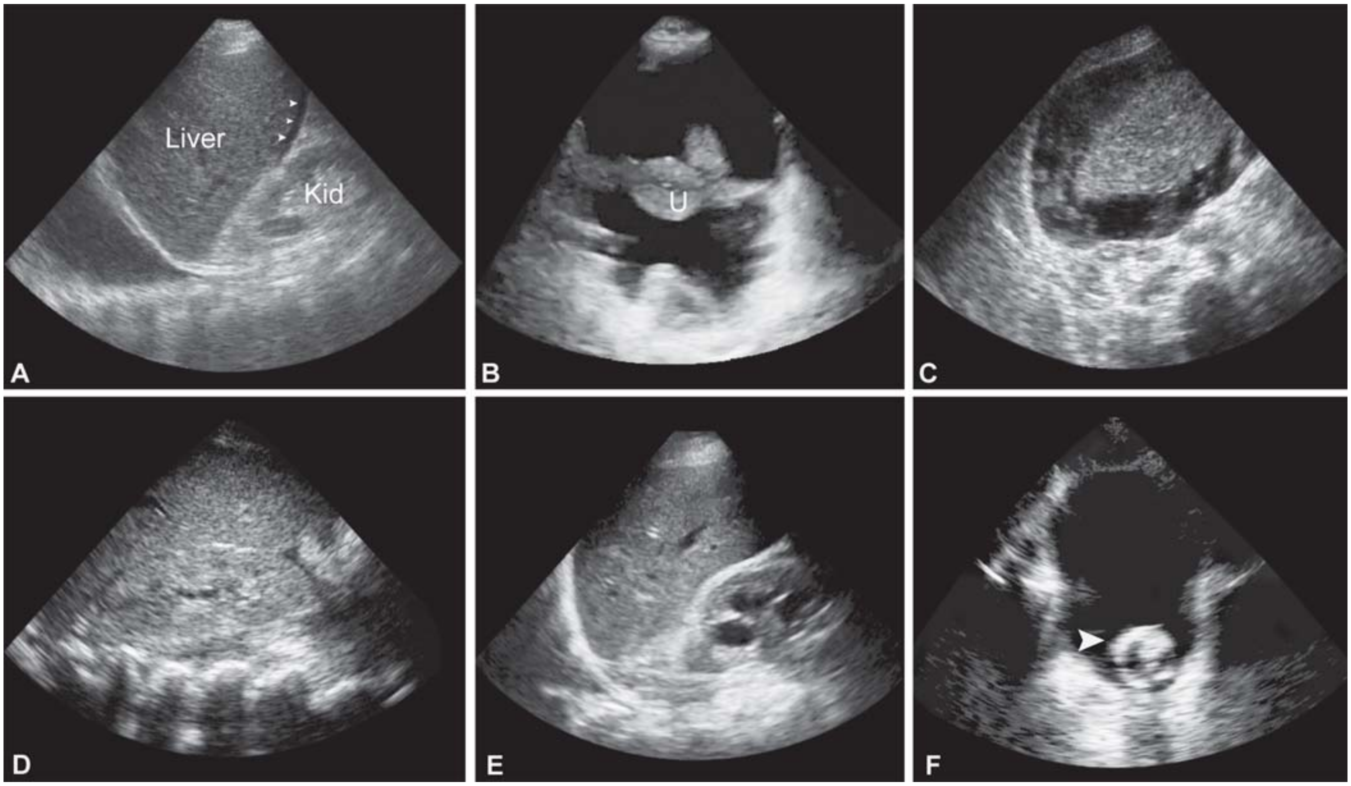
Equipment

Modern portable machines have full capability for abdominal ultrasonography. Doppler is not required for applications typical to the ICU. A curved array transducer that is specifically designed for abdominal ultrasonography is desirable, but adds significant cost to the purchase price of the ICU machine. A phased array cardiac transducer provides acceptable image quality while reducing acquisition cost.

Clinical Applications

Identification of Intraabdominal Fluid (Ascites)

A focused abdominal ultrasound examination performed by nonradiologists originated from the concept of Focused Assessment with Sonography for Trauma (FAST).[85,86] The FAST is a limited abdominal examination performed by emergency department physicians or trauma surgeons specifically to determine whether the



Figs 144.24A to F: Common applications of abdominal ultrasound in critical care unit. A. Minimal ascites in the hepatorenal recess (arrowheads). In a patient with blunt abdominal trauma, such findings are highly significant; B. Pelvic scan showing large amount of anechoic ascites (uterus is indicated by U); C. Complex ascites. Echogenic ascitic fluid may indicate exudative and often infected ascitic fluid; D. Small kidney with loss of corticomedullary differentiation in a patient with chronic renal failure; E. Hydronephrosis of right kidney; F. Distended urinary bladder in a patient with blocked Foley's catheter. The balloon of the catheter can be seen inside the distended bladder (arrowhead)

patient has intra-abdominal fluid collection. Ultrasonography can detect as little as 100 cc of free fluid in the peritoneal cavity.[87] The FAST protocol was developed to detect blood in patients with blunt abdominal trauma. It consists of three abdominal views; examination of the hepatorenal recess, the splenorenal recess and the rectovesical/rectovaginal region. A variation of the FAST examination includes a subxiphoid window for pericardial fluid and examination of the aorta. The FAST examination has reduced the need of diagnostic peritoneal lavage in trauma patients.[88]

The FAST exam has utility in the ICU, as the presence of ascites has implications for diagnosis and management. Identification of ascites requires the operator to perform the standard components of FAST exam. In addition, the intensivist should examine the paracolic gutter and subphrenic regions for a more comprehensive evaluation (Figs 144.24A and B). Ascites is hypoechoic, subtended by typical anatomic boundaries (intra-abdominal organs) and has typical dynamic findings. Unlike pleural fluid, it undergoes shape change with force application by the transducer on the abdominal wall. Mimickers of ascites include fluid-filled intestine, distended bladder and distended gall bladder. Anechoic ascites (Fig. 144.24B) is generally transudative while exudative ascites is often hyperechoic. Ultrasound cannot differentiate between fresh blood and ascitic fluid as both are usually anechoic. The presence of fluid with echogenicity or internal loculations/septations usually indicates an exudate and suggests need for further investigation (Fig. 144.24C). Identification of ascites is an important ultrasound finding in itself but always has to be interpreted within the clinical context. A patient with cirrhosis and a large amount of anechoic fluid may not require further diagnostic evaluation. Intra-abdominal fluid with increased echogenicity and loculations, combined with signs of sepsis or findings of acute abdominal presentation, suggests peritonitis with hollow viscous perforation or a neglected hemoperitoneum. The identification of ascites mandates a decision whether to perform paracentesis as part of a diagnostic or therapeutic response.

Evaluation of Kidneys: Both the kidneys can be readily imaged at the bedside in the ICU. The optimal position for kidney imaging is with the patient in lateral decubitus position. This is usually not feasible in the critically ill patient because of hemodynamic and respiratory instability. Given this limitation, the left kidney may be difficult to image in the supine position. The operator may need to hold the transducer placed close to posterior axillary line. The examination starts with the longitudinal axis view of the kidneys followed by transverse axis imaging. A single tomographic plane is not sufficient and the intensivist should scan through the organs in multiple tomographic planes in order to develop a three dimensional construct of the kidneys. The longitudinal length, parenchymal thickness, parenchymal echogenicity and corticomedullary differentiation are determined. Normal longitudinal length is 9–12 cm; normal cortical thickness is between 1.5–1.8 cm. Normal renal cortex is hypoechoic or isoechoic compared to the liver or spleen. A visible distinction between the cortex and the medulla is normal. Renal parenchyma surrounds the renal sinus which contains the pelvis, the calyces and major branches of renal vasculature. It appears hyperechoic because of the presence of fatty tissue.

Ultrasonography is the preferred imaging modality for patients with acute renal failure in the ICU. A primary objective of the examination is to rule out obstructive uropathy as the cause of renal failure. A dilated pelvicalyceal system indicates obstructive uropathy and can be diagnosed with high level of sensitivity (Fig. 144.24E). The severity of the obstruction may be classified and its chronicity can be estimated by the morphologic characteristics of the dilatation. Stones within the collecting system may be observed with accompanying acoustic shadow artifact. There may be pitfalls in the examination for hydronephrosis. A patient with significant coexistent intrinsic renal parenchymal disease, who also has a urinary obstruction, may not develop hydronephosis due to lack of urine production. Rarely, infiltrative diseases of the kidney may restrict pelvicalyceal dilatation in the obstructed kidney. Acute obstruction will not result in discernible hydronephrosis immediately and the finding may be delayed for many hours.

Acute kidney injury with renal failure results in normal or enlarged kidney size. Chronic renal disease causes increased cortical echogenicity and reduction in cortical thickness (Fig. 144.24 D).

A problem facing intensivists in performing renal ultrasonography is the discovery of an abnormality that is beyond their level of competence. Renal cysts, both simple and complicated, unusual variants of normal anatomy or malignancy, may present as ambiguous findings on ultrasound examination when the intensivists' primary concern is to rule out obstruction. In this case, the screening ultrasonographer has an obligation to call for a definitive examination by a fully trained ultrasonographer or by other diagnostic modalities like CT scan.

Evaluation of the Urinary Bladder

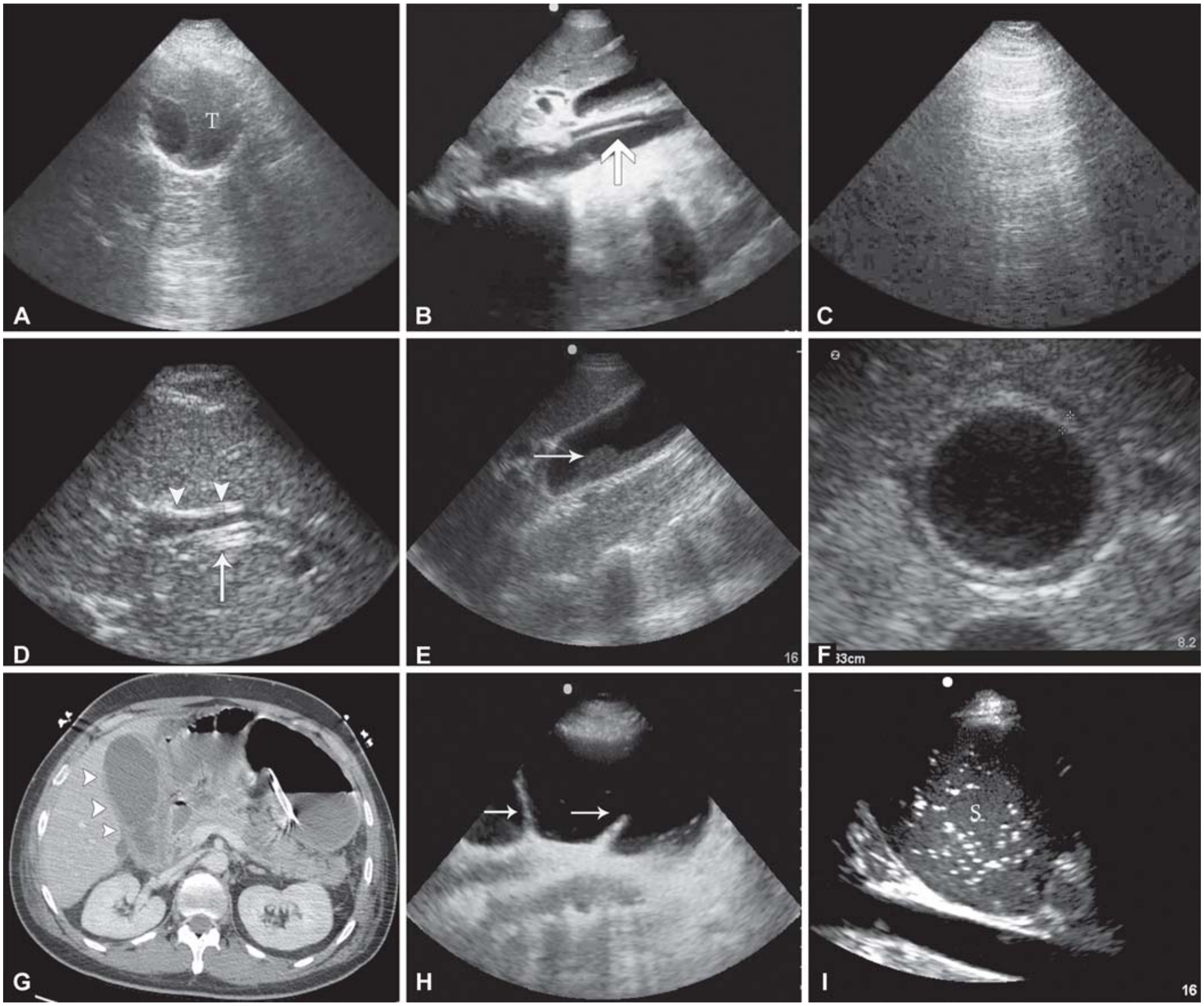
The urinary bladder is readily imaged using a transverse and longitudinal axis approach at the suprapubic area. The distended bladder appears as a large anechoic space in the appropriate anatomic location (Fig. 144.24 F). A primary indication for bladder ultrasonography is in the evaluation of anuria. This often results from blockage or misplacement of a urinary catheter. In the case of a blocked urinary catheter, the fluid filled catheter balloon is readily visualized in the distended bladder (Fig. 144.24F). Flushing or manipulating the catheter will result in renewed urine flow in these cases. The examination of the urinary bladder should always be performed in conjunction with the kidneys. In imaging the urinary bladder, the intensivist must be prepared for the possibility of ambiguous ultrasonography findings, such as bladder tumor. Just as is the case with the kidneys, this requires definitive imaging by a fully trained ultrasonographer.

Evaluation of Abdominal Aorta

The Abdominal aorta may be imaged in both longitudinal and transverse axis in order to determine whether an aortic aneurysm or other major pathology exists (Figs 144.25A and B). An enlarged aorta (>3 cm, measured from outside wall to outside wall) with luminal thrombus and irregularity suggests an aortic aneurysm.

Evaluation for Pneumoperitoneum

Ultrasonography has been described as a more sensitive modality than plain radiography for the diagnosis of pneumoperitoneum with a high sensitivity, specificity and positive predictive value.[89,90] To detect pneumoperitoneum, the epigastric area and right upper quadrant are scanned in the supine patient. Sonographically, air will appear as echogenic areas with posterior reverberation artifacts.[91,92] Pneumoperitoneum also causes enhancement of the peritoneal stripe.[93] Presence of air bubbles within ascitic fluid will also point to a diagnosis of pneumoperitoneum.[92] A lack of peritoneal



Figs 144.25A to I: Other applications of abdominal ultrasound. A. Abdominal aortic aneurysm with partial thrombosis of the lumen (T); B. Aortic dissection, the intimal flap can be seen in this longitudinal view of the aorta (arrow); C. A case of pneumoperitoneum. Note that no abdominal organ could be visualized in this upper abdominal scan. Exclusive air pattern, as seen in this photo, can raise the suspicion of pneumoperitoneum in the right clinical scenario; D. Dilated intrahepatic biliary duct in a case of obstructive jaundice (arrowheads). Note that the accompanying normal looking portal vein branch (arrow); E. Gallbladder sludge (arrow); F. Dilated gallbladder with thickened wall in a case of acalculous cholecystitis; G. Abdominal CT scan of the patient in F shows large dilated gallbladder (arrowheads); H. Dilated loop of colon. Note the colonic haustra (arrow); I. Dilated fluid filled stomach seen in a preintubation scan (S).

sliding also indicates the possibility of pneumoperitoneum. Massive pneumoperitoneum may make it impossible to visualize any abdominal organ, indirectly suggesting the diagnosis (Fig. 144.25C).

Evaluation of Other Abdominal Organ Systems

Ultrasonography may be used to assess all organ systems within the abdomen. However, the intensivist needs to be aware that developing comprehensive skill in all aspects of abdominal ultrasonography requires dedicated and time consuming training. The authors suggest that this is not necessary for routine critical care function. The intensivists may appropriately limit abdominal ultrasonography to a specific targeted screening approach.

The liver is imaged in longitudinal and transverse planes. If sepsis is suspected, assessment of liver can give valuable clues like presence of single or multiple hypoechoic lesions may be indicative of abscesses. For suspected biliary disease, ultrasonography is the initial investigation of choice. Intrahepatic biliary ductal dilatation is the hallmark of obstructive biliary pathology (Fig. 144.25 D). In patients with jaundice, abnormal liver function tests, sepsis of unknown etiology or new fever, biliary ductal dilatation assumes importance. The gallbladder should be imaged in multiple tomographic planes to look for stone and biliary sludge (Fig. 144.25E). Features of acute cholecystitis include gallbladder wall thickening, pericholecystic fluid and sonographic elicitation of Murphy's sign. In the absence of stone, the above signs along with an enlarged gallbladder indicate a possible diagnosis of acalculous cholecystitis[94] (Fig. 144.25F and G). Evidence of gallbladder stone, sludge and biliary obstruction has important implications in a patient admitted with pancreatitis.

Ultrasonography is useful for evaluation of the gastrointestinal tract; for example, typical finding of enteritis include thickened bowel wall (>4 mm) and echoic bowel content. Toxic megacolon may be identified by imaging fluid filled ascending colon greater than 10 cm in diameter (Fig. 144.25 H). The presence of bowel peristalsis by ultrasonography rules out ischemic bowel or peritonitis with a high level of certainty.

The pancreas is frequently difficult to image with ultrasonography in the poorly prepared critically ill patient. Identification of retroperitoneal pathology, such as retroperitoneal LN or hematoma, is also challenging to anyone other than a fully trained ultrasonographer. The spleen may be readily imaged for such abnormalities as abscess but much splenic pathology is not readily visible to a screening ultrasonographer, e.g. splenic hematoma may be isoechoic to adjacent normal splenic parenchyma.

ULTRASOUND ASSESSMENT OF VENOUS THROMBOEMBOLISM

There are several circumstances in which an intensivist may wish to search for Deep Vein Thrombosis (DVT). These include physical examination findings that suggest DVT or an acute deterioration of respiratory or circulatory status where DVT is sought as a surrogate marker for PE. Deep vein thrombosis may be observed as an incidental finding while examining veins for cannulation. When the intensivists decide to obtain a study for DVT, they have two choices, either they may call for a study being performed by a vascular technician/radiologist or they may choose to perform the study themselves at point-of-care. Waiting for a radiology performed study introduces a dangerous delay in the process of diagnosis and management of DVT. Intensivists and other nonradiologists may perform DVT study with the same level of accuracy as radiology department based services.[95,96] The study technique is easy to learn and has immediate bedside application. The intensivist who is skilled at DVT study can obtain immediate diagnosis very rapidly at bedside.

Equipment

Modern portable bedside ultrasound machines, equipped with a high frequency linear vascular transducer, are suitable to detect DVT. Doppler capability, while desirable, is not a requirement in order to perform an accurate study; DVT can be diagnosed using 2-D compression ultrasonography alone.[97,98]

Examination Protocol

For lower extremity examination, if possible, the patient should be placed in reverse Trendelenberg position with the leg externally rotated and the knee slightly flexed. The examination should be bilateral and comparative. The examination starts at the level of the inguinal ligament (femoral crease) where the external iliac vein becomes the common femoral vein. Careful consideration should be given to the area where the great saphenous vein drains into the common femoral vein. The common femoral vein is scanned at multiple points up to its bifurcation into the superficial femoral vein and the deep femoral veins. The superficial vein is examined at multiple points until it enters the adductor canal. The popliteal vein is assessed where it runs behind the knee joint, in the popliteal fossa. In the upper extremity and neck vein examination, the veins are imaged at regular intervals in transverse plane along their course to avoid missing a clot.[99,100] While compressions on transverse scan are used for internal jugular, axillary and brachial veins, the subclavian vein cannot be compressed effectively so that Doppler study may be necessary. After obtaining a satisfactory picture on a transverse scan, the transducer can be rotated 90° to get a longitudinal image of the vessel, suitable for rapid survey of veins and assessment of extent and nature of a thrombus when seen.

At each site of examination, the vein is identified by its location, by the company of an artery and on occasions by visualizing valve movement within the vein. Before compression, the vein is examined for visible clot, seen as distinct echogenic material that can be mobile and/or adherent to the vessel wall. Visible clot is diagnostic of

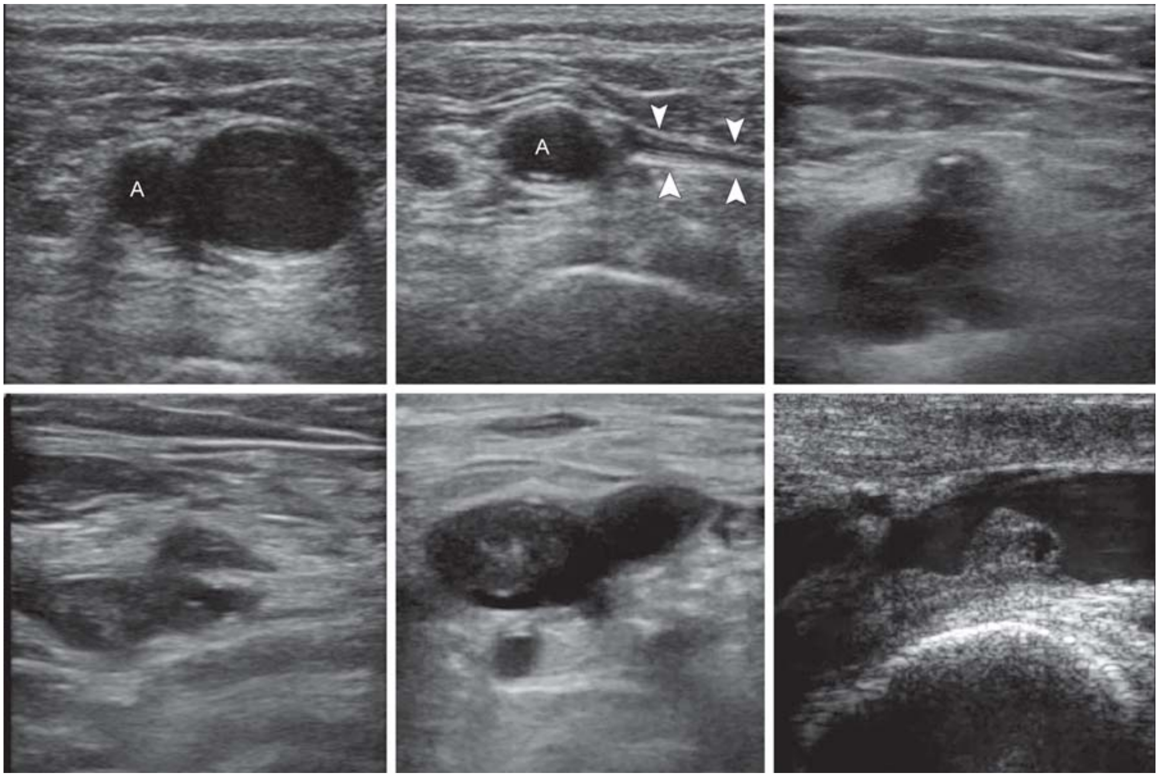


Fig. 144.26: Ultrasonography in the diagnosis of DVT

Upper left panel: A normal common femoral vein before compression (A= Arterial lumen). Upper right panel: A normal common femoral vein after compression. Note the complete obliteration of venous lumen on application of compression (arrowheads).
Upper middle panel: Common femoral vein DVT before compression.
Middle panel, right: Common femoral vein DVT after compression. Note that the lumen cannot be obliterated. The thrombus is also visible as echogenic material within the venous lumen after compression.
Lower panel, left: Common femoral vein thrombosis. The thrombus is visible within the venous lumen. Compression should not be applied if the thrombus is already visible. Lower middle panel: A longitudinal view of the common femoral vein shows the clot

DVT; (Fig. 144.26, lower panel); no compression maneuver is required in this circumstance. If no clot is visualized, the examiner applies sufficient pressure to deform the vein. A normal vein is compressible with mild pressure (0.5–1.0 kg/cm^2). Complete compressibility is defined as apposition of walls with effacement of lumen (Fig. 144.26, upper panel) Complete compressibility excludes DVT at the site of examination. Incomplete compressibility of vein indicates presence of DVT and is the only validated diagnostic criterion for DVT. Abnormal compression ultrasonography (Fig. 144.26, middle panel) has high sensitivity and specificity for diagnosis of femoropopliteal DVT.[101,102]

Clinical Issues

Deep vein thrombosis as a surrogate marker for PE: Compression ultrasonography shows a DVT in 30–50% of patients with PE. Finding a proximal DVT in patients suspected of PE is sufficient to start anticoagulion treatment without further testing.[103,104]

Importance/frequency of upper extremity DVT: About 10% of all cases of upper extremity DVT have been reported to result in pulmonary embolism.[105] Certain groups of patients are more prone to develop upper extremity DVT such as cancer patients with central venous port systems,[106] patients with peripherally inserted central venous catheters[107] and patients with central venous catheters (both internal jugular, axillary/subclavian).[108,109] Few studies have examined ultrasonography for the diagnosis of upper extremity DVT. These studies are of inferior methodology. In the absence of a good alternative test in ICU patients, compression ultrasonography remains a practical choice for diagnosis of upper extremity DVT.[110]

Importance of studying calf veins: Ultrasound study of calf veins for DVT requires operator experience, significant additional time and difficulties in positioning the patient. The accuracy of ultrasonography in the diagnosis of calf DVT has been reported to be lower than in the diagnosis of proximal DVT.[111] Our opinion is that it is not realistic for intensivists to develop this skill level. One strategy is for the intensivist to repeat the DVT study of the popliteal and femoral veins serially at 24–48 hours in those patients who are very high risk for DVT.

DVT proximal to femoral veins: In non-trauma patients, isolated iliac vein or IVC thrombosis is very uncommon, but is always a concern especially in cases of previous femoral vein cannulation.[112] These veins may not readily be imaged with ultrasonography except in patients with slender body habitus. In trauma patients, as well as in patients with pelvic disorders and obstetric patients, isolated pelvic vein thrombosis may need to be explored with use of Doppler or other imaging modalities.

Limitations

1. The examiner must have adequate training and familiarity with the venous anatomy.
2. Patients who are obese, edematous, or who have wounds or dressings may have inadequate image quality.
3. The identification of a thrombus does not indicate its age. There are criteria that can be used to identify recent or old (presumably) inactive thrombi. However, these are not completely reliable.
4. The subclavian vein may not be compressible particularly in obese or muscular individuals. Unless an echogenic clot is visualized within the subclavian vein, lack of compressibility does not necessarily indicate the presence of an isoechoic clot within the subclavian vein.

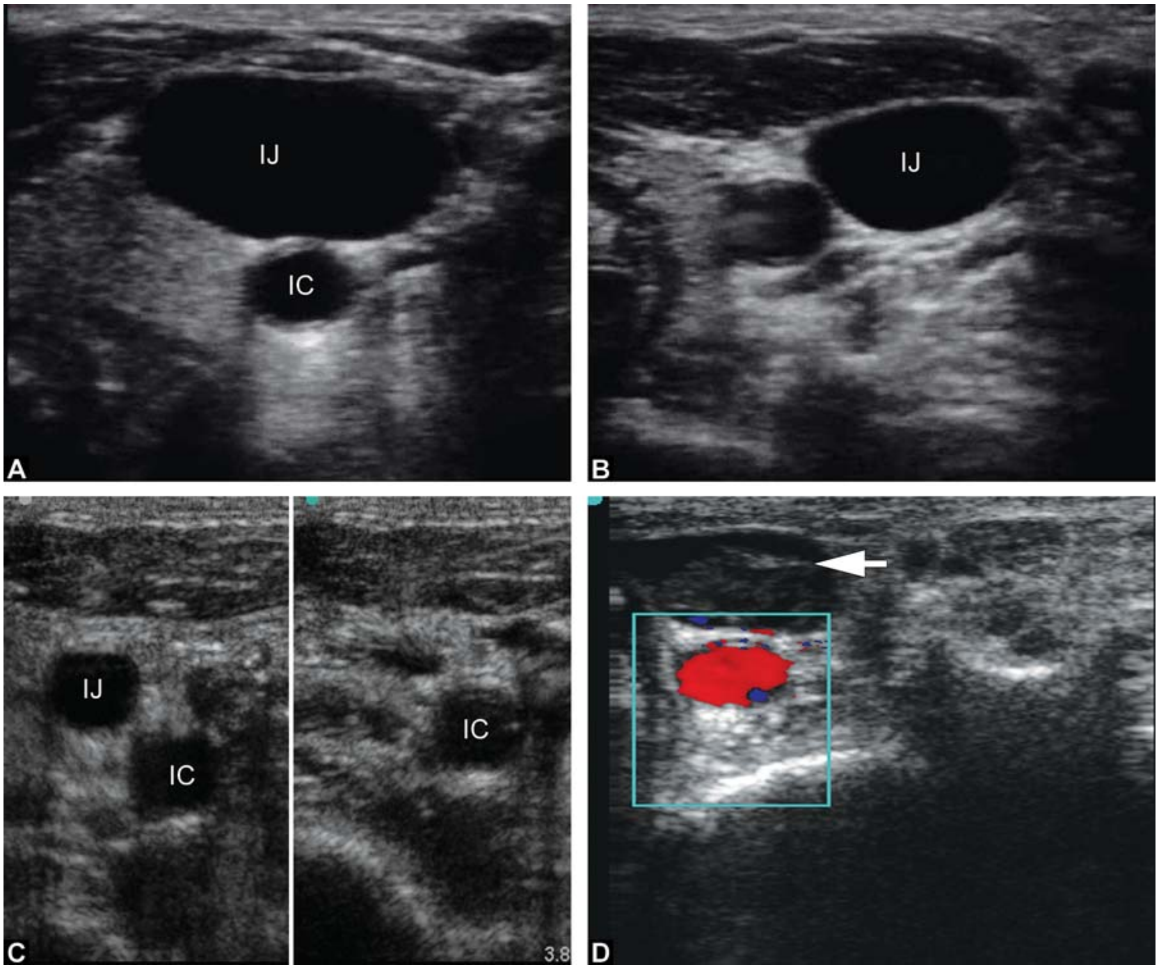
ULTRASOUND GUIDANCE FOR PROCEDURES

Ultrasound Guided Vascular Access

Ultrasonography may be used to guide vascular access in the ICU. Several studies and two meta-analyses have shown the benefits of ultrasound guidance in central venous catheter placement.[113-116] Ultrasound guidance for central venous access is recommended by national quality organizations in the United States and the United Kingdom.[117,118] It improves success and reduces complication rate for central venous access and can be used for arterial and peripheral vascular access. In this section, we will discuss the general principles for performing vascular access under ultrasound guidance. This discussion assumes that the reader has full knowledge of the mechanical aspects of vascular access such as site preparation and physical manipulation of needle, dilator and cannula. For detailed site specific discussion, the reader is referred to comprehensive review articles.[119-121]

Advantages of Using Ultrasound to Guide Vascular Access

- *Localization of vessels:* Following identification of the anatomical landmarks, prepuncture ultrasound examination of the proposed site helps in the identification of the target vessel and its relationship with surrounding structures (e.g. carotid artery, thyroid gland and trachea in case of internal jugular vein cannulation). The ultrasound images are used to identify anatomical variations and to fine tune the selection of the puncture site (Fig. 144.27A and B).
- *Assessment of suitability for vascular cannulation:* Examination of the target vessel allows for determination that the vessel is suitable for line placement. Ultrasonography permits visualization of features that prohibit vascular access which cannot be identified by simple visual examination. There may be marked difference in vessel caliber (Fig. 144.27C)[122,123] and variability of vessel position relative to the adjacent artery in approximately 5% of the general population.[124,125] A partial or complete thrombosis of the vessel, a vascular stenosis or a perivascular hematoma, can only be identified with ultrasonography (Fig. 144.27C). Hypovolemia may reduce the size of target vessel and marked respiratory efforts may cause variability of vascular size (Fig. 144.27D), making it impossible to cannulate the internal jugular and subclavian veins. These cannot be identified without ultrasonography. Use of ultrasound, therefore, reduces the chances of failure associated with blind technique.
- *Reduction of procedure time:* Ultrasound guidance of central venous access reduces the number of attempts required and improves first-pass success rate, improving the safety and comfort of the patient.
- *Use in arterial puncture and peripheral venous access:* Ultrasonography is useful in guiding all forms of arterial access and is particularly useful in patients who are hypovolemic or hypotensive, or who develop vasospasm secondary to multiple cannulation



Figs 144.27A to D: Ultrasonography helps in selection of a suitable vessel for cannulation: A. Internal jugular vein (IJ) is located directly in front of the internal carotid artery (IC). Attempted cannulation at this site will carry high risk of inadvertent puncture of the carotid artery. B. As the internal jugular vein is imaged at different points along its course in the neck, at this location the vein lies outside the carotid artery. Attempted venous puncture will not have much risk of accidental carotid artery puncture. C. Small left IJ with near complete obliteration of the lumen during spontaneous breathing. Cannulation of this vessel will be very difficult. D. IJ thrombus (arrow). Note that the thrombosed IJ does not show any color flow signal while the carotid artery does

attempts.[126,127] The diameter of the radial artery is only approximately 3 mm,[128] so that blind line insertion at this site may be challenging. Ultrasound guidance improves success rate of peripheral venous access.[129,130]

- *Evaluation of potential complication:* Ultrasonography may be used to immediately identify procedural complications of vascular access such as hematoma or pneumothorax. Ultrasonography may be used to confirm guidewire placement prior to dilatation. This is useful to avoid inadvertent arterial injury during central venous access. The correct placement of the guide wire and catheter can be checked immediately at bedside (Fig. 144.28, right upper panel and lower panel).

Equipment Requirement

- Vascular access is generally performed by using a high frequency (7–10 MHz) linear transducer. The higher frequency provides excellent resolution with the trade off that penetration is limited. Fortunately, barring massive obesity, vessels commonly accessed for cannulation, are superficial.
- In performing real-time ultrasound guidance of vascular access, the use of a purpose designed sterile probe cover is mandatory. An attempt to jerry-rig a sterile transducer cover using a glove, is inappropriate and violates basic principles of central line sterile precautions.

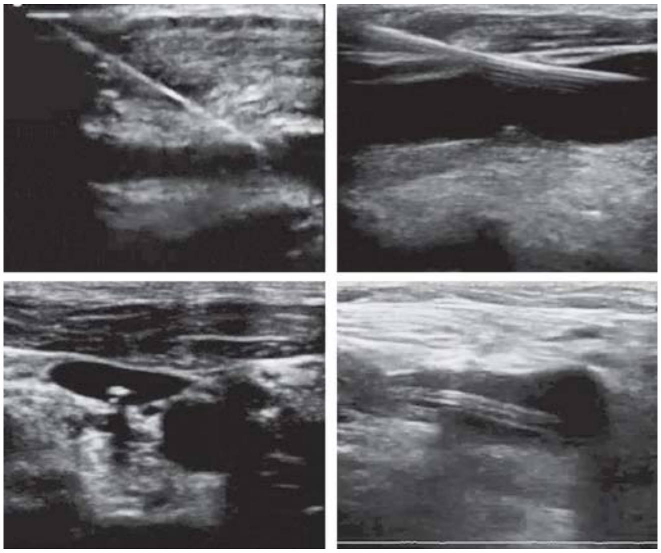


Fig. 144.28: Vascular cannulation under ultrasound guidance

Left upper panel: Subclavian vein is punctured under ultrasound guidance. The vein is visualized in the long axis and the needle trajectory is under direct visual control.

Right upper panel: Correct placement of guide wire is confirmed before dilatation.

Left lower panel: Correct placement of catheter can easily be confirmed using ultrasound. A cross sectional view of IJ shows the catheter inside the vascular lumen.

Right lower panel: The catheter can also be visualized inside the vein in longitudinal view.

General Principles of Ultrasound Guidance of Vascular Access

- In addition to full mastery of machine control and transducer manipulation, the operator must place the machine in such a way that the screen is easily visible without much movement on the part of the operator. This might require rearrangement of equipment and bed position in a crowded work environment. The operator should avoid a situation where the screen is not easily visible.
- The operator must have knowledge of local anatomy. With the understanding of the anatomy, a key objective of using ultrasonography is to unequivocally identify the target and to differentiate veins from arteries. A vein is identified initially by its typical location and relationship with the surrounding structures. Once identified, the operator must confirm that the vascular structure is in fact a vein. The vein is easily compressible whereas the adjacent artery is not. The vein has respirophasic change of caliber and may have mobile venous valves that are visible with ultrasonography. Performance of Valsalva maneuver increases caliber of the vein but has no effect on caliber of the artery. The artery is pulsatile. In general Doppler analysis is not required to differentiate veins from arteries with the exception of subclavian position. In the subclavian position, particularly in muscular or obese individuals, compression of subclavian vein may be difficult; venous valve and respirophasic change may also be difficult to recognize. Doppler may be used to identify subclavian vein.
- Before performing subclavian or internal jugular venous access, the contralateral vein should be examined in order to identify the best site in terms of vessel position, size and condition. In addition, the operator should document the presence of sliding lung bilaterally before starting the procedure in order to rule out pneumothorax.
- Following insertion of the guide wire and before dilatation of the vessel, the operator should always document that the guide wire is in the vein (Fig. 144.28, right upper panel). Inadvertent placement of a guide wire into the adjacent artery is of no clinical consequence as the vessel defect is small. The wire may be removed with local vascular compression to follow. However, inadvertent dilatation of the artery due to unrecognized wire insertion leaves a much larger defect and constitutes a major complication.
- Following the procedure, the operator should document sliding lung. Its presence rules out procedural pneumothorax. Loss of lung sliding following internal jugular or subclavian venous access, where it was known to be present before the procedure, is a strong evidence of procedure related pneumothorax.

Technique for Vascular Cannulation

There are two general approaches to ultrasound guidance for vascular access, the short axis and the long axis approach.

Using the short axis approach, the transducer is oriented such that the image shows a cross-sectional view of the vessel. The needle is inserted at a point away from the transducer and angled towards the center of the image. Some operators track the needle tip as it moves forward by moving the transducer along with the needle in synchrony, thereby guiding the needle tip real-time in the vessel. The alternative is to hold the transducer in a stable position and estimate the angle and depth in which the needle should be inserted in order that the needle tip intersect the scanning plane in the lumen (center) of the target vessel. Neither method is known to be superior to the other and should be used according to operator preference.

Using the long axis approach, the transducer is oriented such that the image shows a longitudinal image of the vessel. The needle is introduced at the side of the transducer and advanced so that the entire needle is visualized throughout the insertion process (Fig. 144.28, left upper panel).

At internal jugular and femoral insertion sites, both short axis and long axis approaches are effective. In the authors' experience, scanning the vessel in transverse axis is the preferred method for accessing femoral and IJ vein. Most operators prefer to use this approach. Final choice should be predicated to operator experience.

Specific Issues Related to Access Site

Internal jugular vein (IJV): In the authors' experience, most operators image the jugular vein in its transverse axis, although some prefer a longitudinal approach.[131] In using ultrasound for guidance of IJV access, it becomes clear that the landmark based blind posterior approach places the carotid artery deep to the IJ vein. This risks inadvertent puncture of the carotid artery as the needle can easily pass through the IJV. The anterior approach is favored when using ultrasound guidance as a point of puncture can be chosen, so that the vein is positioned lateral to the artery. This underlines one major advantage of using ultrasound for vascular access; the angle of needle insertion is determined by the image rather than relying on blind landmark method.

Subclavian vein: Traditional landmark based technique requires the operator to use the clavicle as the definitive landmark for the procedure. When using the ultrasound for subclavian vein access, the operator should choose a much more lateral position for insertion than is used for blind technique.[132] Using ultrasound, the vein may be punctured near the point where the axillary vein becomes the subclavian vein (before it crosses the outer border of first rib). The vein in this location is more caudal and superficial. Several advantages of this ultrasound guided (more lateral) axillary vein puncture over traditional blind subclavian puncture have been suggested which are as follows:

a. There is a reduction of accidental arterial punctures.
b. There is less discomfort, as there is no contact of the needle with the periosteum of the clavicle.
c. The catheter enters the vein well before the vein passes the narrow space between first rib and clavicle, so there is a less risk of pinching and transection of the catheter.[133]
d. With ultrasound guidance, the vein can be entered close to the clavicle; here we have the attachment of the vein to the clavicle preventing the anterior wall from collapsing during puncture.[120]
e. After the guide wire is placed, the distal internal jugular vein can be examined; if the wire is seen into IJ vein, it can be repositioned under ultrasound guidance.[134]

Subclavian venous access under ultrasound guidance is best performed with the vessel imaged in longitudinal axis (Fig. 144.28, left upper panel). In this way, the needle can be visualized in its entirety throughout the insertion. This level of needle control is important as the pleural surface is close to posterior vessel wall.

Femoral vein: The femoral vein is usually accessed using transverse imaging axis. If the image plane is below the inguinal ligament, the vein will be positioned deep to the artery. This is inappropriate position for access, as there is high risk for arterial injury. The transducer position should be adjusted such that the common femoral vein is imaged medial to the artery. Slight external rotation of the leg helps to bring the vessels side by side.

Arterial catheterization: Ultrasound guided radial artery cannulation has been shown to have a higher success rate than blind technique.[127] Radial artery cannulation may be difficult at the standard wrist site due to vasospasm, hematoma formation, or intimal dissection after repeated attempts. In these cases, successful cannulation of the radial artery at a more proximal (mid forearm) location, deep to the brachioradialis muscle, has been reported using real-time ultrasonography.[135] Femoral artery cannulation is similar to central venous line placement at this site in terms of ultrasound technique.[136] Ultrasound may identify significant atheromata at the femoral artery precluding that site.

Peripheral venous cannulation: For those patients who have difficult peripheral venous access, ultrasound improves the success rate, reduces the number of unsuccessful attempts, requires less time and improves patient satisfaction.[129,130]

ULTRASOUND GUIDANCE OF THORACENTESIS

Ultrasonography may be used to guide thoracentesis with improved success and reduced pneumothorax rate.[137] Ultrasound guidance for thoracentesis is important in the ICU as standard supine chest radiographs have severe limitations in identification of a safe site for needle insertion. In the patient on mechanical ventilatory support, a pneumothorax resulting from a thoracentesis effort may have catastrophic complications. Several studies have addressed the safety of US for guidance of thoracentesis in mechanically ventilated patients and have shown that the procedure may be performed with a low complication rate.[32,138]

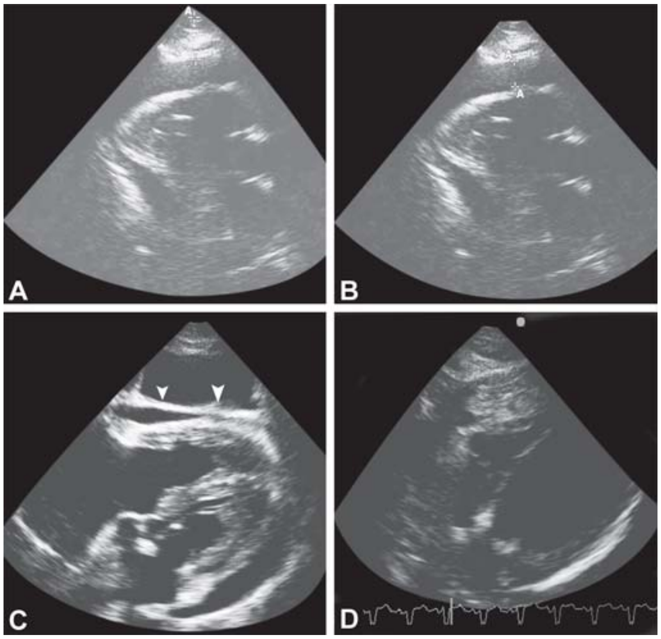
The purpose of ultrasonography for procedural guidance of thoracentesis is to identify a safe site, angle and depth for needle penetration that avoids injury to lung, subdiaphragmatic organs and the heart. The critically ill patient is often supine, so by gravitational effect the pleural fluid takes a dependent posterior position in the thorax (unless loculated). The scanning plane should be in the longitudinal axis in the posterior to mid-axillary line. The transducer is angled and/or moved to find an anechoic space that is subtended by typical anatomical boundaries and that has typical dynamic findings, consistent with a pleural effusion. Before any consideration of needle insertion, the examiner must make unequivocal identification of the diaphragm. The neophyte ultrasonograpgher may misidentify the hepatorenal or splenorenal space, which is curvilinear as the diaphragm. This is a serious error, as this could lead to laceration of these organs. There should be at least 10 mm space between the inside of chest wall and the visceral pleural surface.[32,138] Once a suitable site is identified and marked, the depth of the penetration is measured from a frozen ultrasound image. Thoracentesis should be performed promptly after ultrasound marking without any patient movement to avoid shifting of fluid from the intended aspiration site. The syringe and the needle assembly should be introduced in the same angle in which the transducer was held while determining the best access site. This is best accomplished when the operator performs the procedure immediately following the examination. Following the procedure, the operator should check for pneumothorax by examining for lung sliding.[139] Ultrasound guidance of needle insertion may be used for simple thoracentesis or for insertion of pleural drainage system of any size.

An important pitfall is that firm pressure by the probe on the skin, particularly in an edematous patient, may indent the skin at the site of examination. This leads to the underestimation of the depth at which fluid will be reached when aspiration is attempted. The operator should be able to recognize this problem and needs to insert the needle more than the measured distance.

ULTRASOUND GUIDANCE OF PERICARDIOCENTESIS

Echocardiography guided pericardiocentesis is the current standard of care for drainage of pericardial effusion. The traditional subxiphoid approach to pericardiocentesis, with or without fluoroscopic guidance should be replaced in favor of ultrasound guided pericardiocentesis.[140] In a report of 1127 consecutive echocardiography guided pericardiocenteses, success was achieved in 97% cases, including 89% cases, where fluid could be obtained with a single needle pass. Major complications (chamber laceration or injury to an intercostal vessel necessitating surgery, pneumothoraces requiring chest tube placement, ventricular tachycardia and bacteremia) were reported in 1.2% cases with death of one patient.[141] Similar success rate has been reported in another large series.[142]

To perform pericardiocentesis under ultrasound guidance, the examiner scans using multiple windows in order to determine a safe site, angle and depth of needle penetration (Figs 144.29A and B). The ideal entry site is the point where the largest collection of fluid can be reached by the shortest distance from the skin following a straight trajectory and avoiding any vital structure.[140] Under ultrasound guidance, the left anterior chest wall is the entry site of the needle in the majority of the cases. The subxiphoid approach is often not indicated as the effusion is not of sufficient size or the liver blocks safe needle insertion. The patient's body position may be shifted in order to redistribute the pericardial fluid for better access. At least 10 mm of fluid depth is required to perform safe pericardiocentesis. The heart may exhibit marked movement both in swinging form as well as between systole and diastole, so that the safe depth of needle penetration needs to be measured within the context of cardiac movement. Once the clinician marks the site for access, the patient should not move until the procedure is performed, out of concern that patient movement will cause redistribution of fluid within the pericardium. The site is prepared with sterile technique and all equipment is prepared. A sterile transducer cover should be included in the set up. After the preparation and before needle insertion, the intensivist performs a confirmatory scan to document the best site, angle and depth for needle insertion. Real-time guidance of needle insertion is not required for pericardiocentesis (similar to thoracentesis), provided the operator performs the scan immediately before the needle insertion. The needle and syringe assembly is held in the angle in which the transducer was held. Skin



Figs 144.29A to D: Pericardiocentesis under ultrasound guidance. A & B: Large pericardial effusion. In PSL view, anterior effusion of 1.91 cm thickness was seen at a depth of 3.16 cm from the skin. Pericardiocentesis was performed from left parasternal access. C: The drainage catheter in the pericardial space (arrowhead) shown in the subcostal view. D: Injection of agitated saline through the catheter helped to confirm the position of the catheter by opacification of the percardial space

compression artifact may be problematic. This occurs when the transducer is applied firmly to the skin of the patient so that the measured depth underestimates the depth required to access fluid. The operator must take care to avoid asymmetric force application to the skin mark, as this may cause an inaccurate site of insertion. Placing a depth guard on the needle and introducing the needle in a straight line without any lateral movement ensure further safety of needle advancement. Once the needle has penetrated the pericardial fluid space, a wire and/or catheter may be introduced with prompt removal of the needle. The final catheter type is up to the discretion of the operator. The catheter position may be confirmed either by directly identifying the catheter within the pericardial space (Fig. 144.29C) or by injecting agitated saline through the catheter and visualizing the same in the pericardial space (Fig. 144.29D).

ULTRASOUND GUIDANCE OF PARACENTESIS

Diagnostic and therapeutic paracentesis are common procedures performed in intensive care units. Often, paracentesis is performed by a blind technique with reliance on physical examination to identify a suitable site. The safety and success of paracentesis can be improved by use of ultrasonography.[143] Ultrasound guidance of paracentesis is preferable under certain circumstances such as advanced pregnancy, significant bowel distension and extensive/multiple previous abdominal surgeries. The blind paracentesis is relatively contraindicated if any of these conditions are present.[144] In patients who have peritoneal adhesions from previous surgeries or peritonitis, the fluid may not be located at typical abdominal sites where blind paracentesis is attempted. The chance of success with blind paracentesis depends on the amount of fluid present. In patients who have a small amount of fluid, ultrasonography helps to confirm the presence of fluid and locate the best site for performing the procedure. In some patients thought to have ascites by clinical examination, ultrasonography may negate the presence of the same or may show too little fluid for safe paracentesis. Ultrasonography reduces unsuccessful blind attempts.[145]

Ultrasound guided paracentesis uses the same skill set required to perform thoracentesis and pericardiocentesis. The operator scans the lower lateral abdomen and suprapubic area in order to indentify the best site, angle and depth for needle entry. The epigastric artery runs in the lateral rectus sheath and is generally sufficiently medial in position that it is not at risk for inadvertent needle injury. For maximal safety, the operator may examine the proposed insertion site for aberrant vascular structures. Ascites has its mimics; a distended bladder or fluid filled intestinal structures may be mistaken for ascites. They have anatomic patterns that allow the operator to differentiate from intra-abdominal fluid. Ascites changes in shape when the transducer is pushed into the abdominal wall. Like thoracentesis and pericardiocentesis, paracentesis need not be performed with real-time guidance provided the operator performs the procedure immediately following site identification without any interval patient movement. For ultrasound guidance of paracentesis, a suitable site is one where a collection of fluid is seen and a straight path of approach to the fluid from the skin surface avoids bowel loops and other organs.

ULTRASOUND FOR AIRWAY MANAGEMENT

Ultrasonography can be helpful in airway management of critically ill patients.[146] It has been studied for preintubation measurement of anterior neck soft tissue thickness, particularly in obese patients, showing positive correlation with difficulty in laryngoscopy.[147]

Ultrasonography can be used to confirm endotracheal intubation in two ways. By obtaining a midline longitudinal section of the trachea at the level of the cricoid cartilage, the endotracheal tube can be visualized as an echogenic line below the anterior tracheal wall. Whereas the endotracheal position of the tube can be confirmed, it is not possible to determine where the tip of the endotracheal tube is located. As an alternative, the presence of bilateral lung sliding and diaphragmatic movement with ventilation confirm endotracheal tube position. Ultrasonography may also be used to identify inadvertent main stem bronchial intubation. In this case, if the endotracheal tube has been advanced to right main stem bronchus with the inflated cuff blocking air entry to left, the patient will exhibit lung sliding with ventilation on right side but will lack the same on the left side as no air entry occurs. The patient will have lung pulse on the left.[14] Very soon after the main stem intubation, the left lung will develop resorptive atelectasis, particularly if the patient is on high FiO_2; the left lung will develop consolidation pattern on ultrasonography. Drawing back of the ETT may be guided by lung ultrasonography.

Ultrasonography has been studied to predict extubation outcome. The degree of diaphragmatic movement during spontaneous breathing trial, measured as displacement of liver/spleen, has been reported to have more accuracy in predicting successful extubation than traditional weaning parameters.[148]

Ultrasonography has been used to guide percutaneous dilatational tracheostomy.[149-151] Ultrasound study of the thyroid and cricoid cartilages, tracheal rings, paratracheal soft tissues, thyroid gland and vascular structures allows the intensivist to select the optimal puncture site of the trachea. The identification of a large aberrant midline vein or an innominate artery that is unusually high in position allows the intensivist to avoid catastrophic complication of major vessel injury. With the help of ultrasonography, patients who have unfavorable anatomy for percutaneous dilatational tracheostomy can be identified and referred for surgical tracheostomy.[152]

During emergency endotracheal intubation, unrecognized gastric fluid collection may result in life-threatening aspiration event. Ultrasonography can be used to rapidly identify a significant gastric fluid collection during set up of emergency ETT (Fig. 144.25I). This allows the team to empty the stomach with the insertion of a gastric tube, thereby avoiding the risk of dangerous aspiration event. If the patient is too unstable for gastric tube insertion, the team may take specific measures to prevent aspiration of gastric contents with the fore knowledge of the risk.

ULTRASOUND FOR CONFIRMATION OF GASTRIC TUBE PLACEMENT

Ultrasonography can be used to confirm the proper location of a gastric tube. By scanning the left upper quadrant, the gastric tube may be seen as a discreet structure. Injection of air or fluid yields a characteristic pattern of air bubbles within the stomach. Bedside ultrasonography has been used to guide placement of nasoenteric feeding tubes[153,154] and to replace dislodged gastrostomy tubes.[155] The tip of the tube is visualized with ultrasonography; visualization can be improved by injecting air through the tube as air acts as a contrast for ultrasound imaging.[154]

LUMBAR PUNCTURE

Use of ultrasonography to facilitate spinal puncture has been reported in obstetric anesthesia literature. Using an initial paramedian longitudinal scan plane approach, the level of vertebral interspaces such as L5-S1, L4-L5 are identified and marked. A transverse scan of each individual space is then performed. The processes flanking each vertebral interspace are identified as small hyperechoic signals. When the plane of transverse scanning passes exactly through an interspace, a hyperechoic band-like shadow of the ligamentum flavum and the dorsal dura is visualized. The best site, angle and depth of puncture can be accurately judged. Use of ultrasound decreases procedure time and improves patient comfort.[156]

OTHER PROCEDURES

Ultrasonography allows for accurate placement of needle, wire or a drainage device into a wide variety of clinically important targets. For example, abscesses, lymph nodes, lung masses, mediastinal masses and fluid collections of all types may be accessed under ultrasound control. The principles of ultrasound guidance remain the same regardless of the procedure. The operator identifies the target and adjacent anatomic structures that must be avoided during the needle insertion. The best site, angle and depth are determined. In many cases, real-time control is not necessary. For small targets, the operator must be proficient with real-time guidance. In the authors' experience, this is best done with the needle being scanned in its entirety along its long axis throughout insertion. Entry of needle into the target allows for simple aspiration or biopsy or may be followed by the drainage device of operator's choice.

CONCLUSION

Ultrasonography has major utility in critical care medicine. High quality portable machines are widely available and permit point of care scanning by the frontline intensivist. Ultrasound imaging of the lung, pleura, vascular structures, heart and abdominal organs allow rapid diagnosis and guides management at the bedside of the critically ill patient. Ultrasonography increases the safety and success rate of many common ICU procedures. We hope that this chapter serves to inform and motivate the intensivists to develop competence in the field of CCUS as defined in the ACCP-SRLF statement on competence in the field.

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Interpretation of Chest X-rays in the ICU

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INTRODUCTION

The chest radiograph has a high diagnostic accuracy for detecting radioopaque tubes and devices inserted in the critically ill patient, but only a moderate accuracy in detecting various cardiopulmonary abnormalities and pinpointing their exact etiology.[1] Despite this limitation, the chest radiograph serves as a vital and objective adjunct to the bedside physical examination in the rapidly changing clinical course of critically ill patients.

The current widespread use of chest radiography in the Intensive Care Unit (ICU) is based on studies that have shown that daily films in the ICU often reveal significant and/or unsuspected abnormalities in 34 to 65% cases that may change the patient's diagnosis or management.[2-4] For example, in a review of 1,354 Chest X-ray (CXR) studies on 167 patients in the ICU, Bekemeyer et al.[2] reported an incidence of 34.5% of new or increased abnormalities, or tube or catheter malposition. Excluding catheter malposition adjustments, as many as 28.5% of the CXR studies led to a change in the diagnostic approach or therapeutic interventions. More recent studies have arrived at a different conclusion, reporting that only 1.9 to 13.3% of daily routine CXRs in the ICU lead to a change in clinical management.[5-7] Ordering a CXR only when clinically indicated rather than on a daily routine basis translated into significant cost savings without adversely affecting ICU length of stay or mortality.[5,6]

Assimilating the somewhat contradictory findings of different studies, the consensus opinion of the American College of Radiology (ACR) Expert Panel, revised as of 2008, recommends that routine daily radiographs are indicated for ICU patients with acute cardiopulmonary problems, including those on mechanical ventilation. Stable patients admitted for cardiac monitoring, or in stable patients admitted for extrathoracic disease only, an initial admission radiograph is recommended, with follow-up radiographs obtained only for specific clinical indications. Patients who require cardiac monitoring but are otherwise stable require only an initial admission film. Additional radiographs are indicated only when a new device is placed or when there is a specific question regarding cardiopulmonary status.

The advent of computed radiology has given us the ability to acquire, store and transmit chest radiographs in digital format, as well as view images on computers using Picture Archiving and Communication Systems (PACS), thereby cementing the role of chest radiology in the ICU setting. Nevertheless, the utility of chest radiography in the ICU goes hand-in-hand with important pitfalls in interpretation. The standard postero-anterior (PA) chest radiograph is rarely feasible in the ICU patient and is usually substituted by an Antero-Posterior (AP) film, often in a supine or semi-recumbent position, with varying degrees of inspiratory effort. This technique renders a magnified view of the heart and mediastinum, diverts blood to the lung apices, allows pleural effusions to layer and disguise themselves as airspace opacities, and renders small pneumothoraces, all but invisible.[8]

A suboptimal inspiratory effort can create a spectrum of illusions ranging from basilar atelectasis to pulmonary edema. Compounding this picture is often an array of wires and tubes as well as varying folds of subcutaneous and breast tissue. The well-trained intensivist must learn to walk the fine line between detecting subtle yet important findings and dismissing potential artifacts. Having a strong clinical suspicion for expected problems, investing the time to compare with previous films and ordering a repeat film with a different technique or position, when necessary, can often save the day. In the ensuing sections, we will briefly discuss commonly encountered patterns of disease on plain chest radiography in the critical care setting.

Cardiopulmonary Imaging

The radiological findings in cardiac as well as pulmonary parenchymal diseases are often nonspecific, underscoring the importance of clinical correlation.

Pneumonia

Radiographically, pneumonia presents as air-space opacities, which may be hazy (as in *Pneumocystis jiroveci* or viral pneumonia (Fig. 145.1) or dense (as in bacterial pneumonia). The opacities may be focal or diffuse, or may be concealed in the retrocardiac area. The opacities may silhouette the right heart border, suggesting involvement of the right middle lobe. Pneumonia may affect gravity-dependent portions of the lung and have air bronchograms mimicking Acute Respiratory Distress Syndrome (ARDS) and atelectasis. Although, pleural effusions can be differentiated from pneumonia by the lack of air bronchograms and the presence of the meniscus sign, they often coexist with pneumonia and may indeed suggest the progression to complicated parapneumonic effusions or empyema. The importance of clinical correlation, such as the persistence of fever and pleuritic chest pain, cannot be stressed enough in this setting.

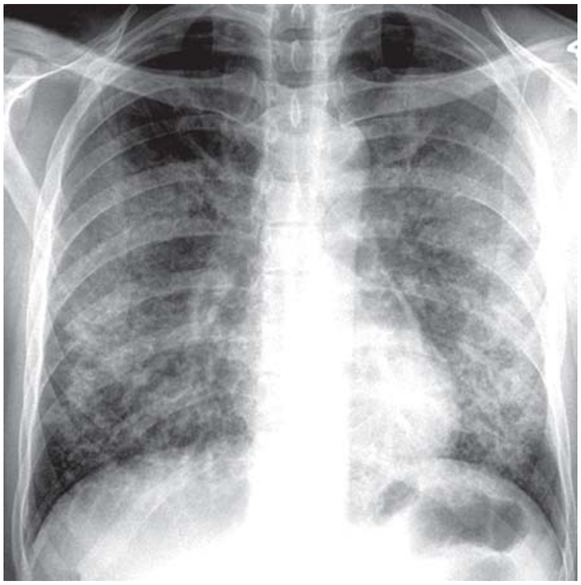

Fig. 145.1: *Pneumocystis jiroveci* – diffuse bilateral alveolar opacities in a 45 years old woman with HIV

Other radiographic patterns associated with pneumonia include the formation of cavities (as in necrotizing pneumonia from *Staphylococcus aureus* bearing the Panton Valentine Leukocidin gene), cavities in the upper lobes (as in pulmonary tuberculosis) and the development of bronchopleural fistulas. Finally, the appearance of a new opacity suggestive of pneumonia after 72 hours of mechanical ventilation, in conjunction with clinical and microbiological data, confers the diagnosis of ventilator-associated pneumonia (VAP).

Atelectasis

Atelectasis results from mucus plugging and secretions, concomitantly with a difficulty in clearing secretions. This may result from general anesthesia, sedation, neuromuscular blockade or postoperative pain causing splinting. Minimal basal subsegmental or discoid atelectasis appears as linear streaks and is quite common in the ICU patient but of no major physiological significance. More extensive atelectasis, varying from total lung collapse to subsegmental collapse, may cause or worsen hypoxemia. Although, atelectasis can disguise itself as pneumonia with the presence of air bronchograms and fever, there are some important distinguishing clues. Loss of volume on the side of a parenchymal opacity, with crowding of the vasculature, elevation of the ipsilateral hemidiaphragm or ipsilateral shift of the mediastinum, suggests atelectasis.

The rapid appearance of a parenchymal opacity as well as disappearance on a subsequent film after adequate pulmonary toilet is an indicator of atelectasis. In the setting of surgical ICU, atelectasis is often caused by splinting from pain following surgery. Radiographic resolution can often be seen following ambulation, chest physical therapy and incentive spirometry. Atelectasis occurs in the left lower lobe in 66% cases, right lower lobe in 22% cases and right upper lobe in 11% cases.[9] Compression of the left lower lobe by the heart in the supine patient, combined with relative difficulty of blindly inserting a suction catheter into the left lung, is thought to account for the increased predisposition of atelectasis of the left lower lobe atelectasis.[10]

Collapsed lung segments and lobes follow well-recognized anatomical pathways, unlike other causes of air-space diseases such as pneumonia or ARDS. The

TABLE 145.1: Radiographic appearance of atelectatic lung segments

Atelectatic segment	Radiographic appearance
Right upper lobe	The right upper lobe collapses into a triangular opacity, with the lesser fissure migrating toward the anterior, superior and medial portion of the chest.
Right middle lobe	Loss of definition (silhouetting) of the right heart border. (similar to pneumonia affecting the right middle lobe)
Right lower lobe	The collapsed lobe moves centrally and inferiorly towards the lower thoracic spine, where it is seen as a triangular opacity. Silhouetting of the right hemidiaphragm and air bronchograms are often seen. The minor fissure may show some inferior displacement. Right-lower-lobe atelectasis can be differentiated from right–middle-lobe atelectasis by the persistence of the right heart border.
Left upper lobe	Left-upper-lobe atelectasis appears differently than right–upper-lobe atelectasis because the left lung lacks a minor fissure. The collapsed left upper lobe moves anteriorly, with loss of the left upper cardiac border. The left lower lobe expands and migrates superior and posterior to the left upper lobe. The left main bronchus rotates to a nearly horizontal position. There is “veil-like” or hazy opacification of the left hilum, elevation of the left hilum, and aerated lung abutting the arch of the aorta, between the mediastinum and the collapsed left upper lobe (Luftsichel or air crescent sign)
Left lower lobe	The left lower lobe collapses medially and posteriorly to lie behind the heart. It classically displays a dense triangular opacity visible through the cardiac shadow, often giving the heart an unusually straight lateral border. Silhouetting of the left hemidiaphragm and air bronchograms are also seen.

intensivist must familiarize himself with these anatomical patterns as outlined in Table 145.1.[10]

Aspiration Syndromes

Impaired consciousness from disease or sedatives, ineffective cough from neuromuscular blockade or critical care neuropathy or myopathy, the placement of endotracheal and nasogastric feeding tubes, as well as inadequate elevation of the head of the bed, all contribute to the development of aspiration syndromes in the critically ill patient. The intensity of resulting pulmonary inflammation is related to the amount of fluid aspirated as well as its pH.

The most commonly aspirated fluid is gastric content (Mendelson’s syndrome). Aspiration of this fluid, with a pH <2.5, causes severe bronchospasm within minutes,[11] followed later by fever and leukocytosis. Chest radiographs usually show progressive opacities in the perihilar and basilar regions in the first 24 hours. In the subsequent 24 to 48 hours there is stabilization of these opacities and usually by 48 to 72 hours there is some evidence of clearing. In up to 25% of patients, this chemical pneumonitis is complicated by bacterial infection, which should be suspected when the radiographic opacities fail to clear in 3 to 7 days.

Pulmonary Edema

The accumulation of fluid in the lung interstitium or alveolar space, generally referred to as pulmonary edema, is a common occurrence in the critically ill patient. The etiology may be increased hydrostatic pressure, as seen in Congestive Heart Failure (CHF), renal failure and fluid overload; or increased permeability of the pulmonary capillaries, as seen in ARDS, inhaled irritants, near-drowning, altitude sickness, transfusion reactions, etc. These two distinct types are often referred to as cardiogenic and non-cardiogenic pulmonary edema respectively. Milne et al[12] in a classic study of 216 CXRs, found 91% accuracy in differentiating capillary permeability edema (e.g. ARDS) from other varieties (Table 145.2).

Several subsequent studies attempted to correlate the degree of CHF, as estimated by Pulmonary Artery Occlusion Pressure (PAOP) or Left Ventricular End-Diastolic Pressure (LVEDP), with CXR findings—the results were generally disappointing.[13,14] One exception is the Vascular Pedicle Width (VPW), described by Milne et al.[12,15], which continues to be studied as a radiologic aid in assessing the patient’s volume status (Fig. 145.2). The VPW is measured by dropping a perpendicular line from the point at which the left subclavian artery exits the aortic arch and measuring across to the point at which the superior vena cava crosses the right main stem bronchus. When the right border of the pedicle is indistinct, the vertical lateral border of the superior vena cava or right brachiocephalic vein has been used in VPW measurements.[16] Factors that might influence VPW measurements include; VPW varies with patient height and body build, VPW measured with the patient in a

TABLE 145.2: Cardiogenic vs. Non-cardiogenic pulmonary edema

Features	*Cardiogenic*	*Non-cardiogenic*
Causes	Eg. CHF	Eg. ARDS
Pathogenesis	Increased hydrostatic pressure	Increased capillary permeability
Cardiac shadow	Enlarged	Normal in size
Distribution of opacities	Basal predominant opacity, even from chest wall to heart, with perihilar component (“bat wing” appearance)	Patchy, peripheral opacity sparing the costophrenic angles
Pulmonary blood flow distribution	Upper lobe vessels larger compared to lower lobe vessels	Normal or balanced
Peribronchial cuffing	Very common	Not common
Pleural effusions	Very common	Not common
Air bronchograms	Not common	Very common
Septal lines	May be present	Not usually present
Vascular pedicle width on CXR shot in upright position	Enlarged (>53 mm)	Reduced (<43 mm)

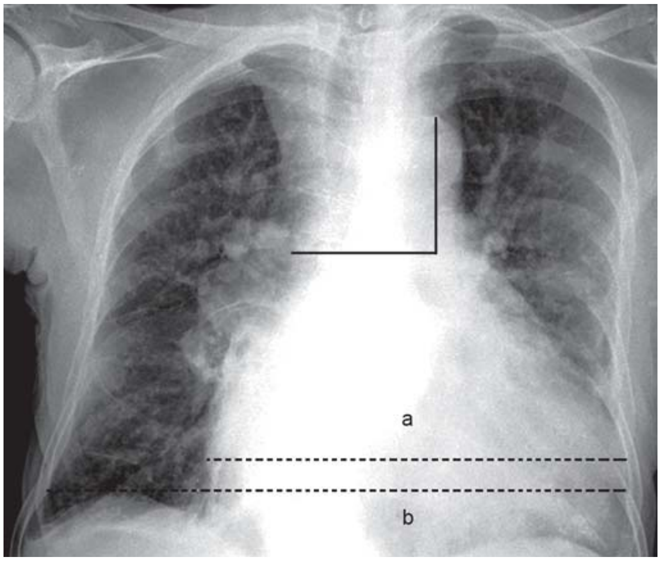

Fig. 145.2: Congestive heart failure. A 65 years old woman admitted with shortness of breath. The vascular pedicle width (VPW), (see solid lines), measured by dropping a perpendicular line from the point at which the left subclavian artery exits the aortic arch and measuring across to the point at which the superior vena cava crosses the right main stem bronchus, is 75 mm in this case. (A value >70 mm is strongly suggestive of volume overload.) The cardiothoracic ratio, measured as the ratio of the largest transverse cardiac diameter (see dotted line) to the largest transverse thoracic diameter (a/b), is also increased. (A value >0.55 suggests cardiomegaly)

supine posture is approximately 17% greater than that with the patient in an upright position, the rotation of the patient to the right (i.e. a left anterior oblique projection) increases VPW, whereas the rotation of the patient to the left (i.e. a right anterior oblique projection) decreases the VPW. ICU CXRs should therefore be taken in a reproducible fashion, with similar body positioning and focal film distance (40 inches from the chest wall), widening of the VPW is a normal postoperative CXR finding following cardiac transplantation.[16]

In a prospective study of 33 mechanically ventilated ICU patients with supine AP CXRs, there was a significant correlation between the PAOP and the VPW, ($r = 0.45$, $p = 0.0076$) and the cardiothoracic ratio (CTR, calculated by dividing the maximum cardiac width by the maximum thoracic width) ($r = 0.52$, $p = 0.0016$), as well as between the VPW and CTR ($r = 0.49$, $p = 0.0032$).[17,18] In a subsequent prospective study of 100 patients (all of whom had volume status assessed by pulmonary artery catheters), it was found that patients with a VPW of >70 mm coupled with a CTR of >0.55 were more than three times more likely to have a PAOP >18 mm Hg than were patients without these radiographic findings.[18] It has also been reported that an increase in VPW of 5 mm corresponds to an increase in 1 liter of total blood volume in upright, nonmechanically ventilated patients,[19] a widening of the VPW on serial CXRs precedes the development of pulmonary edema in burn patients receiving fluid resuscitation.[20]

VPW decreases significantly with fluid removal during hemodialysis[21] and a decrease in VPW also correlates with the volume of diuresis after recovery from acute lung injury.[22] It appears, therefore, that serial measurements of VPW can give crucial and reliable

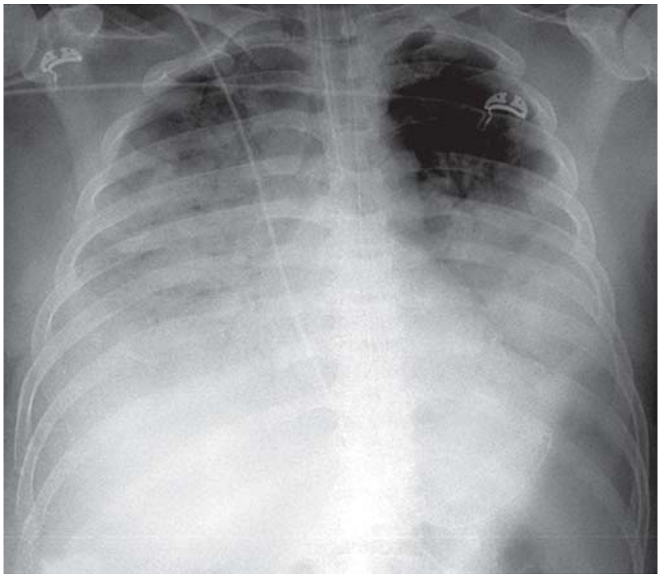

Fig. 145.3: ARDS in a 50 year old male who was found to have H1N1 Influenza. Note the dense bilateral opacities with air bronchograms

information regarding the ever-changing volume status in critically ill patients. Nevertheless, this simple technique unfortunately remains underreported and underutilized.

Acute Respiratory Distress Syndrome (ARDS)

The acute onset of bilateral opacities on the CXR, along with a PaO_2/FIO_2 ratio <200, in the absence of clinical CHF, defines the presence of ARDS. Pulmonary as well as nonpulmonary sepsis, aspiration, blood transfusions and trauma are just some of the many causes of ARDS. ARDS is the final common pathway of lung injury regardless of the etiology and is characterized by damage to the alveolar capillary endothelium, increased vascular permeability, and subsequent development of interstitial followed by alveolar pulmonary edema.

Differentiation between ARDS versus CHF can be difficult; several radiographic clues are listed in Table 145.2. The chest radiographs may be normal in the first 12 hours of development of ARDS. Subsequently, diffuse, ill-defined alveolar opacities appear which may progress to a complete white-out of the lungs (Fig. 145.3). The radiographic phases of ARDS are presented in Table 145.3.[23]

Evaluation of Lines, Tubes and Devices

A plethora of invasive tubes and devices have now become routine in the management of critically ill patients. The CXR has assumed a crucial role in ascertaining the correct positioning of these devices as well as in detecting complications related to their placement. The intensivist must insist on obtaining a CXR promptly after the placement of these devices and should be skilled in their interpretation. Furthermore, while reviewing CXR films in the ICU, it is advisable to develop the habit of identifying all placed devices first before looking for cardiopulmonary disorders.

TABLE 145.3: Radiographic phases of ARDS

Phase	*Radiographic features*
Acute phase (0-12 hours)	Radiograph often normal
Acute phase (12-24 hours)	Diffuse, bilateral patchy alveolar opacities present. Air bronchograms present, pleural effusions are uncommon.
Subacute phase (5-10 days)	With progressive lung destruction, there is transition from alveolar to interstitial opacities. A frequent complication is barotrauma (pneumothorax, pneumomediastinum, pneumoatceles)
Chronic phase (2-3 weeks)	Lung fibrosis and destruction manifested on chest radiography by fibrosis and focal emphysema.

Endotracheal Tube

Endotracheal tubes (ETT) are used to secure airway access in critically ill patients and allow mechanical ventilation. Unfortunately, these tubes are malpositioned

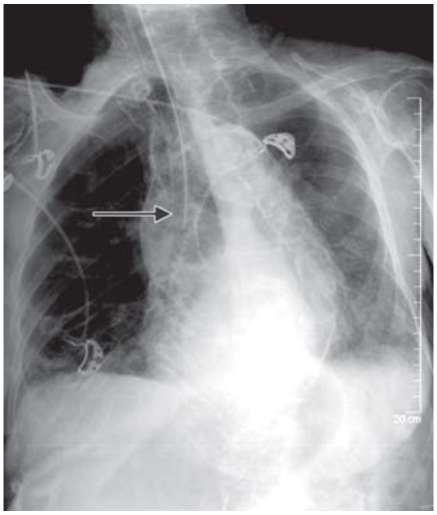

Fig. 145.4: Right mainstem intubation. The endotracheal tube has passed the carina and slipped into the right main bronchus (see arrow). Note the hyperlucency in the overinflated right lung and the diffuse haziness in the non-ventilated left lung

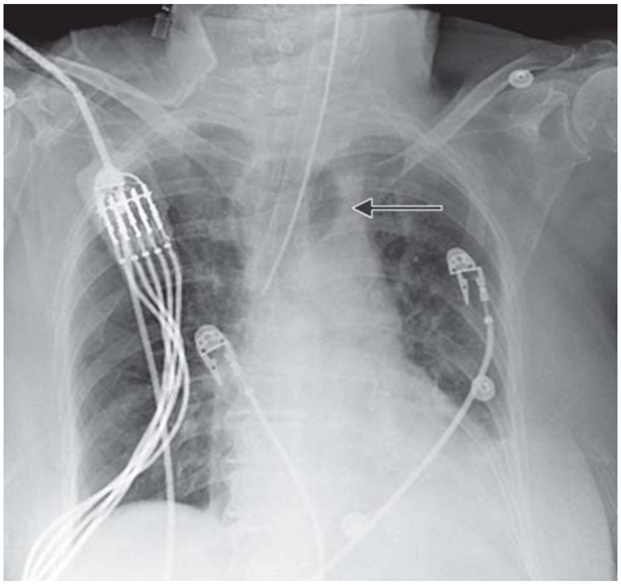

Fig. 145.5: Overinflated cuff of the endotracheal tube. The ratio of the diameter of the cuff and the trachea should be 1:1. In this case, the ratio is 2:1

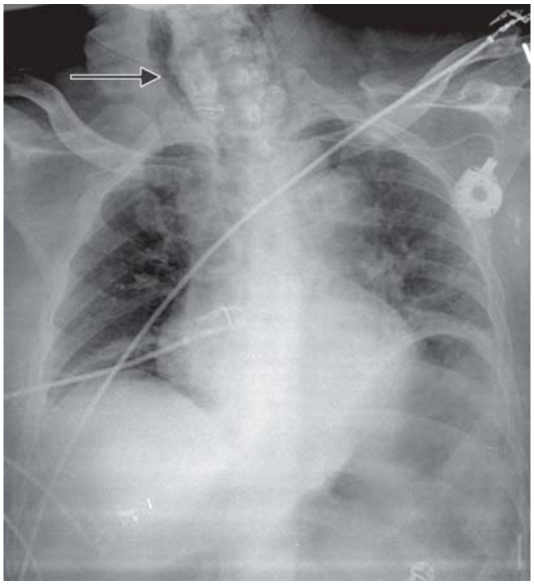

Fig. 145.6: Subcutaneous emphysema. The patient developed cervical esophageal injury during attempted intubation prior to general anesthesia. The surgery was postponed, the patient complained of throat pain and odynophagia in the recovery unit. Note the presence of hypolucent shadows suggestive of air in the soft tissues of the neck. (see arrow)

in about 10% cases[24] (Fig. 145.4). Therefore, all intubated patients should have a CXR immediately post-intubation to confirm the correct position of the ETT. The ideal position of the ETT is in the mid-trachea, 5 to 7 cm above the carina, with the head in the neutral position. The inflated cuff of the ETT should fill the tracheal lumen but not bulge its walls (Fig. 145.5). An overinflated ETT cuff can compromise capillary blood flow in the tracheal mucosa, resulting in tracheal injury and eventually tracheal stenosis.

A difficult intubation should raise the suspicion of tracheal, laryngeal or cervical esophageal perforation, which would manifest on the CXR as subcutaneous emphysema in the neck, pneumothorax or pneumomediastinum (Figs 145.6 and 145.7). Esophageal intubation is suggested by the ETT appearing lateral to the tracheal air shadow.

ETTs also have a tendency to migrate and potentially jeopardize the airway, so, daily CXRs are recommended in all intubated patients to ascertain the correct position of the ETT. It is important to remember that flexion of the head allows the ETT tip to migrate approximately 2 cm distally and therefore, an ETT tip too close to the carina could potentially slip into the right main bronchus. Likewise, extension of the head allows the ETT to migrate approximately 2 cm proximally and therefore an ETT tip too far proximal to the carina could potentially slip out above the vocal cords. Poor chest X-ray exposure may

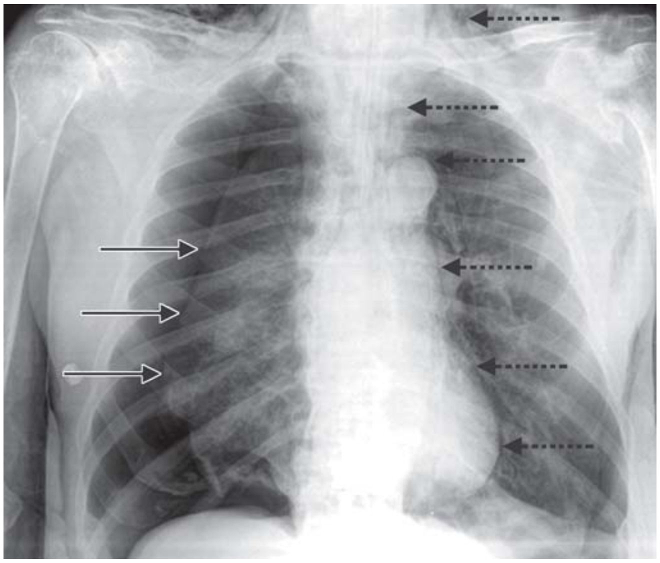

Fig. 145.7: Right pneumothorax+ pneumomediastinum following traumatic intubation with tracheal injury. The right lung has collapsed (see solid arrows pointing at right pleural margin). There is a thin margin of air adjacent the left heat border extending above the aortic knob (see dotted arrows). Also note the subcutaneous emphysema – the fibers of the left pectoralis major muscle are highlighted by shadows of air. The soft tissues of the neck also show hypolucent areas suggestive of air

sometimes not allow recognition of the carina. If a previous radiograph is available, anatomical landmarks may be used to estimate the position of the carina.

Tracheostomy Tube

The tracheostomy tube is initially sutured in place after insertion and is subsequently held in place with a neck strap. Consequently, it does not have the same potential to migrate as the ETT and it typically does not change position with neck flexion or extension. The tip of the tracheostomy tube should again lie well above the level of the carina, usually at the level of the T3 vertebra. Once appropriate placement is confirmed via CXR or bronchoscopy, daily CXRs are not required to confirm the position of the tracheostomy tube.

Nasogastric Tube

Nasogastric Tubes (NGTs) are commonly placed in the ICU for nutritional support or gastric decompression. It is advisable to confirm the placement of every NGT by a CXR prior to use, as an NGT inadvertently inserted into the tracheobronchial tree can deliver enteral feeds to the lungs leading to catastrophic pneumonitis and pneumonia (Fig. 145.8). The tip of the NGT should be visualized beyond the gastroesophageal junction, inferior to the level of the left hemidiaphragm. An NGT sitting at the gastroesophageal junction or in the distal esophagus should be advanced in further to prevent aspiration. Once placement is confirmed and the tube is securely fastened, daily CXRs are not required to confirm position unless migration is suspected.

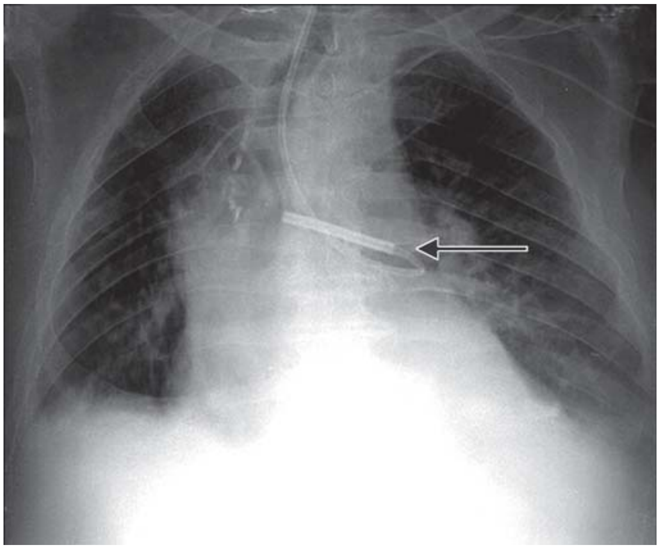

Fig. 145.8: Nasogastric-tube malposition in left mainstem bronchus

Central Venous Catheter

Central venous catheters, inserted via the internal jugular or subclavian vein, are routinely used in the modern ICU for administration of fluids and vasopressors, as well as to monitor the central venous pressure in patients with shock. Again, the intensivist must insist on obtaining a CXR promptly after the placement of a central venous catheter, to confirm its appropriate placement and evaluate for any complications. The catheter tip should ideally lie in the superior vena cava between the right atrium and the most proximal venous valves. The proximal venous valves are usually located 2.5 cm distal to the junction where the subclavian and jugular veins meet to form the brachiocephalic vein. On the CXR, this position usually lies at the anterior part of the first rib, as many as one third of central venous catheters are malpositioned at the time of insertion.[25] These include the subclavian catheter going up the ipsilateral internal jugular vein, contralateral brachiocephalic vein, right atrium, right ventricle, inferior vena cava and hepatic veins, as well as the pleural space. A catheter tip lying in the right atrium or ventricle could induce cardiac arrhythmias by irritating the myocardium.

Pneumothorax is a very well described complication of central venous catheter placement. In a mechanically ventilated patient, a pneumothorax caused during catheter placement could rapidly expand leading to respiratory and hemodynamic compromise. Infusion of fluids and parenteral nutrition formulae into the pleural space via malpositioned catheters have been described, leading to rapidly accumulating pleural effusions with abnormally high glucose or lipid levels.

Pulmonary Artery Catheter

The right heart catheter, which is also referred to as the pulmonary artery catheter, nowadays used primarily to evaluate pulmonary arterial hypertension and to guide vasopressor therapy in patients with combined septic and cardiogenic shock. The catheter is floated to the pulmonary artery via the right ventricle and is usually wedged 5 to 8 cm distal to the bifurcation of the main pulmonary artery. The tip of the catheter should lie within the mediastinal shadow or no more than 3 cm away from the midline on a CXR.[26] A prompt CXR to confirm proper placement and exclude complications such as pneumothorax is a prudent approach. Subsequent daily reconfirmation of proper placement and exclusion of catheter migration can be accomplished by clinical criteria, with a CXR performed only if migration or complication is suspected.

Appropriate clinical criteria used to exclude catheter migration are as follows:

a. Amount of air required to obtain a pulmonary capillary wedge pressure tracing, 1.25 to 1.5 ml (normal) versus less than 1.25 ml (abnormal). When less than 1 ml of air is required to obtain a pulmonary capillary wedge pressure tracing, the balloon should be deflated and the catheter pulled back regardless of the findings on a chest radiograph.
b. Centimeter marking of the pulmonary artery catheter at the introducer hub: 1 cm or less migration in or out from the initial position (normal) versus more than 1 cm migration (abnormal).[26] Locking the hub in place after catheter placement and periodically noting the centimeter marking at the hub are therefore crucially important.

Complications of right heart catheter include rupture of the pulmonary artery and pulmonary infarction, both of which could manifest with hemoptysis and rapidly appearing infiltrates on the CXR. Pneumothorax can occur during placement, as with central venous catheters.

Intra-Aortic Balloon Counterpulsation or Pump (IABP)

The IABP is a device used to augment cardiac function and coronary perfusion in the setting of cardiogenic shock. The device is inserted percutaneously via the femoral artery, and the tip of the balloon should come to lie in the proximal descending thoracic aorta, 2 to 3 cm distal to the origin of the Left Subclavian Artery (LSCA).[27-29] The balloon is distended in diastole, causing increased pressure in the proximal aorta, thus improving coronary artery perfusion, increased oxygenation of the myocardium and improved cardiac output. The balloon is subsequently deflated during systole, thereby decreasing cardiac afterload, left ventricular work and oxygen requirements.

The tip of the device is radioopaque, which facilitates visualization on CXR to confirm proper placement. If positioned too proximal in the arch of the aorta, the balloon can enter the left subclavian artery and become a source of embolism to the brain via the vertebral artery. If positioned too distal in the descending thoracic aorta, the balloon can potentially block the ostia of the renal or superior mesenteric arteries, causing catastrophic end-organ damage. On CXR, the recommended position for the tip of the balloon is at the inferior aspect of the "aortic knob",[30] which is a radiographic term, not an anatomic one. The "aortic knob" is opacity on the CXR representing the shadow of three anatomical structures; the LSCA, the distal aortic arch and the proximal descending aorta. An alternate approach is to position the IABP tip at 2 cm above the carina, which will place the tip 1.5 to 3.5 cm distal to the origin of the LSCA.[31] The advantage of this approach is that the carina is a more clearly defined and visualized anatomic structure.

Transvenous Pacemakers

Transvenous pacemakers are introduced via the internal jugular or subclavian veins into the right ventricle in patients with heart block. Besides detecting a paced rhythm on an electrocardiogram, a CXR should also be performed promptly after the procedure to confirm correct placement of the leads and exclude complications such as pneumothorax. On a PA view CXR, the tip of the catheter should be at the apex of the right ventricle. Abnormal positions of the catheter tip, including coiling in the right atrium, and passage into the pulmonary artery, inferior vena cava as well as coronary sinus, have been described.[32] There should be no sharp angulations along its length—this would suggest fracture of the pacing wire or a strong predisposition for this complication to occur.

Non-displaced or partial fractures of the leads may not be detected on CXR at all—failure of pacing would then need further investigation with a CT. On the lateral view CXR, the tip should be 3 to 4 mm beneath the epicardial fat stripe. If the tip projects beyond this point, it may have perforated the myocardium. Perforation can be very subtle, since the right ventricle myocardium is only 4 to 5 mm in thickness and the lead can come to lie in the pericardial space within the shadow of the mediastinum (Fig. 145.9).[32] Failure of pacing, the appearance

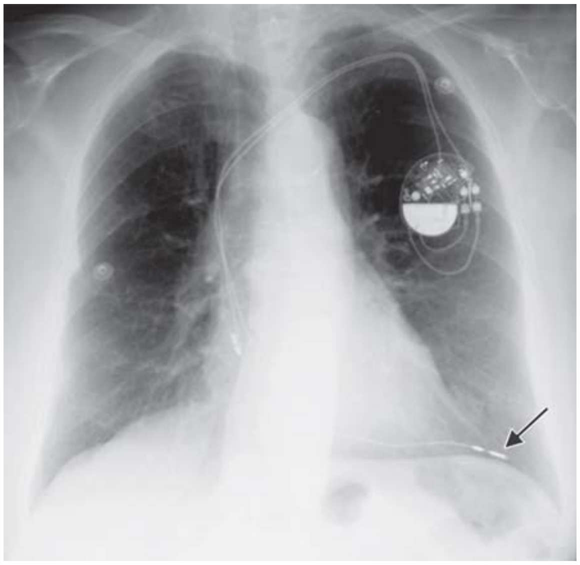

Fig. 145.9: Perforation of myocardial wall by pacemaker wire (see arrow)

of a new right bundle branch block, intractable hiccups from stimulation of the phrenic nerve or diaphragm, or signs of cardiac tamponade from hemopericardium are clinical clues that may herald myocardial perforation. Again, a CT may clinch the diagnosis if the CXR is inconclusive.[33]

Abnormal Air Collections in the Chest

Collection of air outside the tracheobronchial tree is not an uncommon occurrence in the ICU patient and heralds the presence of trauma from instrumentation or barotrauma from mechanical ventilation. The CXR is an invaluable tool for the prompt recognition of such complications, which can manifest as pneumothorax, pneumomediastinum, pneumopericardium or subcutaneous emphysema.

Pneumothorax

Pneumothorax is noted as a complication of internal jugular vein cannulation in 0.1 to 0.2% of cases and with subclavian vein cannulation in 1.5 to 3.1% cases.[34] In patients with ARDS, the reported incidence of pneumothorax from barotrauma varies widely from 6.5 to 60%.[35,36] Finally, rupture of lung bullae or cavities into the pleural space, either spontaneously or in the setting of positive pressure ventilation, can also give rise to pneumothoraces, as can traumatic attempts at intubation (Figs 145.6 and 145.7). The area on the CXR where a pneumothorax is likely to be visualized depends on the position of the patient when the CXR image was acquired. In the erect patient, air rises to the apicolateral surface of the lung and appears as a thin, white pleural line with no lung markings beyond it, unless the patient has a localized pneumothorax. In the recumbent position, air accumulates anterior to the lung and medially, surrounding the mediastinal structures. These anteromedial pneumothoraces can further be divided into those which are superior or inferior to the pulmonary hilum. On the right, sharp visualization of the superior vena cava and azygous vein suggest a superior anteromedial pneumothorax, whereas on the left this is suggested by sharp visualization of the left subclavian artery. Inferior or infrahilar anteromedial pneumothorax results in sharp delineation of the heart border and a lucent deep cardiophrenic sulcus.

Although the anteromedial location of the pneumothorax is more common in the supine patient (38% cases), an alternative location is the subpulmonic region, where air is trapped between the lung and the diaphragm (20% cases).[37] Air may extend into the costophrenic sulcus causing radiolucency, this is called the “deep sulcus sign” (Fig. 145.10). Alternatively, air may highlight both the relatively more superior anterior diaphragmatic surface and the inferior posterior diaphragmatic surface, resulting in what is known as the “double diaphragm sign”.[38]

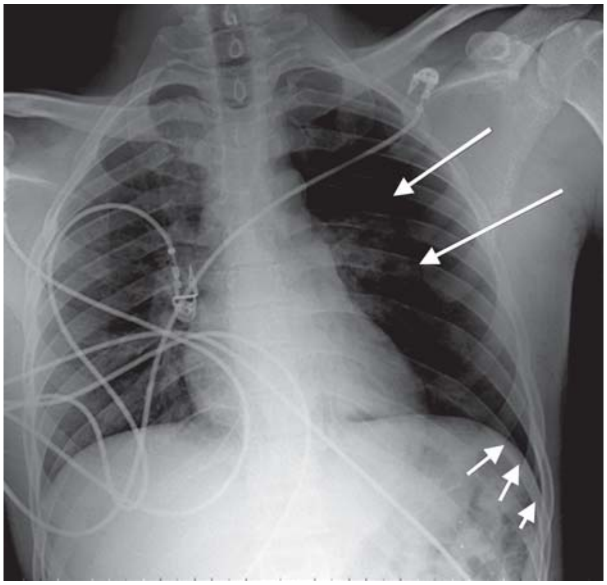

Fig. 145.10: Left pneumothorax (large arrows pointing to collapsed lung margin). Note the left costophrenic angle (small arrows) which is deepened due to the accumulation of air – the “deep sulcus sign”

Entry of air into the pleural space with no mechanism for exit (the so-called ball-valve effect) can result in a tension pneumothorax. This is a clinical diagnosis and should be managed with immediate decompression of the pleural space using a wide-bore IV catheter followed by a chest tube; no time should be lost waiting for a CXR to make this diagnosis. On CXR, the usual signs of total lung collapse and contralateral mediastinal shift may be absent in the setting of severe parenchymal lung disease and resulting low lung compliance. Flattening or even inversion of the ipsilateral hemidiaphragm, and flattening or shift of the superior or inferior vena cava, may be the only signs heralding a tension pneumothorax.

The presence of skin folds, wires, tubes and superimposed bony shadows can make the detection of a pneumothorax on CXR a treacherous business. Skin folds usually cause a broad, opaque band, with a zone of increased density leading up to the actual fold line and lung markings visible beyond the edge (Fig. 145.11). Furthermore, skin folds may extend across the midline or beyond the confines of the chest wall. In contrast, a pneumothorax is ideally visible as a thin pleural line with no lung markings beyond it.

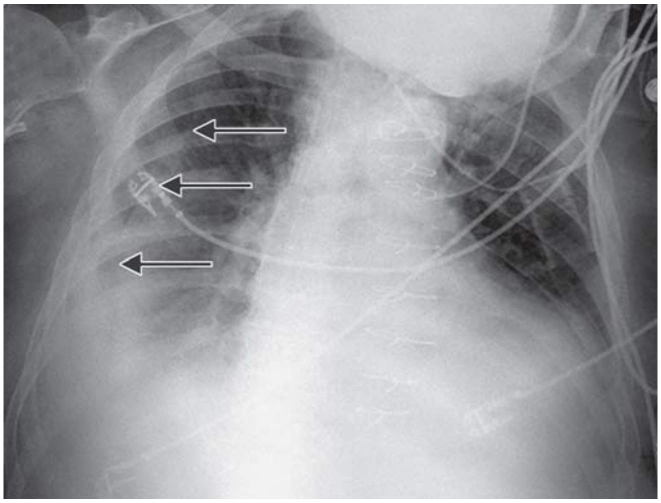

Fig. 145.11: CXR on an obese patient showing a broad, opaque band, with a zone of increased density leading up to a line (see arrows), and normal lung markings visible beyond the edge. This is typical of a skin fold, but can easily be mistaken as a pneumothorax. Note also a dense opacity at the right base tracking up the right lateral chest wall, suggestive of a pleural effusion. Sternotomy wires, EKG leads and ventilator tubing complete the picture

Pneumomediastinum

Pneumomediastinum usually occurs from barotrauma in the setting of ARDS. Inhalation of cocaine or marijuana may also induce pnemothorax and pneumomedisatinum (Fig. 145.12). Air from ruptured alveoli dissects via the pulmonary interstitium into the mediastinum. Less commonly, tear of the posterior membranous tracheal wall during traumatic intubation, rupture of the esophagus or blunt thoracic trauma can also introduce air into the mediastinal space (Figs 145.6 and 145.7). Air then tracks into the cervical and retropharyngeal tissues, the retroperitoneal tissues as well as the chest and abdominal wall. On CXR, lucencies mark the medial borders of the superior vena cava, azygous vein, aortic knob, pulmonary arteries or the descending thoracic aorta. Air can also outline the central portion of the diaphragm under the cardiac silhouette, resulting in the "continuous diaphragm sign".

Pneumopericardium

Pneumopericardium can be seen in postoperative cardiothoracic surgical patients as well as with penetrating chest trauma. Just like a tension pneumothorax, a pneumopericardium with tamponade physiology warrants immediate decompression; management should not be delayed awaiting a CXR. Unlike pneumomediastinum, the air in pneumopericardium does not rise above the level of the aortic knob—the air is contained by the superior pericardial recess, which reflects off the root of the aorta and pulmonary artery (Fig. 145.13). Also unlike pneumomediastinum, the air in pnuemopericardium can track around the pulmonary artery. In pneumopericardium, a band of lucency is

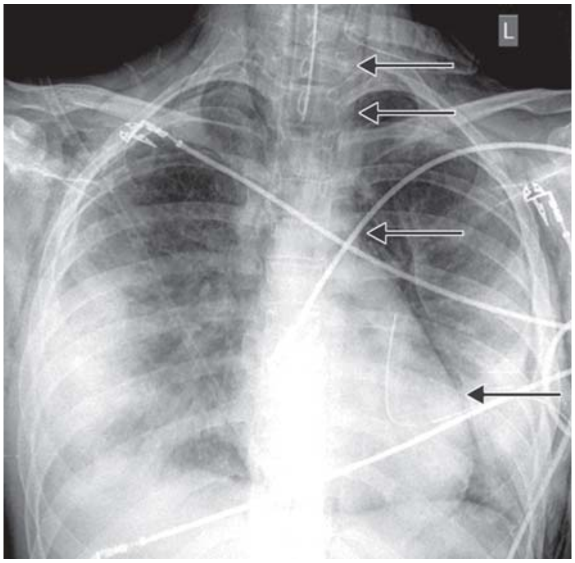

Fig. 145.12: Pneumomediastinum and left pneumothorax after marijuana use. There is a margin of air adjacent the left heart border extending above the aortic arch into the subcutaneous tissues of the neck (see arrows). An endotracheal tube is seen, as also multiple wires from EKG leads

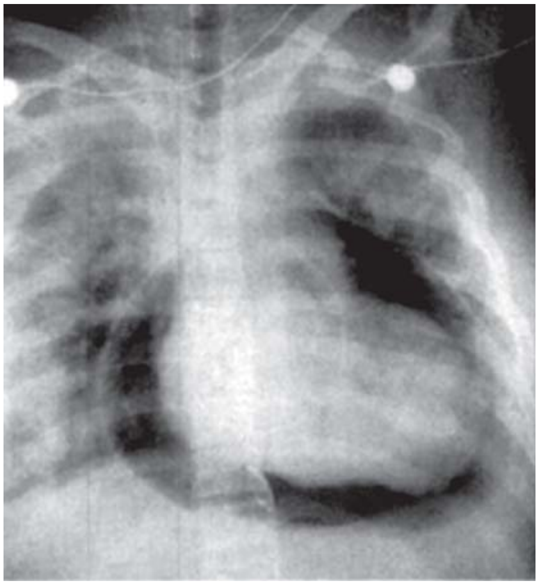

Fig. 145.13: Pneumopericardium. Note the air around the cardiac shadow, which does not extend above the aortic arch into the trachea or soft tissues of the neck

usually seen around the lateral and inferior aspects of the heart; a "continuous diaphragm sign" may be seen as well.

Subcutaneous Emphysema

Subcutaneous emphysema results from the dissection of air into the facial planes; as such the etiology is often similar to pneumothorax or pneumomediastinum. Iatrogenic subcutaneous emphysema can also occur as a complication of chest tube placement. It usually resolves spontaneously. Subcutaneous emphysema tracking through the pectoralis major muscles may sometimes obscure the underlying lung on CXR and make the evaluation of pleural and parenchymal disease difficult—a CT chest may be warranted in these situations.

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Right Heart Catheterization

Vishal K Patel, Anthony Saleh

INTRODUCTION

In 1929 Dr Warner Forssmann introduced a catheter into his own heart and demonstrated that right heart catheterization is feasible in humans, although the catheter was advanced only into the right atrium. Later, Drs Cournand and Richards enhanced this catheter, which could be advanced into the pulmonary arteries. Drs Forssmann, Cournand and Richards were honored with the Nobel Prize in medicine for this invention in 1956.[1]

In 1969, after various improvements in the catheters, Drs Scheinman, Abbott and Rapaport developed a flow-directed right heart catheter to measure right heart pressures.[2] A year after that in 1970, Drs HJC Swan and William Ganz improvised the previous flow directed catheter by adding a balloon flotation feature and hence they are currently known as "Swan-Ganz catheters".[3] Further modifications in these catheters enabled them to measure cardiac output by thermodilution technique, to pace the right atrium and right ventricle, and to measure right-sided pressures including pulmonary capillary occlusion pressure.[4]

After its introduction into clinical practice, the catheter was used extensively in the management of critically ill patients. Most of the recent literature has suggested that while the catheter certainly offers significant theoretical advantages in the management of critically ill patients, there is no mortality benefit from this relatively invasive procedure. For this reason, Pulmonary Artery (PA) catheterization is now used in a very limited subset of patients (Table 146.1).

Setup

The PA catheter is a multilumen catheter of 110 cm length (Fig. 146.1). It is constructed from polyvinylchloride and is pliable. The most commonly used external diameter is 5 or 7 Fr. (1 Fr = 0.0335 mm). The distal port or PA port is located at the tip with a 1.5 cc balloon just proximal to it. When inflated, it guides the catheter from the right heart chambers into the pulmonary artery and it also protrudes beyond the catheter tip minimizing the chances of endocardial damage or arrhythmia. Typically the balloon is inflated with air, however, if a right-to-left intracardiac shunt or a pulmonary arteriovenous fistula is suspected then the balloon should be inflated with filtered carbon dioxide to avoid rupture.[6] If carbon

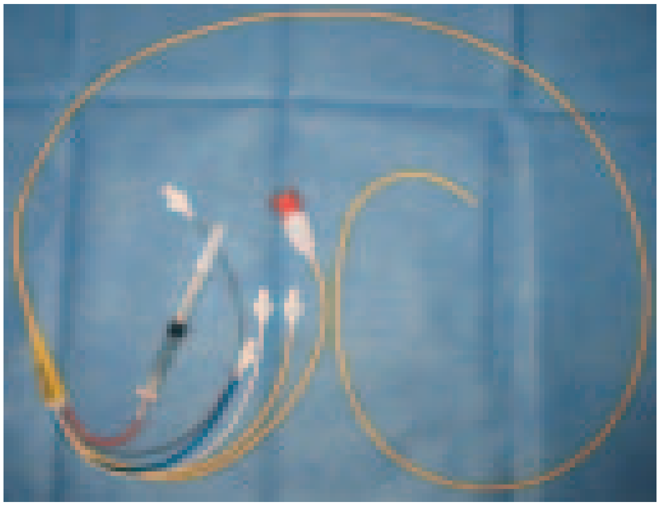

Fig. 146.1: A pulmonary artery catheter

TABLE 146.1: Indications and contraindications of PAC[5]

Indications	*Contraindications*
Diagnostic Diagnosis of shock states	1. Tricuspid or pulmonary valve mechanical prosthesis 2. Right heart mass (thrombus and/or tumor)
Differentiation of high versus low pressure pulmonary edema	3. Tricuspid or pulmonary valve endocarditis
Diagnosis of primary pulmonary hypertension (PPH)	4. Coagulopathy
Diagnosis of valvular disease, intracardiac shunts, cardiac tamponade, and pulmonary embolus	5. Uncooperative patient
Monitoring and management of complicated acute myocardial infarction (AMI)	
Assessing hemodynamic response to therapies	
Management of multiorgan system failure and/or severe burns	
Management of hemodynamic instability after cardiac surgery	
Assessment of response to treatment in patients with primary pulmonary hypertension (PPH)	
Therapeutic Aspiration of air emboli	

dioxide is used, periodic deflation and inflation is required as carbon dioxide diffuses through the latex balloon at a rate of 0.5 ml per minute. Liquids should never be used for balloon inflation.

Approximately 4 cm proximal to the balloon is the thermistor to measure temperature changes for calculation of Cardiac Output (CO). In the most commonly used quadruple-lumen catheter, two additional ports are present at 19 cm and 30 cm from the tip. Also available, a five-lumen catheter has an additional port at 40 cm from the tip, which can be used for fluid or medication infusion. Some catheters are coated with heparin and some have connections for temporary ventricular pacing.

Pressure Transducer

The conversion of the changes in the intravascular pressures into an electrical signal is done by a catheter-tubing-transducer system. Transmission of pressures from the catheter to the display system is achieved via connecting it to a semi rigid, noncompliant tubing filled with isotonic saline. This is then connected to a fluid-filled pressure transducer. This system accurately transmits intracardiac pressures to the transducer, causing small amounts of movement in the transducer membrane. This movement generates a proportional electric current that is amplified and transmitted to the monitor.

Insertion

The PA Catheter (PAC) is usually inserted percutaneously into the internal jugular, subclavian or femoral veins. The right internal jugular has the shortest and straight path to the heart and the left subclavian does not require the PAC to pass and course at an acute angle to enter the SVC (preferred over left internal jugular and right subclavian). The femoral vein approach may make it difficult to pass a PAC into the heart given the distance from the heart and often requires fluoroscopy; especially if the right sided heart chambers are enlarged.

Venous access is done in the Trendelenburg position, while the insertion of the PAC can be done in a flat or slightly upright position under sterile technique. Before insertion, it is important to check the PAC for kinks and balloon integrity. Connect all the lumens to stopcocks and flush them all with isotonic saline to eliminate air bubbles. Flick the PAC tip to check the response on the monitor after connecting it to the transducer. Finally, the PAC is passed through a sterile sleeve before insertion to ensure sterility.

The preformed curve of the PAC is adjusted before insertion to facilitate entry into the PA. Once the catheter displays the right atrial pressure waveforms (at approximately 10–20 cm mark), the balloon is slowly inflated with air. The catheter is passed down stream to obtain Right Ventricular (RV), PA and PA Occlusion Pressures (PAOPs). Inflation of the balloon facilitates the advancement of the catheter and prevents perforation.[7] The catheter is always withdrawn with the balloon deflated to avoid rupture or injury to the vessel. Usually, the right atrium is entered at 15–20 cm, the right ventricle is entered at 25–30 cm and the PAOP can be identified at

40–50 cm. It is essential to monitor the electrocardiogram during the insertion of the PA catheter in the RV because of the possibility of arrhythmias.

Special Considerations

Patients should have normal coagulation parameters before a central venous access is attempted; however, patients on anticoagulation are frequently seen in the ICU setting. Intravenous heparin should be discontinued 3–4 hours prior to the procedure. If the patient is on warfarin, then the INR should be normalized using fresh frozen plasma prior to the procedure.

In certain conditions such as, severe right atrial or right ventricular dilatation, severe pulmonary hypertension, severe tricuspid regurgitation and low cardiac output states, it may be difficult to position a flow-directed catheter and this may warrant the use of fluoroscopic guidance. Infusion of 5–10 ml of cold saline through the distal lumen may stiffen the catheter and may help in positioning the catheter.

Interpretation

Once the PA catheter has been inserted it becomes imperative to appropriately interpret the available data. PA catheterization allows measurement of right atrial, right ventricular, PA and PA occlusion pressure along with cardiac output, mixed venous oxygen saturation and oxygen saturation in the right-sided chambers to detect intracardiac shunting.

End exhalation provides an optimal reference point for PAOP because pleural pressure returns to baseline at the end of exhalation. Pleural pressures can be higher with active expiratory muscle contraction or with the use of Positive End Expiratory Pressure (PEEP).[8]

Normal resting right atrial pressure is 2–8 mm Hg. Two major positive right atrial waves are usually recorded; the A wave and V wave. The A wave is produced by atrial contraction and follows the electrocardiographic P wave.[9] The A wave peak generally follows the electrocardiographic P wave peak by 80 msec.[10] The V wave is produced by venous filling of the right atrium while the tricuspid valve is closed. The peak of the V wave occurs at the end of ventricular systole when the atrium is maximally filled. This follows the electrocardiographic T wave. A third wave known as the C wave, is a minor positive wave due to sudden motion of the atrivoventricular valve ring towards the right atrium and can be seen in cases of P-R prolongation. The X descent follows the A wave and is due to atrial relaxation and the Y descent follows the V wave and is due to rapid emptying of the right atrium (Fig. 146.2).

Normal resting right ventricular pressure is 20–30/0–8 mm Hg. The right ventricular systolic pressure equals the PA systolic pressure except in cases of pulmonic stenosis or RV outflow tract obstruction. The right ventricular diastolic pressure equals the mean RA pressure during diastole when the valve is open. The right ventricular waveform is identified by a sudden upstroke (and down stroke) in the tracing.

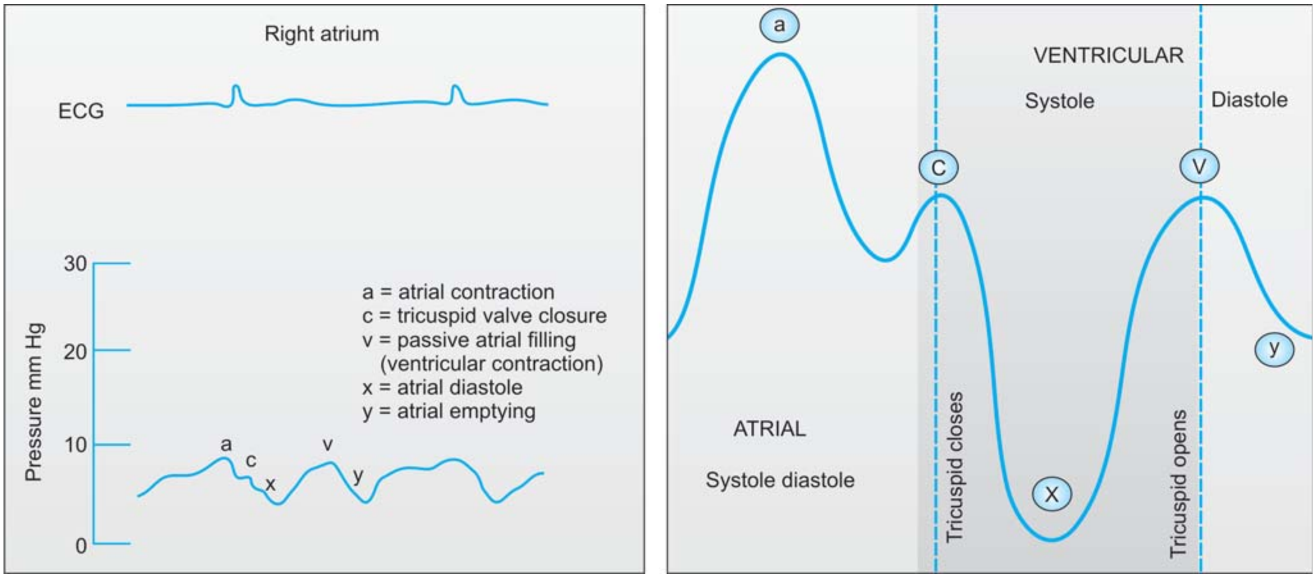

Fig. 146.2: Right atrial waveforms[11,41]

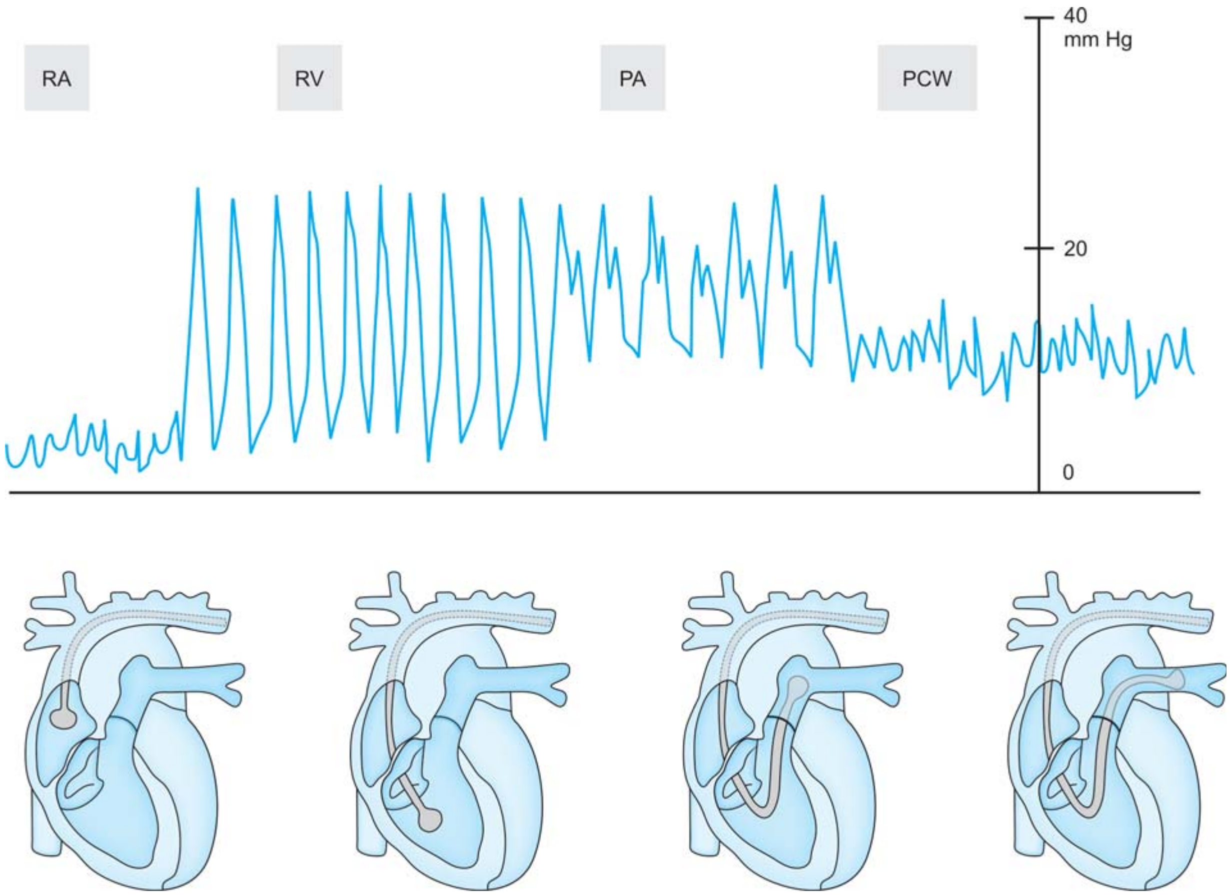

Fig. 146.3: Typical waveform progression as the PAC floats through the cardiac chambers[12]

Normal resting PA pressure is 20–30/5–13 mm Hg. The PA waveform is characterized by a systolic peak and diastolic trough with a dicrotic notch due to closure of the pulmonic valve. PA diastolic pressure is usually 1–3 mm higher than Pulmonary Artery Occlusion Pressure (PAOP) (Fig. 146.3). Thus, the PA diastolic pressure can be used as an index of left ventricular filling pressure in patients in whom an occlusion pressure is unobtainable.

Normal PAOP is 2–12 mm Hg. The PAOP waveform is similar to right atrial waveform except the V waves on PAOP are larger than the A wave. Once the PAOP is obtained, the balloon should be deflated to produce PA waveforms again. Wedge position can be confirmed by withdrawing a blood specimen from the distal lumen and measuring the oxygen saturation from the sample. It confirms the wedge position, if the measured oxygen saturation is higher than 95%. Mean PAOP correlates with left ventricular end diastolic pressure (LVEDP), provided the patient has a normal mitral valve and normal left ventricular function. PAOP estimates pulmonary venous pressure and therefore left atrial pressure, on if the catheter tip is in the zone 3 of the lungs. In zone 3 pulmonary arterial and venous pressures are greater than alveolar pressures, providing an uninterrupted column of blood between the catheter tip and the pulmonary veins.[13] A catheter wedged outside zone 3 shows marked respiratory variations and irregular vascular waveforms which cause a misinterpretation of reading higher pressures (Fig. 146.4).

Once the catheter has been appropriately inserted and adequate position is verified, the critical job of interpreting the data accurately and making the necessary interventions is left up to the clinician. There are a variety of conditions, which can be either definitely diagnosed (VSD, pulmonary hypertension) or highly suggested (cardiogenic pulmonary edema, cardiac temponade) via PA catheterization. Additionally, certain conditions such as septic shock, hypovolemic shock and pulmonary embolism can be confirmed with PA catheterization (Table 146.2).

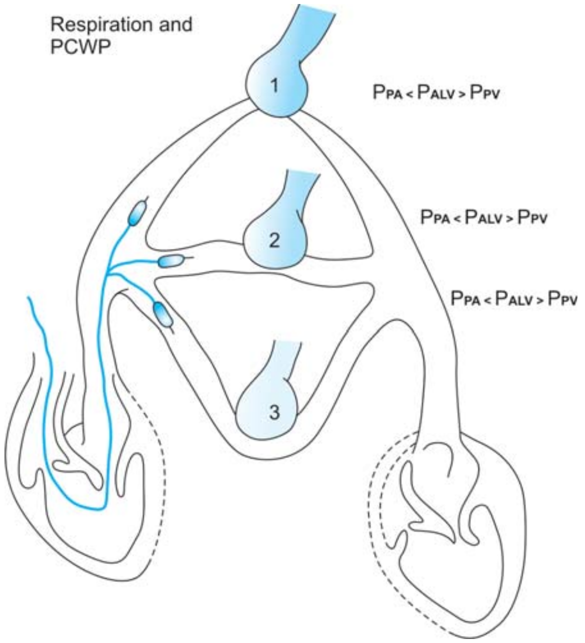
Respiration and PCWP
1
$P_{PA} < P_{ALV} > P_{PV}$
2
$P_{PA} < P_{ALV} > P_{PV}$
$P_{PA} < P_{ALV} > P_{PV}$
3

Fig. 146.4: Physiologic lung zones[42]

Complications

The PA catheterization is associated with a variety of complications. These can be divided into those related to central venous catheterization and those specific to the PA catheter.

The complications associated with central venous access can be seen during right heart catheterization. The reported complications include local hematomas; injury to thoracic duct, carotid artery; pneumothorax and pseudoaneurysm formation. Pulmonary infarction is a potentially preventable complication of PA catheterization caused by distal migration of the PA catheter tip into the smaller branches of the PA causing persistent wedging.[14] It is also seen if the balloon is left inflated in the wedge position for an extended period of the time.[15] A potentially fatal and feared complication of PA catheterization is rupture of the pulmonary artery. It has been reported in 0.1 to 0.2% of patients with a mortality of 45 to 65%.[16,17] It can occur during insertion or a few days after insertion.[18] It presents typically with massive hemoptysis and emergency management includes immediate angiogram with embolization, selective intubation of the unaffected lung and/or lobectomy.

The PA catheter, being a foreign body in a vascular system, can damage the endothelium and cause thrombosis. These thrombi can encase the tip of the catheter or form anywhere in the venous system acting as pulmonary emboli. A changing relationship between PADP and PAOP over a period of time should

TABLE 146.2: A summary of PA catheter findings in selected clinical situations[43]

	RA	*RV*	*PA*	*PAWP*	*AO*	*CI*	*SVR*	*PVR*
Normal	0-6	25/0-6	25/6-12	6-12	130/80	≥2.5	1500	≤250
Hypovolemic shock	0-2	15-20/0-2	15-20/2-6	2-6	≤90/60	<20	>1500	≤250
Cardiogenic shock	8	50/8	50/35	35	≤90/60	<2.0	>1500	≤250
Septic shock								
Early	0-2	20-25/0-2	20-25/0-6	0-6	≤90/60	≥2.5	<1500	<250
Late	0-4	25/4-10	25/4-10	4-10	≤90/60	<2.0	>1500	>250
Acute massive PE	8-12	50/12	50/12-15	≤ 12	≤90/60	<2.0	>1500	>450
Cardiac tamponade	12-18	25/12-18	25/12-18	12-18	≤90/60	<2.0	>1500	≤250
AMI without LVF	0-6	25/0-6	25/12-18	≤18	140/90	≤2.5	1500	≤250
AMI with LVF	0-6	30-40/0-6	30-40/18-25	>18	140/90	>2.0	>1500	>250
Biventricular failure 2° to LVF	> 6	50-60/>6	50-60/25	18-25	120/80	<2.0	>1500	>250
RVF 2° to RVI	12-20	30/12-20	30/12	<12	≤90/60	<2.0	>1500	>250
Cor pulmonale	>6	80/>6	80/35	<12	120/80	<2.0	>1500	>400
Idiopathic pulmonary hypertension	0-6	80-100/40	80-100/40	<12	100/60	<2.0	>1500	>500
Acute VSR	6	60/6-8	60/35	30	≤90/60	<2.0	>1500	>250

RA—Right atrium, RV—Right ventricle, PA—Pulmonary artery, PAWP—Pulmonary artery wedge pressure, AO—mean systemic arterial pressure, PVR—Pulmonary vascular resistance, AMI—Acute myocardial infarction, LVF—left ventricular failure, infarction, RVF—right ventricular failure, VSR–ventricular septal rupture, CI—cardiac index, SVR—Systemic vascular resistance

increase suspicion for thrombosis at the tip. Knotting of the catheter results when the catheter forms a loop in the cardiac chamber and the catheter is repeatedly withdrawn and advanced.[19] Knotting is avoided by not advancing the catheter beyond the approximately anticipated distance. Knotted catheters can be removed transvenously or surgically. Knotting of the PA catheter around intracardiac structures, other intravascular catheters, and intracardiac sutures has been reported.[20-22] The main problem associated with balloon rupture is air emboli gaining intravascular entry and/or balloon fragments embolizing into the distal pulmonary circulation. If the rupture occurs during catheter insertion, the loss of the balloon's protective function can cause endocardial damage and/or arrhythmia. Atrial and ventricular arrhythmias are common during insertion of a PA catheter. Most arrhythmias are self-limited and do not necessitate treatment; however, up to 3% of sustained arrhythmia may warrant treatment.[23,24] Transient right bundle branch block can be seen during catheter insertion. Patients with pre-existing left bundle branch block can be at risk of complete heart block due to transient right heart block during catheter insertion.

Damage to the right atrium, right ventricle, pulmonic valve, tricuspid valve and supporting chordate can occur during insertion or withdrawal of the catheter. It is primarily seen while withdrawing a catheter with the balloon inflated.[3] Catheter related infections, which can be seen with the central venous access catheter, are also seen with PA catheters.

Clinical Controversy

A variety of studies from 1980 to 2000 showed a greater mortality rate in patients who underwent placement of a PAC than in those who did not. A great clinical controversy ensued from these studies as critics claimed the acutely ill patients in the ICU are more likely to undergo PAC. Since, then a number of randomized clinical trials have been published:

- In 2003 a study by Sandham et al of nearly 2000 surgical patients (ASA class 3 or 4) aged 60 years or older, randomized PAC to guide therapy versus central venous catheter and therapy on physician's discretion. Results showed no difference in mortality, length of stay or organ dysfunction.[25]
- A study by Richard et al looked at 700 patients with early shock, ARDS, or both. There was no significant difference in mortality or morbidity in patients treated with or without PAC.[26]
- Rhodes et al showed no difference in 28-day mortality, ICU or hospital length of stay in patients with or without a PAC. However, a formal management protocol was not used.[27]
- An important study, recently published in 2005 was the PACMAN trial. This trial enrolled more than 1,000 patients. There was no difference in mortality (primary outcome) in patients treated with or without a PAC.[28]
- Another trial published in 2005, the ESCAPE trial demonstrated no difference in overall mortality or hospitalization in more than 400 patients who were admitted with severe heart failure. Patients were randomized to clinical assessment guided therapy versus PAC.[29]
- A large meta-analysis done by Shah et al including 13 randomized clinical trials and more than 5,000 patients did not show any significant benefit from the use of a PAC.[30]
- In 2006, the ARDSNET group evaluated the role of the PAC in acute lung injury patients. Patients were randomized to hemodynamic management with either a PAC or a Central Venous Catheter (CVC). It did not show any difference in mortality (primary outcome), ICU length of stay, or lung function.[31]
- Published in 2006, a study of PAC use in cardiac surgery patients by Djaiani et al showed that the use of PAC derived data lead to more interventions but no overall clinical benefit.[32]
- A Cochrane Review of 12 studies was only able to support the need for efficacy studies, to determine optimal the patient groups who could benefit from management with a PAC.[33]

CONCLUSION

In summary, the literature does not show a beneficial effect on patient outcome with PAC use; however, a criticism of the current available research is that the patient groups studied are the ones which gain little or no benefit from PAC use. Chittock et al published an observational cohort study showing that PAC use was associated with increased mortality in less acutely ill patients but decreased mortality in more acutely ill patients.[34]

The use of a monitoring tool, such as the PAC itself, is unlikely to show a significant treatment effect. Some criticize the current literature because a number of studies did not use a predefined treatment protocol. The lack of defined specific treatment based on measured PAC-derived variables could contribute more to patient outcome than merely the presence or absence of a PAC. The other factors that impact mortality outcomes include operator competence, nursing dependent data information from PAC and physician-dependent interpretation of data and subsequent management. A time-trend analysis on national estimates of PAC use in the United States from 1993 to 2004, using data from the Nationwide Inpatient Sample, found a 65% decrease in PAC use during that period; the most prominent decline, by 81%, was in use of PACs for myocardial infarction.[35]

The newer noninvasive modalities to measure cardiac output using ultrasound or arterial pressure waveforms may provide a safer alternative to the PAC; however, more studies are needed to support their use.[36]

In conclusion, PACs remain an important tool, but they should be used only selected patients and only by well-trained physicians.[37-39] A concise review by Chatterjee offers some reasonable indications for ongoing PAC use; however, these unfortunately lack empiric evidence at present.[40]

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Section

19

GENERAL ISSUES IN THE INTENSIVE CARE UNIT

Ritesh Agarwal
SK Jindal

147

Nutritional Management and General Care in the Intensive Care Unit

Navneet Singh

Malnutrition arises from an imbalance between the nutrient intake and the nutrient requirements (Fig. 147.1). Diseases especially the critical illnesses, are unique that they not only affect nutritional intake and requirements, but also increase nutrient losses (urinary, gastrointestinal or from other sites). Infact, multiple mechanisms are believed to be operating simultaneously in majority of the malnourished critically ill patients (Fig. 147.2).

MALNUTRITION IN CRITICAL ILLNESS

Prevalence and Epidemiology

The prevalence of malnutrition among hospitalized patients, including those in Intensive Care Unit (ICU), has increased steadily over the years because of several reasons, such as an increasing age of the general population, development of newer and often aggressive medical and surgical treatment modalities for different chronic debilitating diseases, and finally because of the progress achieved in intensive care management.[1,2] The prevalence of malnutrition among hospitalized patients is estimated to be as high as 30 to 50%.[3] Amongst patients admitted to the ICU, malnutrition is equally common, if not more.[4-6]

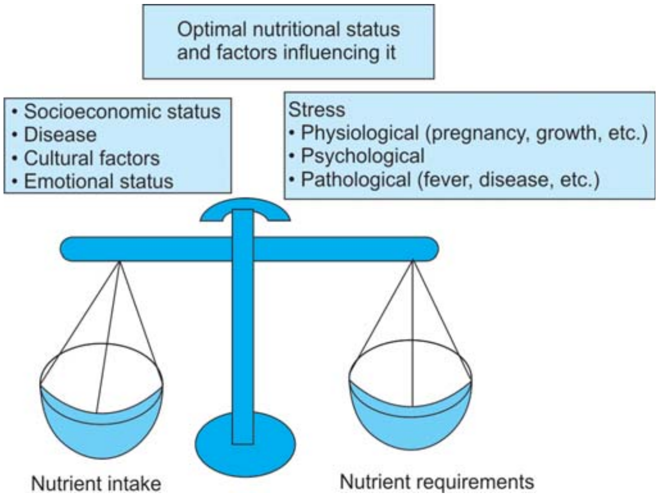
Optimal nutritional status
and factors influencing it
• Socioeconomic status
• Disease
• Cultural factors
• Emotional status
Stress
• Physiological (pregnancy, growth, etc.)
• Psychological
• Pathological (fever, disease, etc.)
Nutrient intake
Nutrient requirements

Fig. 147.1: Factors influencing nutritional status and the balance between intake and requirements

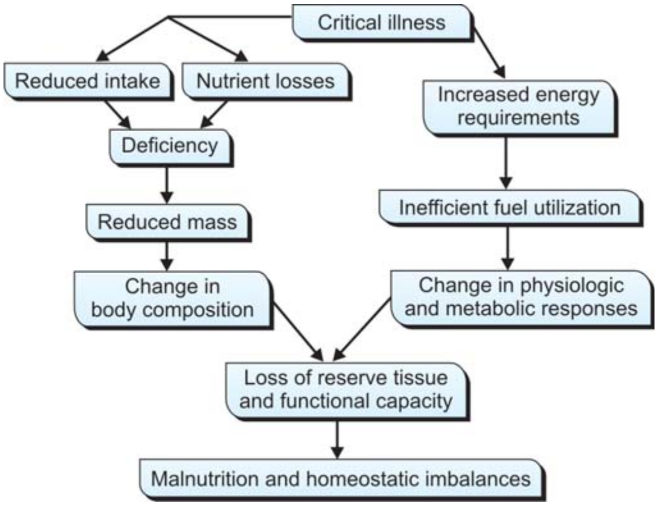
Critical illness
Reduced intake
Nutrient losses
Increased energy requirements
Deficiency
Reduced mass
Inefficient fuel utilization
Change in body composition
Change in physiologic and metabolic responses
Loss of reserve tissue and functional capacity
Malnutrition and homeostatic imbalances

Fig. 147.2: Mechanism of influence of critical illness on nutritional homeostasis

Malnutrition can be either present at admission or develop subsequently as a result of metabolic response to injury. The accelerated catabolic state occurring in critically ill patients can lead to rapid onset of malnutrition. Uncorrected malnutrition is succeeded by metabolic abnormalities, physiologic changes, reduced organ-cum-tissue function and finally, loss of body mass.[7] Malnutrition can affect the pulmonary system directly by causing a reduction in diaphragmatic muscle mass, respiratory muscle strength, maximum voluntary ventilation and functional residual capacity. It can also lead to a rapid shallow pattern of breathing pattern, increase in the quantity of interstitial fluid and predisposition to atelectasis.[8]

Any or all of these can be present in a patient on mechanical ventilatory support and make the process of weaning difficult. Nutritional supplementation provides an opportunity to slow down or even halt the catabolic process and thus prevent malnutrition, which in turn can favorably alter the hospital course of such patients. Optimal nutritional support is thus an essential component of patient care in acute or chronic critical illnesses in order to prevent and treat nutritional deficiencies. Heightened awareness of its importance has led it to become a routine part of management of patients in majority of ICUs.

Differentiation of Catabolism in Critical Illness from Starvation

It is important to differentiate catabolic state of critical illness from starvation (Table 147.1). One of the fundamental differences between the two is the Basal Metabolic Rate (BMR) which is elevated in a critical illness in contrast to starvation where it is depressed.[9] Ketogenesis is a prominent feature of starvation but not of critical illness.[7]

Effect of Malnutrition on Clinical Outcomes in Critically Ill Patients

In some studies, the incidence of complications, hospital length of stay and in-hospital mortality rates have been shown to be significantly higher in malnourished, critically ill patients as compared to those who are well-nourished.[4,6] Furthermore, presence of malnutrition is associated with worse outcomes even with a lesser severity of critical illness.[4] In patients admitted to the respiratory ICU at this institute, the mean daily calorie delivery of less than 50% of recommended values was shown to be independently associated with hospital mortality (Fig. 147.3).[10]

TABLE 147.1: Differentiation of catabolism in critical illness from starvation

Feature	*Catabolism in critical illness*	*Starvation*
BMR/REE	↑	↓
Respiratory quotient	(0.8-0.9)	(0.6-0.7)
Cytokine levels	↑	↓
Primary fuels	Mixed	Fat
Proteolysis	+++	+
Ureagenesis	+++	+
Urinary nitrogen losses	+++	+
Gluconeogenesis	+++	+
Ketone production	+	+++

BMR = Basal Metabolic Rate
REE = Resting Energy Expenditure

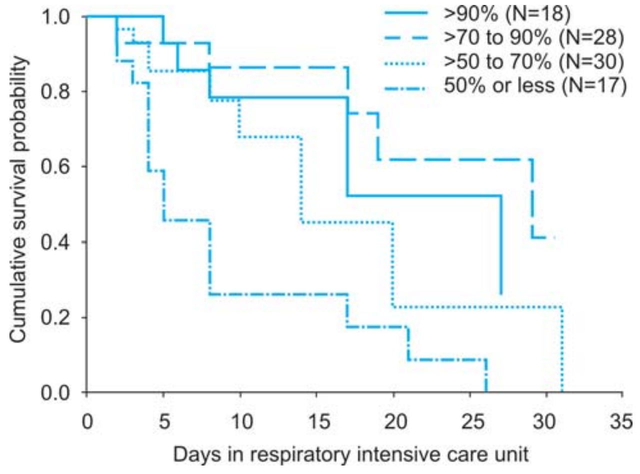

Fig. 147.3: Kaplan-Meier analysis for probability of survival stratified according to mean calorie delivery (as percentage of recommended values). Mean calorie delivery of less than 50% of recommendations reduced the probability of survival significantly. [Reproduced with permission, from Singh N, Gupta D, Aggarwal AN, et al. Respir Care. 2009; 54(12):1688-96]

No differences were seen between the well-nourished and the malnourished patients with regard to either length of stay or in-hospital mortality in other studies.[5] These discrepancies were explained, in part, by the complexity of the relationship between the underlying conditions which mandated ICU admission and mortality.[11] Variations in the reported prevalence of malnutrition as a result of differences in type of screening tools used for its detection can also explain the difference. Among the other clinically relevant outcomes, nosocomial infections have been shown to be more frequent in malnourished ICU patients.[12]

ASSESSMENT OF NUTRITIONAL STATUS IN CRITICALLY ILL PATIENTS

Assessment of nutritional status includes evaluation of clinical, anthropometric, chemical and immunologic parameters. Patient history should include details of diseases that are associated with heightened risk of malnutrition especially of the chronic debilitating diseases, history of inadequate food intake over prolonged periods of time, drug abuse, alcoholism and chronic psychiatric disorders. Physical examination should include nutrition focused physical examination, anthropometry and body composition/circumference measurements.

All the tests used for assessment of nutritional status have their own limitations, hence there is no single test that is sensitive and specific enough on its own to detect malnutrition in critically ill patients.[13]

1. **Body weight:** Alteration of nutritional status and protein calorie malnutrition is usually accompanied by weight loss. Unintentional loss of body weight (more than 10% in six months or more than 5% in one month) is clinically significant and suggestive of malnutrition.[14] Critically ill patients are often edematous due to progressive retention of salt and water. Body weight may not reflect the actual body cell mass in such cases. Moreover the 'normal' reference value for a particular patient is difficult to define because of the marked heterogeneity of race, body built and age in the control population leading to a wide range of normal values. Measured body weight can be compared to Ideal Body Weight (IBW), can also be used in association with height to calculate Body Mass Index (BMI).
2. **Anthropometry:** Anthropometric measurements provide an objective evaluation of fat and lean body mass. They are safe, simple, inexpensive and can be readily performed at the bedside of the patients including the critically ill patients. Body fat reserve and skeletal muscle mass can be assessed by carrying out measurements of Skin Fold Thickness (SFT) and Mid Arm Muscle Circumference (MAMC) respectively.[15] Measurement of SFT is based on the assumption that almost half of the total body fat is distributed in the subcutaneous region but this can vary from 20 to 70% in normal subjects. Commonly, triceps SFT is measured but subscapular, iliac crest and upper thigh are other areas that can be used. The normal values of these anthropometric measurements vary with age and gender.[16] There is also a tendency for over and under-estimation of body fat in the malnourished and obese patients respectively. Fluid shifts that occur acutely in critically patients especially those who receive aggressive fluid resuscitation may alter the reliability of these measurements.[13,14]
3. **Hepatic secretory proteins:** Albumin, prealbumin, transferrin, retinol binding protein and other proteins secreted by liver are used as indicators of nutritional status since they reflect visceral protein stores.[17] Hepatic synthesis of these proteins is reduced in cases of acute infection/inflammation, they are referred to as negative acute phase reactant proteins [as compared to positive acute phase reactants like C-reactive Protein (CRP), fibrinogen and α-1 glycoprotein whose synthesis is increased under similar conditions]. However, these proteins have different half-lives and their serum levels are influenced by factors other than nutritional status such as abnormal hepatic function, hydration status, protein losing diseases and acute infection/inflammation.[13,18,19] Despite the limitations, one or more of these proteins continue to be used for predicting patient outcomes.[20,21] In the author's experience, higher baseline serum albumin levels are observed among critically ill patients who survive, compared to the non-survivors.[10]
4. **Others:** The other parameters that have been used for nutritional assessment include Total Lymphocyte Count (TLC) and Delayed Cutaneous Hypersensitivity (DCH).[22] Blood/serum levels of electrolytes like potassium, phosphorus, calcium and magnesium are useful markers of adequate supplementation, and these key electrolytes should be monitored with a frequency that depends upon the anticipated abnormalities, in their levels.
5. **Multiparameter nutritional indices:** These parameters are used to overcome the sensitivity and specificity problems associated with single nutritional assessment tests. Examples include Subjective Global Assessment, Prognostic Nutritional Index Prognostic Inflammatory and Nutritional index.[5] Even though these multiparameter indices are objectively designed, they rely on the values of different clinical and laboratory parameters, hence are limited by the same concerns as the individual parameters themselves.

GOALS AND PRINCIPLES OF NUTRITIONAL SUPPORT

General goals of providing nutritional support to the critically ill patients include:

1. Provision of nutritional support to the patient after taking into consideration his/her medical condition, nutritional status, existing metabolic requirements and the route available for administration of nutrients.
2. Prevention and treatment of both macro-and micronutrient deficiencies.
3. Avoidance of complications associated with nutritional support (enteral and/or parenteral).
4. Improvement in outcomes related to disease morbidity.

TIMING OF INITIATION OF NUTRITIONAL SUPPORT

The timing of initiation of nutritional support has been an area of intense debate. Nutritional support is indicated in any critically ill patient who suffers from malnutrition (of any etiology) and is unable to eat. Many patients, especially those who are previously well-nourished, can tolerate short periods of starvation (usually of less than one week) during a critical illness. Even in well-nourished patients, nutritional supplementation is necessary if they are unable to resume oral nutrition or if their oral intake is insufficient for more than three to four days.[1] When a greater severity of critical illness is present, this delay should be shortened to one to two days or less since the deprivation of nutrients and/or presence of a hypercatabolic state even for a short period of time is likely to be associated with increased morbidity and mortality. Enteral nutritional support can thus be started as early as 12 to 48 hours of admission to the ICU. In most critically ill patients oral-feeding may not be feasible and hence enteral nutritional support should be attempted after placement of a nasogastric (or in some cases nasojejunal) tube. It has been amply shown that aggressive initiation of early enteral nutrition (EN) to mechanically ventilated patients was associated with greater complications.[23]

In a retrospective analysis of a multi-institutional ICU database involving 4049 mechanically ventilated medical patients, it was observed that 63% of the patients who had received early enteral nutritional support (within 48 hours of initiation of mechanical ventilation [MV] (early feeding group) had better outcomes compared to the remaining 37% patients (late-feeding group).[24] The early feeding group had lower ICU and hospital mortality rates. The lower mortality rates in the early feeding group were most evident in the sickest group as defined by quartiles of severity of illness scores. The early feeding group, however, had a higher incidence of Ventilator-Associated Pneumonia (VAP). Therefore the authors had suggested that routine administration of early feeding may be warranted in medical patients receiving MV who are at high-risk of death.

In a systematic review of 15 prospective Randomized Controlled Trials (RCTs) involving a heterogeneous population of 753 adult ICU patients, effects of early EN were compared to delayed EN (initiation of nutritional support within and after 36 hours respectively).[25] Early enteral nutrition was associated with a significantly lower incidence of infections (relative risk reduction = 0.45 EN) and a reduced length of hospital stay (mean reduction = 2.2 days). Reduction in mortality in the early feeding group (8 vs 11.3%) did not reach statistical significance. No difference was however, found between the two groups in terms of non-infectious complications.

Consensus statements have also chosen to differ over the optimal time of initiation of nutritional support. A consensus statement of the American College of Chest Physicians recommended that enteral EN be initiated as soon as possible after resuscitation in ICU patients when significant preexisting malnutrition is present (BMI under 16).[13] The Working Group on Nutrition and Metabolism of the European Society of Intensive Care Medicine had recommended that enteral feeding should be initiated as early as possible in ICU patients.[1] There are others who recommend that nutritional support should be started in patients who are not expected to resume oral feeding for a "prolonged" period of time (7 to 10 days).[26]

The latest practice guidelines from Society of Critical Care Medicine and American Society of Parenteral and Enteral Nutrition for the provision and assessment of nutrition support therapy in the adult critically ill patient give a grade C recommendation about starting enteral feeding early (within the first 24 to 48 hours following admission).[27] The aim of starting enteral feeding as early as possible is not necessarily to provide nutritional support alone but also to have other beneficial effects on the gut, which can be attained with even small amounts of enteral feeding.

ROUTE OF ADMINISTRATION OF NUTRITIONAL SUPPORT

Nutritional support may be given by either the enteral or parenteral route or both. There is increasing evidence to suggest that, in the presence of a functional gut, nutrition should be administered by the enteral route, whenever possible. It is also becoming quite clear that the consequences of EN go beyond the supply of nutrients to the body.[28] Modulation of the host's immune response and the provision of energy and protein to maintain gut integrity could be some of the possible reasons for the same. Enteral nutrition favors maintenance of structure and functioning of intestinal villi (both by reducing the incidence of mucosal atrophy as well decreasing the abnormal increase in intestinal permeability) and thus promotes gut motility which eventually helps in initiating oral feeding.[29]

The proposed mechanisms for the beneficial effects of EN on the gut include stimulation of epithelial cell metabolism by direct contact with nutrients, increase in mucosal blood flow, and secretion of IgA and enterotrophic hormones like gastrin and enteroglucagon.

Enteral nutrition is also less expensive, leads to improved utilization of nutrients, and possibly helps to avoid some of the infectious complications associated with parenteral nutrition (PN), one of the mechanisms being reduction in translocation of bacteria from the gut.[30]

Comparison of Enteral with Parenteral Nutrition—Evidence from Published Literature

In a meta-analysis based on 'intention to treat' principle of 11 trials that had compared EN to PN in critically ill patients, a mortality benefit was seen in favor of use of PN.[31] However, subgroup analysis showed that the benefit from its use was only apparent in trials wherein initiation of EN had been delayed beyond 24 hours. When the use of PN was compared to the provision of early EN, there was no difference in mortality. Incidence of infectious complications was significantly more with the use of PN. The authors recommended PN among patients in whom EN could not be initiated within 24 hours of ICU admission or injury. However, its relevance to medical ICU patients remains unclear, since a majority of the trials included in this analysis involved surgical and trauma patients.

A systematic review of 13 RCTs which compared enteral and parenteral nutritional support in terms of outcome of critically ill adult patients, and included a heterogeneous population of 807 ICU patients showed that the use of EN in comparison to PN, was associated with significant reduction in the incidence of infectious complications as well as reduction in cost of nutritional support.[32] There was no difference in mortality, duration of MV or length of hospital stay. Moreover, use of PN was associated with an increase in the incidence of hyperglycemia in addition to the total administered calories. This analysis again showed that EN should remain the first choice for nutritional support in the critically ill.

Comparison of early EN with early parenteral nutrition among hospitalized patients was done in a meta-analysis, which involved 30 RCTs and PN, included 2430 critically ill medical, surgical and trauma patients. No significant difference was found between the groups receiving early EN and early PN in terms of hospital mortality.[33] The definition of early EN or PN used herein was the institution of supplemental nutrition within 96 hours of hospitalization, ICU admission or surgery. The results held true even when subgroup analysis was carried out separately for medical, surgical and trauma patients. Use of PN, however, was associated with an increased incidence of infective (including catheter related bloodstream infections) and non-infective complications as well as prolongation of length of stay in the hospital. Importantly among medical patients, in addition to the above, technical complications were also observed to be more frequent with use of PN. The only complication that was observed to be higher with use of EN was the incidence of diarrhea. Thus, even though no mortality benefit was shown in this analysis, EN was shown to have significantly less complications as compared to PN in the setting of early initiation of nutritional support.

In spite of the preferences for the enteral route, PN remains "a valuable yet challenging weapon in our therapeutic armory in the presence of gastrointestinal feed intolerance or failure. It should be used wisely and not indiscriminately, since most intensive care patients with a fully functional gastrointestinal tract can be fed safely with enteral nutrition".[34]

Addition of Parenteral to Enteral Nutrition

There is a school of thought among intensivists that adding PN to EN leads to improvement in calorie delivery and therefore may positively influence patient outcomes. However, published literature seems to suggest otherwise. In a prospective, double-blind RCT, 120 patients admitted in two ICUs were randomized into 2 groups: EN plus PN (treatment group) and EN plus placebo (placebo group).[35] Patients received nutritional support for a period ranging from four to seven days. Although the study met its primary end points (increase in serum levels of retinol-binding protein and prealbumin at day seven in the treatment group), there were no differences between the two groups for the clinically relevant end points (ICU morbidity, length of ICU stay, immediate and long-term mortality).

A systematic review of five RCTs compared combined EN and PN to EN alone and included a heterogeneous population of 248 ICU patients.[36] In these studies, PN was initiated at the same time as the EN. There were no differences between the two groups in terms of mortality, rates of infection, hospital length of stay and duration of MV. Combining PN to EN lead to significant increases in the total amount of calories delivered, as well as the total cost. This review again led to the conclusion that in critically ill patients who are not malnourished and have an intact gastrointestinal tract, starting PN at the same time as EN provides no benefit in clinical outcomes over EN alone.

Contraindications to Enteral Nutrition

It is not uncommon to encounter absolute and relative contraindications for administration of enteral nutritional support. Enteral nutrition is absolutely contraindicated in patients with a nonfunctional gut due to intestinal obstruction, anatomic disruption, generalized peritonitis or severe intestinal ischemia. Normally, splanchnic blood flow increases in response to nutrient load, taken orally/ administered enterally. This response is lacking in patients who have reduced gut perfusion due to severe or prolonged shock. Even if it occurs, it may not be sustained and this ultimately leads to hampered digestion and absorption. Infact, early feeding during hemodynamic compromise/shock can further contribute to mesenteric ischemia, infarction and even perforation. Therefore, it is prudent to withhold enteral nutritional support until hemodynamic stability has been achieved.[27]

Relative contraindications to enteral feeding include the occurrence of abdominal distension with administration of enteral feeds, presence of localized peritonitis, intra-abdominal abscess or severe pancreatitis, patients with a terminal disease, comatose patients at high risk of aspiration and patients with short bowel (less than 30 cm).[1]

QUANTITY AND VOLUME OF NUTRITION SUPPORT

Recommendations and practice guidelines have been revised from time-to-time in relation to the quantity of nutritional support to be administered to critically ill patients.[1,27,37] These recommendations can be broadly discussed under the following subheadings:

1. **Energy (Calorie) requirements:** For most patients, provision of calories in the range of 20 to 30 kcal/kg per day is appropriate. Factors that should be taken into consideration while deciding the optimal amount for a given patient include gender, age, presence/ absence of pre-existing malnutrition, type and severity of critical illness as well as the phase of critical illness (acute vs recovering). The target goals for energy (calorie) delivery should be determined at the time of initiation of nutritional support. It is desirable to achieve the goal of providing the entire energy requirements by the enteral route alone within the first 7 to 10 days of hospitalization. In case the same is not possible, initiation of supplemental PN should be considered.
2. **Protein requirements:** Protein delivery should be fixed between 1.2 to 1.5 gm/kg body weight per day (maximum 2.0 gm/kg body weight per day). Patients with extreme protein losses (e.g. extensive burns, digestive or urinary losses) can be given higher intake.
3. **Volume requirements:** In general, approximately 1 ml of water is needed per kcal while administering enteral feeds. However, fluid requirements and restrictions vary from patient-to-patient and therefore, the total volume to be administered may need to be individualized. The total amount of calories can be administered in a volume that is appropriate for the patient by changing the relative concentrations of the different constituents. The recommended proportion of carbohydrates, fats and proteins is 30 to 70%, 15 to 30% and 15 to 20% respectively of total calories.[1,13] For non-protein calories, carbohydrates and fat should be given in a ratio ranging from 1.5:1 to 2.5:1.
4. **Issues related to body weight:** Determination of body weight is an important issue for critically ill patients. It is neither easy to weigh patients in the ICU nor are such measurements free from errors since critically ill patients can have rapid and significant shifts in body water content. If direct weighing is not feasible, IBW can be estimated from height and anthropometric tables. The body weight used for calculating energy and protein requirements often needs to be modified according to the baseline nutritional status. Malnourished and obese patients generally require calorie delivery based upon determination of an "optimal" body weight.[38] The latter tends to fall in between their ideal and actual body weights and is higher or lower than the actual body weight for malnourished and obese patients respectively. Since, different formulae and methods have been proposed for such calculations and there is a lack of consensus, it is difficult to pinpoint the most accurate or appropriate method.
5. **Issues related to estimation of energy requirements:** More than 200 predictive equations (including the Harris-Benedict equation - the most well known of all of these) have been published for the assessment of energy requirements among critically ill patients.[27] By using the Harris-Benedict equation, the Resting Energy Expenditure (REE) can be calculated and subsequently the Total Energy Expenditure (TEE) estimated by multiplying REE with a Stress/Activity Factor (normally 1.2 to 1.4 in critically ill patients). Indirect calorimetry is another method used for this purpose and is probably more accurate than either the equations or simple formulae. However, using either the predictive equations or indirect calorimetry in routine ICU practice is not easy since these involve a lot of calculations and correction factors or are technically difficult. Also, it is unclear whether patient

outcomes will improve substantially if overworked staff and health care professionals in busy ICUs devote a significant percentage of their valuable time and effort in these calculations.

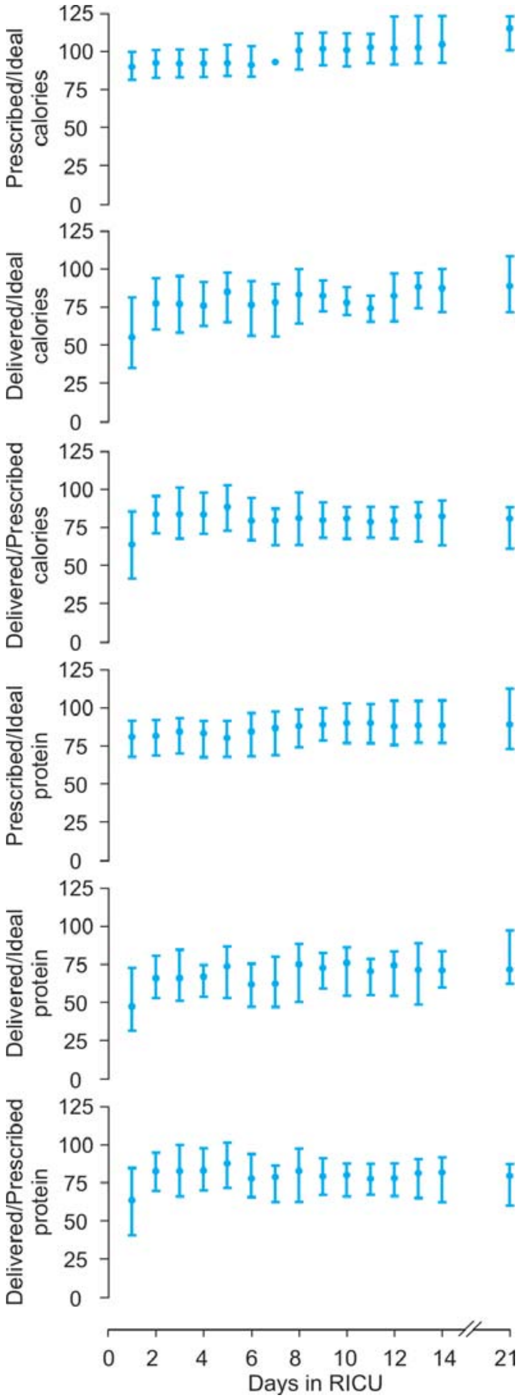

Fig. 147.4: Trend in prescriptions and delivery of calories and protein in relation to duration of stay in Respiratory Intensive Care Unit (RICU). Circles represent median values while lower and upper horizontal bars of plots represent the 25th and 75th percentiles respectively. Ideal calories and proteins correspond to recommend values of 30 kcal/kg/day for calories and 1.2 gm/kg/day for proteins. [Reproduced with permission, from Singh N, Gupta D, Aggarwal AN, et al. Respir Care. 2009; 54(12):1688-96]

DELIVERY OF ENTERAL NUTRITION AND ITS DETERMINANTS

The quantity of enteral feeds administered has been shown to be significantly lower than what is prescribed in as high as 40% of all hospitalized patients.[39] Other studies have shown that patients in ICUs also remain underfed.[40,41]

In a prospective study involving more than 400 ICU patients, successful administration (defined as 90% or more of the prescribed value) was achieved in only 52% of the total (n = 3526) feeding days.[42] Although the percentage of successful feeding days increased from 39% on day 1 to 51% on day 5, the overall average energy, protein and volume intake remained 54%, 66% and 75% respectively of the prescribed values. Feed intolerance was noted as an important impediment to successful nutrition delivery. Use of formulations with a higher energy and protein density has been suggested to enhance the total nutritional intake.

Prescription in Relation to Recommended Values

It is important to remember that, both the prescription and delivery are lesser for protein in comparison to those for calories. In a prospective study conducted at the author's institute, the median calorie and protein delivery for patients admitted to the Respiratory ICU (RICU) were 55.1 and 46.7% of the recommended values respectively on day 1.[10] It was not just delivery that was suboptimal. Even the median prescription of calories and proteins was 88.9 and 80.1% respectively of the recommended values on day one. The daily prescription and delivery of both calories and protein (as a percentage of recommended values) improved during the subsequent days of ICU stay (Fig. 147.4). A similar trend has been documented in previously conducted studies also.[43] Other studies that have compared actual prescription with recommended intake have also revealed protein delivery to be the area of largest overall deficit.[42,43]

Feeding interruptions because of diagnostic or therapeutic procedures remain an important reason for this reduced intake. High gastric residual volumes and mechanical feeding tube problems are other common reasons for decreasing or discontinuing feeds after initiation. Potential factors implicated for intolerance to feeds include the admission diagnosis, pre-existing illnesses, electrolyte and metabolic abnormalities, advanced age, and use of drugs (such as narcotics or catecholamines) and shock.[44] Elevated plasma cholecystokinin concentrations have also been shown to correlate with feed intolerance.[45]

Position of Feeding

Adoption of a semi-recumbent position while feeding patients is likely to have the best effect in terms of both tolerance to enteral feeds and patient outcomes. The frequency of clinically suspected and microbiologically confirmed pneumonia has been shown to be lower among patients fed in the semi-recumbent position as compared to those in the supine position.[46]

Nasogastric versus Nasojejunal Feeding

Nasogastric feeding is the most commonly employed method for administration of EN in critically ill patients. Abdominal X-ray should be obtained, if possible, after placement of a nasogastric tube to detect any malpositioning (looping inside the oral cavity or in the lower esophagus, or introduction into the trachea). Nasojejunal feeding has been shown to be associated with improved tolerance of EN, and therefore with a reduction in the requirement for PN.[47]

Although nasojejunal feeding leads to lesser gastrointestinal complications mainly because of a lesser incidence of high gastric residual volumes, it is also associated with increased frequency of tube related complications (occlusion, accidental withdrawal and dislodgement), and these can often negate its advantage(s) over nasogastric feeding. Moreover, in a prospective RCT, there were no differences between patients fed via the two routes in terms of feeding duration, length of ICU stay, and incidence of nosocomial pneumonia or mortality.[48]

Since nasojejunal tubes require endoscopic placement, use of this method, as is followed at the author's institute, should be reserved for patients who are intolerant to nasogastric feeding and in whom the intolerance is associated with inadequate nutrient delivery.[10]

Residual Volumes

Gastric residual volumes should ideally be measured prior to administration of each feed, or earlier if indicated. It is advisable to have minimal residual volumes (ideally less than 150 ml) in order to reduce the risk of aspiration of feed contents into the tracheobronchial tree. There is no 'minimum' level of residual volume that can identify patients at risk for aspiration.[49] It was observed that the frequency of aspiration and regurgitation did not change appreciably even if the residual volume increased from 0 ml to greater than 400 ml. Even when the residual volume was less than 150 ml, the frequency of aspiration was 23%.[49] There was also no correlation between the frequency of regurgitation/aspiration and the incidence of pneumonia.

In the presence of high gastric residues, a reduction in the frequency and volume of enteral feeds may be necessary along with more frequent monitoring of gastric residual volumes. Prokinetic agents (metoclopramide, cisapride or erythromycin) can be used to improve gastric emptying although the relative efficacy of one drug over the other or use of a combination versus a single drug is debatable.[50,51] In most cases, it is the gastric motility that is hampered (gastroparesis or gastric atony) and true ileus (dilated and non functional small intestine) is rare.

Role of Bowel Sounds

Bowel sounds should not be used as a criterion to determine initiation or interruption/discontinuation of enteral feeding.[27] The reasons are:

1. They do not correlate well with gut motility in critically ill patients.
2. Bowel sounds are produced due to movement of air through the small intestine and require the presence of both gastric air and gastric emptying. Critically ill patients who have nasogastric tubes *in situ* may not have either or both of these. Hence, there may be minimal or no movement of air from the stomach into the small intestine, and decreased/absent bowel sounds even in the presence of a normally functioning small intestine.
3. Most clinicians do not listen for bowel sounds for more than a few seconds, while one needs to listen for them for two to four minutes in each of the abdominal quadrants.

   Passage of flatus or stool is also not required for initiation of enteral feeding.[27,52]

Diarrhea and Enteral Nutrition

Patients on enteral nutritional support who develop diarrhea that persists for more than three days may need evaluation for *Clostridium difficile* infection after other common causes have been excluded, since these patients are usually receiving broad spectrum antibiotics. A decrease in the frequency and volume of enteral feeds may be required and in certain cases, transient use of PN may be needed to ensure adequate nutritional support. Administration of anti-diarrheal agents or probiotics like *Saccharomyces boulardii* can be considered, but are of unproven benefit.

GENERAL CARE IN ICU

Recommendations for general care of the critically ill patients often vary with the indication for ICU admission.[53-58] Several aspects of general care of the critically ill patient (Table 147.2) are covered in detail in the chapters on sepsis and sedation/analgesia as well as in the sections on respiratory monitoring and MV.

TABLE 147.2: Key components of general care of the critically ill patient

Hemodynamic and respiratory monitoring
Judicious use of sedatives, analgesics and neuromuscular paralyzing agents
Periodic assessments for weaning and tracheostomy
Prophylaxis against stress related mucosal disease
Prophylaxis against deep venous thrombosis
Glycemic control – avoid intensive insulin therapy
Prevention of pressure ulcers
Implementation of infection prevention strategies
Avoidance of unnecessary transfusions

Airway Protection

For most critically ill patients, supportive measures including the "ABC" (Airway, Breathing, Circulation) are required. Ensuring patency of the airway is a must for all patients admitted to the ICU. Endotracheal intubation is not always necessary when there is adequate presence of cough and gag reflexes, as well as of spontaneous ventilation. If there are any concerns regarding airway protection and/or of clinical deterioration, it is advisable to have the airway secured pre-emptively since endotracheal intubation reduces the risk of aspiration. Intubation is also indicated in cases of acute (or sometimes in acute-on-chronic) respiratory failure for providing assisted MV. (These issues are discussed in detail in a subsequent chapter on airway management).

Deep Venous Thrombosis Prophylaxis

Two important issues related to the management of critically ill patients need mention: prophylaxis against Deep Venous Thrombosis (DVT) and Stress Related Mucosal Disease (SMRD). In the absence of any specific contraindication, some form of DVT prophylaxis is advocated for most ICU patients. Both DVT and Pulmonary Embolism (PE) remain under-diagnosed among patients admitted to ICUs.[59,60] In a retrospective analysis of 12,338 patients from 12 ICUs, 2.0% patients were detected to have radiologically confirmed DVT or PE while 0.5% had possible DVT or PE.[59] A significant percentage of medically ill patients admitted to the hospital and the ICU, develop DVT-PE despite receiving prophylaxis.[59,61]

There is a general need for increased suspicion among clinicians for its diagnosis, renewed efforts at prophylaxis, and evaluation of superior prevention strategies. In a recent study from India, it was seen that only 12.5% of medically ill patients received DVT prophylaxis within the first two days of admission. Clinical signs and symptoms of DVT and PE were present in only about 25 and 10% of patients respectively.[62] Transthoracic echocardiography is being increasingly used as a triage tool for suspected PE.[63,64] A recently published review provides a concise overview on the management of PE in ICU patients.[65]

Mucosal Ulcer Prevention

Stress related mucosal disease or stress related mucosal ulceration is an important and frequently occurring gastrointestinal complication among ICU patients. This can be associated with increased length of stay in the ICU, can possibly adversely influence other clinically important outcomes. Suppression of gastric acid production is fundamental to preventing stress-related mucosal ulceration and its clinically important manifestation gastrointestinal bleeding.[66] Drugs commonly used for prophylaxis of SMRD include sucralfate, histamine 2-receptor antagonists (H2 blockers) and Proton Pump Inhibitors (PPIs). Enteral or intravenous administration of PPIs to critically ill patients has been shown to elevate and consistently maintain gastric pH $\geq$ 4.0. PPIs are therefore as safe and as efficacious as H2 blockers or sucralfate for prevention of bleeding from SRMD.[67,68] Sucralfate, on the other hand, can protect the gastric mucosa without raising gastric pH. The benefit of SRMD prophylaxis in all ICU patients has not been convincingly proven.[69] An increased risk of nosocomial pneumonia with use of H2 blockers and PPIs as well as of reduced absorption of concomitantly administered oral medications with sucralfate has lead several authors to recommend against routine prophylaxis against SMRD in the ICU.[69,70] There is a need to carry out a risk-benefit assessment for each critically ill medical patient prior to initiation of SRMD prophylaxis.

Pressure Ulcers

Another common problem in intensive care settings is the occurrence of pressure ulcers (previously called 'bed sores'). There is a wide variation in the reported prevalence (4 to 49%).[71] Age, duration of MV, bowel incontinence, presence of diabetes mellitus, spinal cord injury and renal failure are proven risk factors for its occurrence.[72-74] Pressure reducing devices such as special mattresses (alternating pressure air, low air loss and foam) can be used for prevention of pressure ulcers among ICU patients.[75] Enteral diet, enriched in eicosapentaenoic acid, gamma-linolenic acid and vitamins A, C and E has been associated with a significantly lower occurrence of new pressure ulcers among critically ill patients with acute lung injury.[76] Implementation of guidelines for pressure ulcer care has been shown to result in a significant and sustained decrease in the development of grade II-IV pressure ulcers in critically ill patients.[77] Timely transfer to a specific pressure reducing mattress prior to the occurrence of a pressure ulcer is the most important factor. Undoubtedly, pressure sore development is a complex phenomenon, and no single intervention can tackle the problem effectively. A multidisciplinary team approach is the most appropriate way to improve prevention as well as treatment.[78]

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Airway Management

Arjun Srinivasan, Ritesh Agarwal

Airway management is an obligatory skill of critical care physicians and paramedical staff which is tested on regular basis by the susceptibility of critically ill patients to hypoxic injury when emergency intubation is required. These patients typically have varying degrees of acute hypoxemia, acidosis, and hemodynamic instability when intubation is required, and tolerate poorly any delays in establishing an airway. Essentially, the approach comprises of attempts at securing an appropriate airway in minimal time (Fig. 148.1). A systematic study of complications associated with airway management in the Intensive Care Unit (ICU) reported major complications in a significant number of patients, such as Difficult Intubations (DIs) (8%), esophageal intubation (8%), pulmonary aspiration (4%), and an associated mortality rate of 3%.[1] Respiratory failure and shock were independent predictors of complications.

Aforementioned conditions also predispose the patients to become combative during attempts at securing the airway; this in addition to inadequate knowledge of the anatomy, positioning and absence of skilled assistants is a sure recipe for disaster. Physicians who are faced with these challenges should be well versed in noninvasive bag and mask ventilation which help in preoxygenation and thus decreases the hypoxic damage as well as provides with time for sedation with or without muscle relaxation to facilitate intubation. Basic knowledge of nose, oral cavity, pharynx and larynx is necessary for successful management of airway as well as for prevention of injury to these structures.[2]

In the supine position, during unconsciousness, relaxation of the muscles supporting the airway frequently leads to upper airway obstruction. This occurs primarily at the level of the soft palate/tongue, can usually be overcome by jaw thrust, chin lift, “sniffing” position, or insertion of an oropharyngeal or nasopharyngeal airway. A number of structures may obstruct the laryngoscopist’s view of the laryngeal inlet. Mouth opening at the temporomandibular joint, oral cavity size, dental structures, and tongue size are immediately apparent as obstruction to visualization of the glottis. Furthermore, the angle at which one attempts to bring the airway entrance into view is of importance. In neutral position, the line of sight reaches the posterior pharynx, uvula and soft palate. With extension, it is possible to view the hypopharynx, the area just cephalad to the glottic opening. When the patient’s head is placed in the sniffing position (flexion of the cervical spine and extension of the atlanto-occipital joint), the axes of the airway are better aligned.[3]

AIRWAY ASSESSMENT

Critical care setting opens a Pandora’s Box in terms of difficulties not all of which can be anticipated. The principle is to determine whether patient requires non-invasive or invasive ventilatory support, once that is clear, the ease of establishment of either one needs to be assessed. In a critical care setting, a brief and focused examination to assess a patient’s airway prior to performing a potentially difficult endotracheal intubation goes a long way in influencing the strategy for airway management and the success of the procedure. If the patient needs invasive ventilatory support, the individual should quickly be assessed for difficult airway.[4] The American Society of Anesthesiologists (ASA) defines a

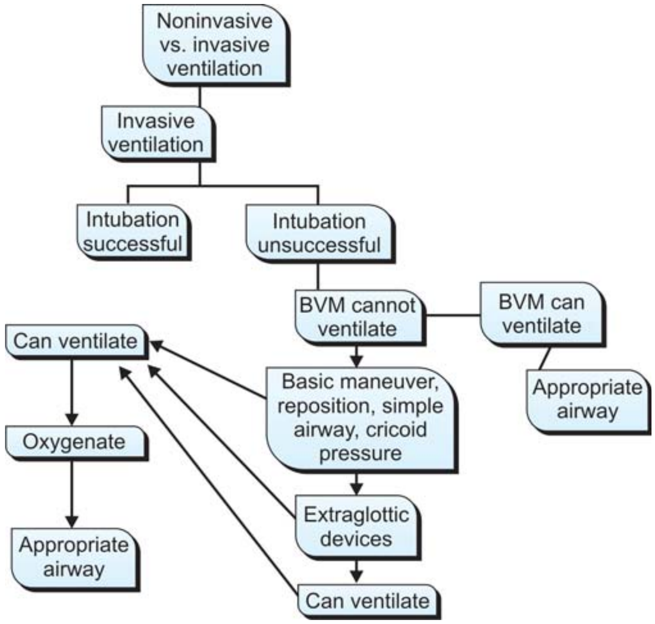

Fig. 148.1: An approach to airway management in ICU

difficult airway as: (1) difficult Bag-Value Mark (BVM) ventilation: The inability to maintain an adequate oxygen saturation greater than 90% or signs of inadequate ventilation (e.g. cyanosis, absent breath sounds or hemodynamic instability) with BVM ventilation or (2) difficult endotracheal intubation: Greater than three failed intubation attempts or failure to intubate after 10 minutes by an experienced operator.[5] Some experts also include difficult placement of extraglottis devices.

Difficult Mask Ventilation

The mnemonic, MOANS which refers to Mask seal, Obesity (BMI of >26 kg/m^2), age greater than 55 years, No teeth and a history of Snoring or Stiff lungs are risk factors associated with difficult mask ventilation in elective setting.[6] In addition to the aforementioned factors altered sensorium, sedation and use of NMBAs result in decrease in the tone of soft palate increasing airway resistance.[7] Because the soft palate rather than the tongue is the site of obstruction, ventilation is assisted by a jaw thrust or head tilt, the placement of either a nasopharyngeal or oropharyngeal airway, and the application of positive-pressure assisted ventilation. On the other hand, pooling of secretions, inadequate sedation and agitation can precipitate laryngeal spasm with similar consequence. This involuntary spasm of the laryngeal musculature may be ablated with positive-pressure ventilation, suctioning of secretions, cessation of airway manipulation, and jaw thrust. Severe instances may require neuromuscular blockade.

Difficult Intubation (DI)

Approximately 30% of critically ill individuals are fit for formal assessment. LEMON airway assessment model has recently been validated in critical care setting (Table 148.1). Of the parameters, Mallampati score was found to be most difficult to assess and large incisors, a reduced mouth opening, and a reduced thyroid to floor of mouth distance were found to be the factors associated with significant risk of difficult intubation. This calls for formulation of a protocol with fewer parameters which is easier to apply in emergency.[8]

TABLE 148.1: LEMON airway assessment model

Parameters	*Points*
Look	
1. Large incisors	1
2. Large tongue	1
3. Facial trauma	1
4. Beard/moustache	1
Evaluate (3-3-2)	
1. Mouth opening < 3 finger breadths	1
2. Hyomental distance < 3 finger breadths	1
3. Thyrohyoid distance < 2 finger breadths	1
Mallampati class > 2	1
Obstruction	1
Neck mobility restriction	1
Total =	10

Difficult Use of Extraglottic Devices

In an emergency, a Laryngeal Mask Airway (LMA) can serve as the primary rescue airway in a 'cannot ventilate/ cannot intubate' scenario or can be used as a bridge or temporary airway while completing a cricothyroidotomy. The LMA is inserted above the glottis into the laryngeal space and then a cuff is inflated to achieve the proper seal. This directs air from above the vocal cords through the glottis into the trachea. A proper seal is essential to create a channel through which oxygen is routed into the trachea. The LMA is an intermediate airway (Table 148.2), allow ventilation across the larynx but do not provide complete airway control. Even though the insertion of extraglottic devices is easier than intubation, several factors (RODS) can interfere with insertion of extraglottic devices.[6] At least some access to the oral airway is necessary for placement of an extraglottic device, so the R in RODS stands for restricted mouth opening; an extraglottic device is not feasible if there is upper airway Obstruction (O); a Disrupted or Distorted airway (D); prevents an adequate seal, thereby resulting in unsatisfactory functioning of the extraglottic device. A Stiff cervical spine or Stiff lungs are the S in RODS.

TABLE 148.2: Examples of intermediate/temporary airway in an emergency

- Laryngeal mask airway
- Esophageal obturator airway (EOA)
- Esophageal gastric tube airway (EGTA)
- Esophageal-tracheal combitube airway
- Laryngotracheal airway
- Laryngeal airway
- Airway management device
- Cuffed oropharyngeal airway

Bag Valve and Mask Ventilation

Providing positive pressure ventilation with a facemask and a bag-valve device is a lifesaving maneuver. Facemask ventilation is used in patients who have respiratory failure but still breathing spontaneously, and in patients with complete apnea. Facemask ventilation can be indicated in any situation in which spontaneous breathing is failing or has ceased, including cardiopulmonary arrest. Though rarely contraindicated, caution needs to be exercised in the presence of facial/eye trauma or foreign body in the oral cavity which can lead to aspiration pneumonitis. Although seemingly simple, the technique requires an understanding of the airway anatomy, the equipment and the indications.

There are several types of masks available in different sizes and materials. Transparent masks allow for inspection of lip color, condensation, secretions or vomitus and are therefore generally preferred. A good fit requires conformation with the facial anatomy, several sizes therefore should be available at hand. A self-inflating bag with a non-rebreathing unidirectional valve which can be connected to the mask, constitutes rest of the equipment. The ability to deliver positive pressure can be checked by compressing the bag while blocking the outlet with the thumb. If there is resistance or if air fizzles out around the thumb, then positive pressure can be delivered. Care should be taken to ensure at hand availability of oxygen supply, suction apparatus and equipment necessary for endotracheal intubation in case of difficulty in ventilation with bag and mask.

Single-Hand Technique

The most common method used to hold the mask requires placing your thumb and index finger on the body of the mask while your other fingers pull the jaw forward and extend the head. Place your middle and ring fingers on the ridge of the mandible and the fifth finger behind the angle of the mandible.[9,10] The tongue is the most common cause of airway obstruction. It is important to minimize the pressure applied to the submandibular soft tissues because pressure may further obstruct the airway by pushing the tongue against the palate. Maintaining an adequate seal while extending the patient's head, thrusting the jaw forward, and squeezing the bag with the other hand may require considerable manual strength and coordination. Extreme caution is advised in patients with cervical spine injuries, in which flexion or extension of the neck is contraindicated. In this situation, the jaw-thrust maneuver alone, without head extension, is recommended.

Two-Hand Technique

You might find it difficult or impossible to maintain an adequate seal with only one hand. This is particularly true in the case of obese or edentulous patients or those with abundant facial hair. In these situations, hold the mask with two hands, with each hand positioned as described in the one-hand technique. A second person should compress the bag-valve device.[10] Regardless of the method used, adequacy of ventilation can be assessed by looking for chest rise and by auscultation for breath sounds. Presence of significant epigastric sounds would mean poor ventilation.[11]

Oropharyngeal or nasopharyngeal airway can facilitate ventilation in otherwise difficult to ventilate patients by overcoming the resistance offered by the soft tissues. This is especially true for obese patients and those with restricted neck mobility. Caution should be exercised while using in patients with preserved gag reflex for the fear of triggering laryngospasm. When the patient is breathing spontaneously, the delivered tidal volume needs synchronization with the patient's inspiration. Regardless of the presence of spontaneous respiratory effort, when excessive pressure is delivered to the airway, gastric insufflation may occur. This may lead to a vicious cycle of increased intra-abdominal pressure, which requires higher peak inspiratory pressures, predisposing patients to vomiting or regurgitation.[11]

Pathophysiology of Intubation

The upper airway reflexes include the glottic closure reflex (laryngospasm), cough, sneeze and swallow reflex. The function of the various upper airway reflexes is to protect the respiratory system and gas exchange surface from foreign or noxious substances. This is why there is a profusion of sensory nerve endings in the airway and rapid motor responses to any stimuli in the airway. Bronchospasm also can occur as a reflex response to endotracheal intubation even in patients who have no history of asthma or obstructive lung disease. Efferent parasympathetic fibers travel to the bronchial smooth muscle and stimulate the M3 cholinergic fibers on the bronchial smooth muscle, causing a cholinergically mediated bronchoconstriction.

In children and newborn, the vagal response to airway manipulation results in bradypnea and bradycardia. Conversely, in adults and adolescents, increased heart rate and blood pressure are the typical responses to airway manipulation.[12] This response is mediated via postganglionic cardioacceleratory nerves from the paravertebral sympathetic chain ganglia, which includes norepinephrine release from adrenergic nerve terminals and the secretion of norepinephrine from the adrenal medulla. Stimulation of the β-adrenergic nerves to the renal juxtaglomerular apparatus activates the renin-angiotensin system resulting in the release of renin, which further raises the blood pressure.

Stimulation of the central nervous system caused by activation of the autonomic nervous system leads to elevations in the cerebral metabolic rate, oxygen consumption, cerebral blood flow and intraocular pressure. This could have disastrous consequences in patients who have impaired CNS autoregulation or elevated intracranial pressure from illness or trauma.

Rapid Sequence Intubation

Rapid Sequence Intubation (RSI) is a process whereby pharmacologic agents, specifically a sedative (e.g. induction agent) and a neuromuscular blocking agent are administered in rapid succession to facilitate endotracheal intubation.[13] When a neuromuscular blocking agent is not used, it is called "facilitated intubation". Though originally described in patients undergoing elective intubation for surgery, this has become the standard of care in critical care setting notwithstanding the controversies and complications (Table 148.3).

RSI generally consists of the following seven steps:

i. Preparation

The lead up to intubation in a critically ill patient can fast deteriorate to panic and chaos if the team members are not fully aware of their respective roles. This is best established by running mock drills to identify deficiencies and assembling an intubation kit according to a preset checklist as per the ICU requirements. The essential equipment needed for intubation is Suction, Oxygen, Airway, Pharmacology, Monitoring and Equipment (SOAPME). For the airway, include the ET tubes of multiple sizes, laryngoscopes, blades, stylets and BVM. For pharmacology, select, draw up, and label the appropriate medications (sedative, neuromuscular blocker, ancillary drugs) based on the history, physical examination and equipment available. Monitoring should include pulse oximetry and cardiac monitoring at a minimum; preferably with capnography. This phase should also include a contingency plan in case of 'can't ventilate and can't intubate' scenario.

TABLE 148.3: Merits and pitfalls with rapid sequence intubation

Merits	*Pitfalls*
Prevents aspiration and its complications	Adverse effects of the drugs used
Prevents/limits physiological stress response to intubation	Convert partial obstruction to total due to loss of tone
Limits cervical spine movement in trauma patients	Crash airway resulting in cannot ventilate and cannot intubate
Decreases tracheal trauma	Hypoxia
Increases patient comfort and decreases recall	

ii. Preoxygenation

The principle consists of replacing nitrogen in the lungs with 100% oxygen so as to allow adequate time for intubation before desaturation occurs. It can be delivered by tight fitting mask or in the presence of apnea by BVM. In the absence of apnea BVM is discouraged as it can lead to gastric distention and aspiration. It is adequate to prevent desaturation for up to three mins even in the presence of apnea. Obese and hypoxic respiratory failure tends to desaturate early. Patients, who have respiratory failure as a result of underlying cardiopulmonary disease, frequently do not respond to the standard mode of preoxygenation. Only one-half of such patients had an increase in PaO_2 greater than 5% above baseline with the standard four-minute preoxygenation.[14] Better PaO_2 and pulse oximetry values were found using Noninvasive Positive Pressure Ventilation (NIPPV) than conventional preoxygenation before endotracheal intubation.[15]

iii. Premedication

It is important for prevention of negative physiological responses to intubation. This should ideally precede induction by three minutes, simultaneously with preoxygenation. Lidocaine 1.5 mg/kg, fentanyl 2 to 3 µg/kg, and atropine 0.02 mg/kg (minimum 0.1 mg, maximum 0.5 mg) are usually the drugs used. Use of these drugs is governed by the associated co-morbidities. Some general caveats to be remembered are: (a) use lidocaine and fentanyl for patients with elevated ICP and impaired autoregulation, (b) fentanyl for patients with major vessel dissection or rupture or those with significant ischemic heart disease, (c) avoid fentanyl in any patient with shock as these patients are dependent on their sympathetic drive to maintain circulation, (d) use lidocaine for patients with underlying airway obstruction, and (e) atropine is indicated for pediatric patients and in adults with significant bradycardia especially if use of succinylcholine (Sch) is being contemplated. In patients at risk for raised ICP, which may be precipitated by fasciculations which occur with the use of succinylcholine, one tenth the paralyzing dose of Non-depolarizing neuromuscular blocking agent (ND-NMB) may be given along with premedication to prevent fasciculations, example for rocuronium, the dose would be 10% of 0.6 mg/kg = 0.06 mg/kg.[16]

iv. Induction and Paralysis

The step which reduces patient discomfort, and recall as well as increases the chance of successful intubation is surprisingly, also the most controversial. Facilitated intubation refers to the use of sedative alone without paralysis. Detractors of RSI advice against the use of paralysis in case a difficult airway is anticipated. A study in the prehospital air medical setting, using 0.3 mg/kg of etomidate as the sedative without any NMB reported an 89% rate of successful intubation, difficult intubation in 16%, and episodes of clenched jaws and orofacial muscle spasm.[17] A later study from the same investigators prospectively compared facilitated intubation using etomidate vs RSI using etomidate and succinylcholine showed higher incidence of failure with use of sedative alone (63% requiring additional medication vs 4% in RSI).[18] Summarizing, the available evidence favors the use of paralyzing agent unless specifically contraindicated in an individual patient.

The choice of sedative for induction is dictated by patient characteristics as well as the physician and institutional preferences. According to the National Emergency Airway Registry (NEAR) study, the most frequently used induction agents were etomidate (69%), midazolam (16%), fentanyl (6%) and ketamine (3%).[19] Generally the dosages of the sedatives when used for induction are slightly higher than the dose used for sedation.

Etomidate: Etomidate is a nonbarbiturate hypnotic agent that is used for the rapid induction of anesthesia. This imidazole derivative has a rapid onset of action and a short half-life. The usual dose is 0.3 mg/kg or 20 mg in a 70-kg adult. It is often used in trauma patients with known or potential bleeding, hypovolemia, and in patients with limited cardiac reserve, because it does not have significant cardiovascular effects. Etomidate also decreases intracranial pressure (ICP) and the cerebral metabolic rate, which suggests that it may have a neuroprotective effect. In patients of septic shock, the use of etomidate for induction has shown worse outcome.[4,20] This is attributed to inhibition of 11-β-hydroxylase, an enzyme necessary for adrenal steroid production. Myoclonus is another side effect of etomidate that may interfere with intubation if a paralytic agent is not used.

Benzodiazepines: Midazolam is the most commonly used benzodiazepine. It scores over diazepam in being short acting with fewer adverse effects, better amnesia and greater potency. Usual dose for induction is 0.5 to 1.5 mg/kg. This class of drugs has sedative, hypnotic, amnestic, anxiolytic, muscle relaxant and anticonvulsant properties. Negligible cardiovascular effects are an added advantage but significant disadvantages include respiratory depression and apnea. Other uncommon side effects are paradoxical agitation, vomiting, coughing and hiccups.

Barbiturates: Thiopental is the most commonly used drug in this group. Thiopental decreases both cerebral blood flow and the metabolic demands of the brain, which make it an ideal sedative agent in patients with known increased ICP or patients with head injury who are hemodynamically stable. Dose for induction is 3 to 4 mg/kg. Its negative inotropic effect precludes its use in patients with underlying heart disease as well as in the presence of shock. The role of thiopental as an induction agent in critical care setting is limited to hemodynamically stable patients.

Propofol: Propofol is a rapid onset ultra-short-acting sedative hypnotic agent. It has antiemetic properties, but no analgesic effects. It needs no dose modification in the presence of hepatic or renal dysfunction. Side effects include hypotension, bradycardia, hypoxia and apnea, so it should be administered slowly. Propofol also has negative cardiovascular effects so it should be used with caution in patients with volume depletion, hypotension or cardiovascular disease. Because of these side effects/ complications, its use as a sedative for RSI is limited in critically ill patients.

Ketamine: Ketamine, a dissociative anesthetic, exerts its effects by interrupting the connection between the thalamo-neocortical tracts and the limbic system. Unlike all the other sedatives, it has analgesic properties. Ketamine's sympathomimetic effects increase the heart rate, blood pressure, and cardiac output making it an excellent sedative in patients who are hypotensive, especially if secondary to shock, hemorrhage, dehydration, pericarditis or tamponade. However, these sympathomimetic effects are undesirable in patients who already have significant hypertension or tachycardia. Ketamine also causes an increase in ICP by both an increase in systemic blood pressure and cerebral vasodilatation and, therefore, contraindicated in patients with ICP, intracerebral hemorrhage, intracranial mass or head trauma.

Ketamine, through the release of endogenous catecholamines, relieves bronchospasm by dilating bronchial smooth muscles and stimulating the pulmonary β-receptors making it ideal for use in known asthmatics. Ketamine increases tracheobronchial/ oropharyngeal secretions. This can be counteracted with concomitant use of glycopyrrolate or atropine. Use of ketamine has been associated with emergence of reaction which can be disconcerting for the patient.

Paralysis: Once the appropriate sedative is administered, the choice of agents for paralysis is not wide. Neuromuscular Blocking agents (NMBs) are substances that paralyze skeletal muscles by blocking nerve impulse transmission at the neuromuscular junction. Patients given NMB may be aware of their environment, including painful stimuli, even though they are unable to respond. Failure to sedate the patient allows the possibility of negative physiologic responses to airway manipulation such as increased ICP, hypertension and tachycardia. Above all, it is prudent to avoid an ordeal which can be remembered and recalled. All NMBs are structurally similar to the neurotransmitter acetylcholine. They are broadly divided into depolarizing and non-depolarizing NMBs.

Depolarizing neuromuscular blocking agents (succinylcholine): Succinylcholine is the only depolarizing neuromuscular blocking agent currently licensed for use. It acts by binding to the Acetylcholine Receptor (AchR) on the motor endplate, causes depolarization of the postjunctional neuromuscular membrane, resulting in continuous stimulation of the motor endplate AchRs. The initial depolarization manifests a fasciculation all over body and helps an astute clinician to time the onset of paralysis. The action is terminated when the drug unbinds from AchR and diffuses back to circulation where it is hydrolyzed by plasma cholinesterase. It has rapid onset of action occurring within 45 to 60 seconds and short duration lasting only 6 to10 minutes. Actual body weight needs to be used for calculating the dose even in extreme conditions (BMI at either end of spectrum) with a tendency to overdose; inadequate paralysis would hinder chances of successful intubation. A dose of 1.5 mg/kg or 100 mg for an adult patient of around 70 kg is generally used; repeated doses should not be used since bradycardia and hypotension can occur secondary to vagal potentiation; multiple doses may also lead to desensitization blockage, whereby the neuromuscular membrane returns to the resting state and becomes resistant to further depolarization with Sch.

Absolute contraindications to use of succinylcholine consist of a history of malignant hyperthermia in the patient or family and high risk of severe hyperkalemia. Others adverse reactions include bradycardia, and prolonged neuromuscular blockade lasting for 6 to 8 hours after a single dose in patients with aberrant pseudo cholinesterase, raised ICT and IOP, masseter spasm and fasciculation.

Non-depolarizing neuromuscular blocking agents: Non-depolarizing (ND) NMBs competitively block Ach transmission at the postjunctional cholinergic nicotinic receptors. Unlike Sch, which causes a conformational change in the Ach receptor resulting in depolarization of the neuromuscular junction, the non-depolarizing NMB prevents Ach from access to the nicotinic receptor, thereby preventing muscle contraction. They do not cause fasciculations. Based on duration of action, NMB are classified into ultra-short acting (less than 10 minutes), short acting (10 to 20 minutes); intermediate (20 to 50 minutes); and long acting (greater than 50 minutes). Currently, there are no clinically approved ultra-short-acting ND-NMB blockers. Vecuronium, rocuronium, atracurium, and cisatracurium are intermediate acting, rocuronium is the most commonly used agent followed by vecuronium.

Currently the only rapid onset and ultra-short acting NMB available is Sch, doubling the dose of rocuronium from 0.6 mg/kg to 1.2 mg/kg decreases the onset of action to 55 seconds. Sch creates superior intubating conditions when compared to rocuronium. Current indications for use of ND-NMB are: (a) for muscle relaxation, if Sch is contraindicated or unavailable, (b) to maintain postintubation paralysis, and (c) as a pretreatment agent to lessen or eliminate the fasciculations.

v. Positioning and Protection

The aim of position is to align oral, pharyngeal and laryngeal axis along a straight line for easy visualization of cords, the same is usually achieved by 'sniffing position' when there is flexion at neck and extension at head. The position is easy to accomplish by placing a pillow or a folded towel behind the occiput. Prevention of aspiration of gastric contents is achieved by cricoid pressure classically referred to as Sellick's maneuver. The correct performance involves the use of the thumb and index or middle finger to apply firm downward pressure on the cricoid cartilage anteroposteriorly. There are data to suggest that cricoid pressure may worsen the degree of laryngeal exposure.[21-23] This is why there have been instances of regurgitation and aspiration in spite of appropriate use of cricoid pressure. Furthermore, cricoid pressure may cause unwanted significant increases in the heart rate and blood pressure. Therefore, the effectiveness of Sellick's maneuver is currently suspected but would be prudent to give cricoid pressure initially with an immediate decision to terminate the same if there is a compromise of laryngeal view.

vi. Intubation

The operator needs to position the body so that the eyes are far enough from the patient to maintain binocular vision. While holding the laryngoscope in left hand, the patient's mouth is opened with right hand and the laryngoscope blade is inserted to the right of the patient's tongue. Gradually, the blade is moved to the center of the mouth, pushing the tongue to the left. Slowly, the blade is advanced and the epiglottis is identified. Ideal placement of the laryngoscope blade depends on whether a curved or a straight blade is used. When using a curved blade, the tip is placed into the vallecula epiglottica, between the base of the tongue and the epiglottis; and posterior to the epiglottis if a straight blade is being used. With the tip of the blade correctly positioned, the laryngoscope is lifted upward and forward at a 45° angle with adequate care to ensure axis of the laryngoscope's handle, in the direction of the ceiling and not at wrist as that would not only cause poor visualization but also risk dental and soft tissue injury.

Appropriate size endotracheal tube should be ready with the cuff checked for leakage and stylet in situ.[24] Sizes between 7.5 to 8.5 are appropriate for most adults. Stylet should not extend beyond the tip of the tube and the shape of stylet tube combination may be manipulated for easier insertion. With the tube in right hand and clear view of the cords, the tube is inserted into the right side of the patient's mouth. Care must be taken to ensure that the tube does not obstruct the view and the tube is passed until the balloon disappears into the trachea. The stylet is removed at this point and the tube is further advanced till the balloon is 3 to 4 cm beyond the cords. The position is at around 21 cm for females and 23 cm for adult male. The cuff is inflated to a pressure 15 to 25 cm of water required to prevent air leak. The gold standard for confirming the tracheal position of tube is bronchoscopy, but for practical reasons auscultation for equal breath sounds or capnography would suffice.[24]

vii. Management of Crash Airways

Clinician is likely to encounter this situation from time-to-time regardless of the theoretical knowledge, and wealth of experience. Recognition, time management and immediate call for help are key factors that determine the outcome in such situations. Options are a bridge to tide over the crisis situation in form of extraglottic devices or immediate surgical airway according to available infrastructure, ICU protocol and clinical expertise. Laryngeal mask airway is the most commonly used of the myriad of devices. It is a bridge to ensure ventilation when a secure airway is being planned. There are very few reports of failure to secure airway with LMA,[25] hence is recommended by American Society of Anesthesiologist Task Force guidelines for management of difficult airway as the rescue strategy of choice in case of failed airway.[5]

Cricothyroidotomy is an emergency surgical procedure done on patients with failed airway or in whom attempt at securing airway is deemed too risky. The procedure involves making an incision in the cricothyroid membrane, which lies between the thyroid and cricoid cartilages, and inserting a tracheostomy tube into the trachea to allow ventilation. Whenever possible, cricothyroidotomy should be performed by physicians fully trained and skilled in carrying out the procedure, such as the emergency physicians, surgeons and intensivists.[26-28] The only contraindications are massive laryngeal trauma and when intubation is a viable option. Local area preparation involves cleaning and draping. Tracheostomy tube of internal diameter of 6 mm is ideal and can be inserted with ease when compared to a larger tube. A tracheostomy tube placed during a cricothyroidotomy performed under emergency conditions can be left in place for up to 72 hours. Because of the potential complications of cricothyroidotomy (such as subglottic stenosis and damage to the thyroid and cricoid cartilages), it should be converted to a tracheostomy if airway access is needed for more than 72 hours.

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Complex Airways Diseases

Rubal Patel, Ann L Rutt, Arthur Sung

INTRODUCTION

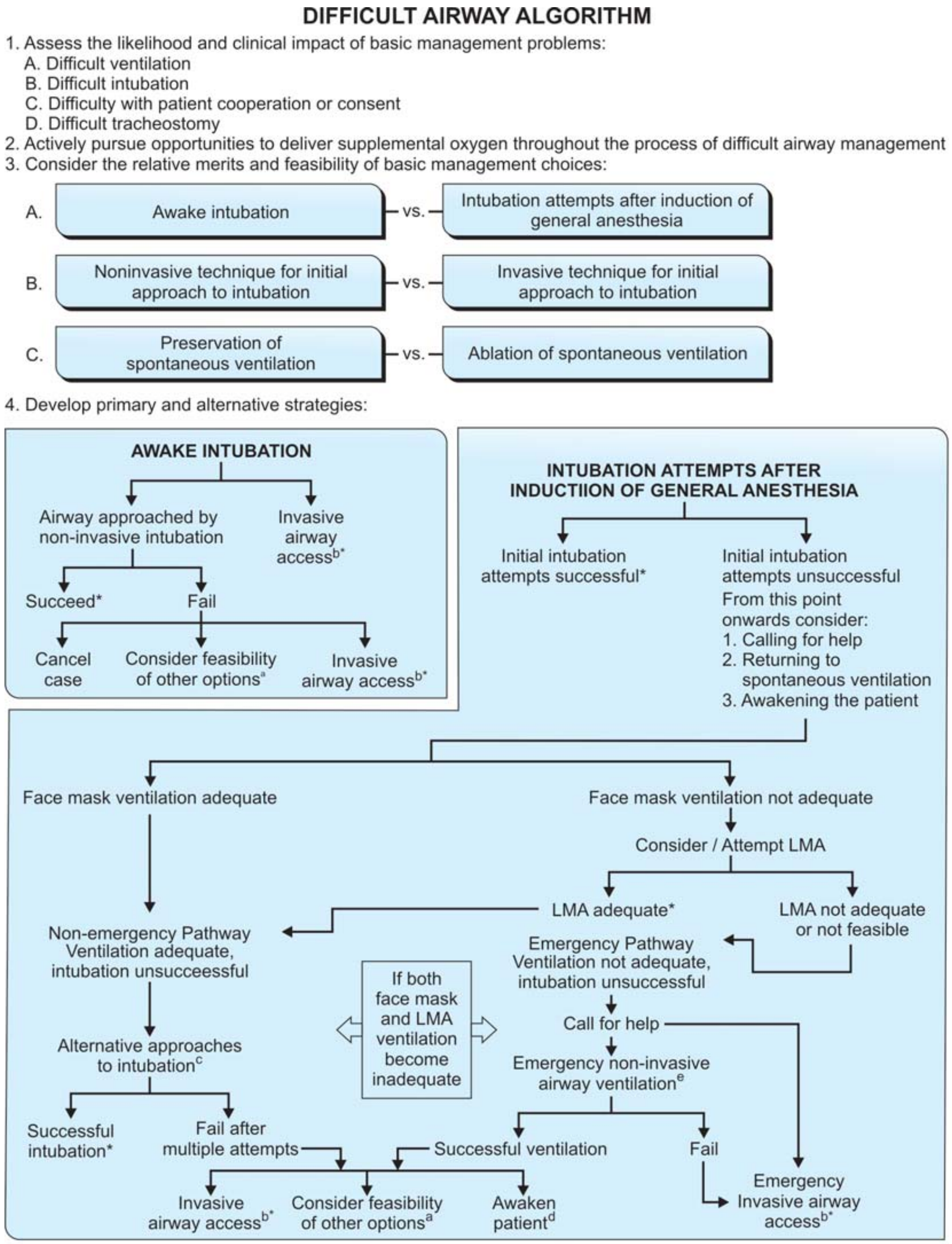
The intensive care unit presents many challenging conditions that require expert knowledge of complex airway management. In the acutely decompensating patient, securing the airway in a timely manner with the best practice approach is critical to ensuring an optimal outcome. The initial evaluation should include historical, clinical and anatomic components in order to consider important factors, such as the neurological status, level of consciousness, hemodynamic status and respiratory reserve. Soliciting assistance from other disciplines with airway expertise is paramount when confronted with a difficult airway. Anesthesiologists, surgeons and otolaryngologists are colleagues, who can offer vital and unique skills to rescue a dire scenario.

The difficult airway is defined as "the clinical situation, in which a conventionally trained anesthesiologist experiences difficulty with mask ventilation of the upper airway, tracheal intubation, or both".[1] Failure to recognize risk factors and inadequate management of the difficult airway usually results in adverse events, such as airway injury, hypoxic brain injury and even death.[2,3] Therefore, in the Intensive Care Unit (ICU) setting, intensivists should be familiar with the equipment and techniques to maintain and secure the airway. Even the most experienced clinician, however, will encounter difficulties with airway management. This chapter aims to discuss comprehensive management of the difficult airway, with a focus on the intensivist and the ICU as the reference environment.

Definition of a Difficult Airway

The difficult airway can be classified into two scenarios, difficult mask ventilation and difficult tracheal intubation. Difficult mask ventilation occurs, when there is inability to maintain oxygen saturation above 90%. Difficult tracheal intubation occurs, when multiple attempts at endotracheal intubation are unsuccessful. The incidence of airway trauma and edema increase and ultimately create a critical airway scenario, such as "cannot ventilate-cannot intubate" when attempts at endotracheal intubation are repeated three or four times.

Difficult intubations are reported in 1.5 to 8.5% of airway emergencies and impossible tracheal intubation occurs in up to 0.5% of the population.[3] Complication rates in the ICU environment are higher than in a controlled setting, such as the operating room due to the limited physiologic reserve and comorbidities of patients. Furthermore in the ICU setting, a thorough evaluation of anatomy may not be adequately performed. Difficult intubations can arise from difficulty in visualization of the larynx or anatomic abnormality (distortion or narrowing of the larynx or trachea). Therefore, implementation of training programs for ICU staff, immediate access to advanced airway devices and knowledge and incorporation of the American Society of Anesthesiologists (ASA), Difficult Airway Algorithm[1] (DAA) (Fig. 149.1) may decrease the incidence of serious complications related to airway instrumentation in the ICU.


DIFFICULT AIRWAY ALGORITHM
1. Assess the likelihood and clinical impact of basic management problems:
A. Difficult ventilation
B. Difficult intubation
C. Difficulty with patient cooperation or consent
D. Difficult tracheostomy
2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management
3. Consider the relative merits and feasibility of basic management choices:
A.
Awake intubation
vs.
Intubation attempts after induction of general anesthesia
B.
Noninvasive technique for initial approach to intubation
vs.
Invasive technique for initial approach to intubation
C.
Preservation of spontaneous ventilation
vs.
Ablation of spontaneous ventilation
4. Develop primary and alternative strategies:
AWAKE INTUBATION
Airway approached by non-invasive intubation
Invasive airway access[b*]
Succeed*
Fail
Cancel case
Consider feasibility of other options[a]
Invasive airway access[b*]
INTUBATION ATTEMPTS AFTER INDUCTIION OF GENERAL ANESTHESIA
Initial intubation attempts successful*
Initial intubation attempts unsuccessful
From this point onwards consider:
1. Calling for help
2. Returning to spontaneous ventilation
3. Awakening the patient
Face mask ventilation adequate
Face mask ventilation not adequate
Consider / Attempt LMA
LMA adequate*
LMA not adequate or not feasible
Non-emergency Pathway Ventilation adequate, intubation unsucceessful
Emergency Pathway Ventilation not adequate, intubation unsuccessful
If both face mask and LMA ventilation become inadequate
Call for help
Emergency non-invasive airway ventilation[e]
Alternative approaches to intubation[c]
Successful intubation*
Fail after multiple attempts
Successful ventilation
Fail
Invasive airway access[b*]
Consider feasibility of other options[a]
Awaken patient[d]
Emergency Invasive airway access[b*]

*** Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO_2**

a. Other options include (but are not limited to): surgery utilizing face mask or LMA anesthesia, local anesthesia infiltration or regional nerve blockade. Pursuit of these options usually implies that mask Ventilation will not be problematic. Therefore, there options may be of limited value if this step in the aligorithm has been reached via the emergency pathway.

b. Invasive airway access includes surgical or percutaneous tracheostomy or cricothyrotomy.

c. Alternative non-invasive approaches to difficult intubation include (but are not limited to): use of different laryngoscope blades, LMA as an intubation,condait (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, retrograde Intubation, and blind oral or nasal intubation,

d. Consider re-preparation of the patient for awake intubation or cancelling surgery.

e. Options for emergency non-invasive airway ventilation include (but are not limited to): rigid bronchoscope, esophageal-tracheal combitube ventilation, or transtracheal jet ventilation.

Fig. 149.1: Illustrative outline of practice guidelines for management of the difficult airway (difficult airway algorithm") formulated by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway[1]

TABLE 149.1: Indications for endotracheal intubation

Cardiopulmonary arrest
Ventilatory support (hypoxemic or hypercarbic respiratory failure)
Inability to protect airway (altered mental status, head injury, drug overdose)
Airway obstruction (malignancy)
Inhalational injury (burns)
Protection from aspiration (secretions, blood)
General anesthesia (surgery, rigid bronchoscopy)

Indications for Artificial Airway (Table 149.1)

Establishing the indication for intubation is the initial step in any airway management algorithm. Regardless of the underlying cause, restoring adequate oxygenation and ventilation is of greatest importance. Indications for endotracheal intubation include:

1. Hypoxic or hypercapnic respiratory failure
2. Inability to protect the airway due to neurologic insults, such as stroke or drug overdose
3. Airway obstruction from malignancy or benign causes
4. Inability to clear secretions, blood or foreign material.

Three principal modalities are available for the delivery of mechanical ventilation to a critically ill patient. These are Noninvasive Positive Pressure Ventilation (NIPPV) via facemask, extraglottic airway and the endotracheal route. The use of NIPPV has shown benefit in specific clinical situations, such as acute exacerbations of obstructive airway disease or cardiogenic pulmonary edema.[4] However, its use in noncardiogenic respiratory failure remains unclear.[5] In addition, NIPPV is contraindicated in various situations, where patients have depressed mental status and copious secretions. Consequently, endotracheal intubation remains the mainstay of mechanical ventilatory support in the intensive care unit and will be the primary topic of this chapter.

Training Strategies

Proficiency in airway management is achieved through various educational tools. Knowledge of normal airway anatomy and its variants is essential to assess for the type of intubation approach and to predict the level of difficulty that may be encountered during the procedure. Airway models and virtual simulators are essential tools to teach trainees basic information regarding airway intubation and equipment without direct patient contact. Performing procedures on patients under the direct supervision of experienced mentors is paramount to accrue experiences that cannot be duplicated with training models. Advancement through the training process should be a stepwise approach, with graded responsibilities and always under appropriate mentorship.

It is essential to understand that airway management is a multidisciplinary skill. Requesting assistance and consultation with other disciplines should always be encouraged. General and thoracic surgeons, otolaryngologists, anesthesiologists and interventional pulmonologists are invaluable members of an airway team. Other team members include, nurses at the bedside and respiratory therapists. Their training and knowledge complements the skill set of the clinician. Communication with the entire team is paramount, when dealing with complex airway issues.

ANATOMY

A key component to competency in complex airway management is familiarity and understanding of airway anatomy. The airway is divided into the upper (nares to glottis) and lower (trachea and conducting bronchi) airway (Fig. 149.2).[6,7]

Upper Airway

Evaluation of the patient for endotrachial intubation begins with examination of the oral cavity and the pharynx. The oral cavity (teeth, tongue, hard and soft palate) is assessed for clues that may impede a smooth

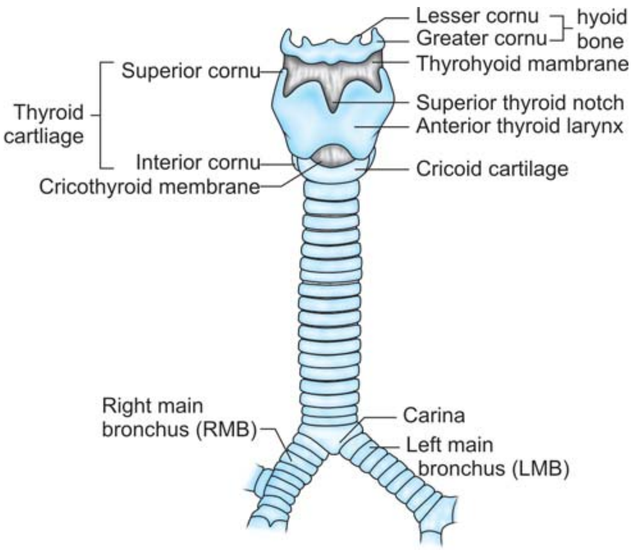


Fig. 149.2: Anatomy of the upper and lower airways. The upper airway is represented by structures above the glottic opening and the lower structure below the vocal cords[5] (Grillo)

intubation process. The tongue lies on the floor of the mouth, is attached to the hyoid bone and innervated by the hypoglossal or cranial nerve XII. The tongue commonly becomes obstructive during intubation. The roof of the mouth is comprised of the hard and soft palate. The posterior margin of the soft palate terminates at the uvula, a midline structure which assists in closing the nasopharynx during swallowing.[8]

The pharynx is divided into the nasopharynx, oropharynx and the hypopharynx. The nasopharynx lies above the soft palate and posterior to the nasal cavities. The oropharynx is inferior to the soft palate, posterior to the mouth and above the hyoid bone (Fig. 149.3).[8,9] Inferior to the oropharynx is the hypopharynx, surrounded by three constrictor muscles and three inner longitudinal muscles that are responsible for swallowing.[10] Traumatic intubations may lead to complications, resulting in dysfunctional swallowing. This area, innervated by the glossopharyngeal and vagus nerves contains the piriform recess, postcricoid region and the posterior pharyngeal wall.[6] The piriform recess is, where the tip of the laryngoscope blade rests during intubation. Due to its rich innervation, adequate topical anesthesia is essential, to prevent excessive cough and discomfort. The hypopharynx terminates at the cricoid cartilage and is separated from the larynx by the epiglottis.

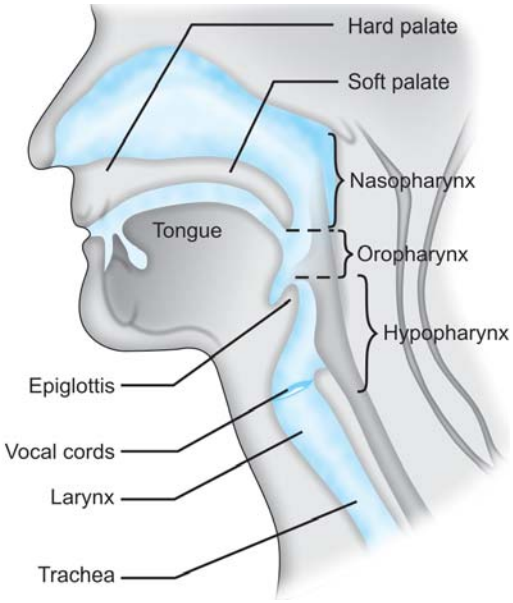


Fig. 149.3: The anatomy of the pharynx

G Edward Morgan, Maged S Mikhail, Michael J Murray (Eds): Clinical Anesthesiology. The McGraw-Hill Companies 2006

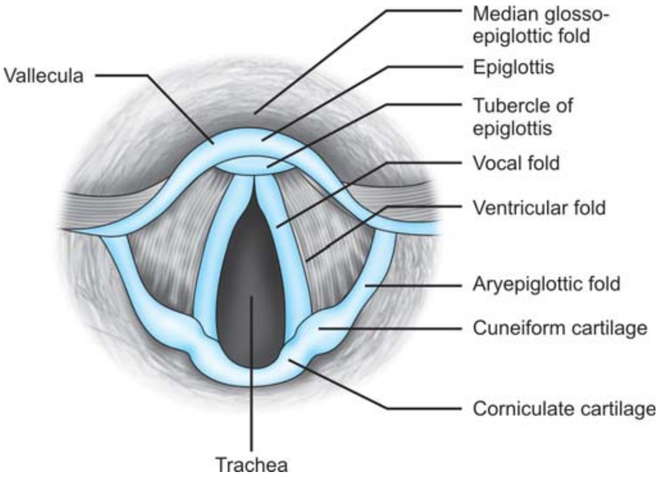


Fig. 149.4: Anatomy of the vocal cords

Wikipedia contributors. "Vocal folds." *Wikipedia, The Free Encyclopedia*. Wikipedia, The Free Encyclopedia, 5 Jun. 2010. Web. 14 Jun. 2010

The larynx located at the level of the third to sixth cervical spine, is inferior to the hyoid bone and superior to the trachea and comprised of nine cartilages. Three of the cartilages are unpaired: The thyroid, the cricoid and the epiglottis and three are paired: The corniculates, the cuneiforms and the arytenoids (Fig. 149.4). The cartilaginous structures are potential sites for trauma and may result in dislocations and injuries. The space between the base of the tongue and the anterior surface of the epiglottis on either side is called the vallecula. The vallecula is a potential harbor for foreign bodies, such as food particles, which can cause upper airway obstruction.[6] The thyroid cartilage is attached to the cricoid, by the cricothyroid membrane, measuring 0.9 x 3.0 cm in the adult. This thin membrane is near the surface of the skin, relatively avascular and serves as the landmark for an emergent cricothyroidotomy. Ligaments and laryngeal muscles attach the cricoid cartilage to the tracheal rings.

The laryngeal muscles that are responsible for opening and closing the glottis are the lateral cricoarytenoid (adduction), the posterior cricoarytenoid (abduction) and the transverse arytenoids. Proper anesthesia and relaxation of these muscles needs to be achieved, to allow adequate glottic opening. The cricothyroid, vocalis and the thyroarytenoid are muscles that control the tension of the vocal ligaments.[11] Injury to this area can cause laryngeal nerve damage, which can lead to tensing of the vocal cords and airway closure.[12] The distal portion of the upper airway is the glottis, comprised of the true and false vocal cords and the rima glottidis (opening between the true cords). The glottis is the narrowest point in the airway in persons over 8 years of age, while the cricoid cartilage is the narrowest point in the infant airway.

Lower Airway

The lower airway is comprised of the trachea and conducting bronchi. The trachea is a fibrous, muscular tube that extends approximately 10 to 12 cm in length and 2 cm in width in the adult, from the cricoid cartilage to the carina.[13] Sixteen to twenty U-shaped cartilages support the trachea (rings facing anteriorly), which bifurcates at the carina into the right and left mainstem bronchus. The right mainstem bronchus is approximately 2.5 cm long, with a takeoff angle of 25° to the right upper lobe. The left mainstem bronchus is approximately 5 cm long with a takeoff angle of 45° to the left upper lobe.[11]

Tracheal Blood Supply

Branches of the inferior thyroid artery provide blood supply to the upper trachea and bronchial arteries supply the lower trachea. Vascular perfusion to the trachea may adversely affect critically ill patients with hypotension. Pressure trauma from the endotracheal cuff may result in ischemic necrosis in these situations (Fig. 149.5).[14]

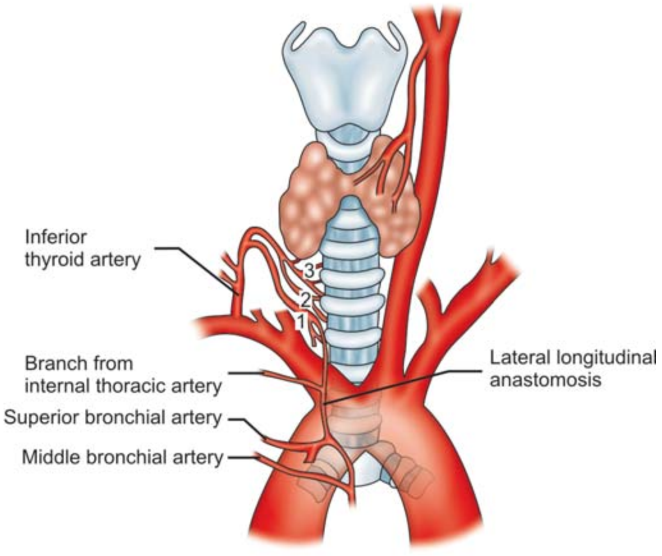

Inferior thyroid artery
3
2
1
Branch from internal thoracic artery
Superior bronchial artery
Middle bronchial artery
Lateral longitudinal anastomosis

Fig. 149.5: Arterial blood supply to the larynx and upper trachea F Charles Brunicardi MD, FACS, (Ed): Schwartz's Principles of Surgery. New York. McGraw-Hill Health Professions Division 2010

Preintubation Assessment

Several factors need to be optimized prior to attempting intubation. Preparation for an unforeseen complication should be considered. Environmental conditions, patient features, such as past medical history and airway anatomy should be assessed, in order to allow for an uneventful intubation.

Environment

The physical environment should be carefully assessed, when examining a patient with respiratory distress. A general medical ward is not as well stocked with intubation tools as is the intensive care unit, while the operating room offers the most controlled environment. The environment should be altered, to make it as conducive as possible to administer care to the patient. Personnel should be limited to essential providers and spectators should be asked to leave. A cogent and concise history should be obtained from the primary care provider, nurse and family members. A recent witnessed aspiration event, for example, should alert the clinician to be aware of significant secretions and foreign materials in the upper airway. A traumatic fall, involving the cervical spine should prompt stabilization of the neck. If an artificial airway is required after potential cervical injury, hyperextension of the neck should be avoided and special techniques should be performed to avoid further injury.

In the intensive care unit, the conditions for intubation should be as close to ideal as possible. Adequate personnel, optimal patient positioning, proper lighting and the necessary equipment for endotracheal intubation should be readily available. A supply of 100% oxygen, a well fitting mask with attached bag-valve device, suction equipment, oral and nasal airways should be available prior to attempting intubation. Different instruments needed for intubation are shown in Table 149.2. The bed should be positioned with the head of the patient at the level of the physician's midchest.

TABLE 149.2: Equipment needed for intubation
Oxygen source, tubing, bag-valve mask
Suction apparatus
Oral and nasal airways
Laryngoscope with curved and straight blades
Endotracheal tubes of several different sizes
Stylets

Patient Factors

It is imperative for the experienced practitioner to consider comorbidities, in predicting problems that may be encountered during endotracheal intubation. A history of a previous difficult intubation is the best predictor of a challenging airway.[11] The American Society of Anesthesiologists Task Force on Management of the Difficult Airway has developed practice guidelines, to facilitate the management of the difficult airway and to reduce the incidence of adverse outcomes, which include but are not limited to death, brain injury, cardiopulmonary arrest, unnecessary tracheostomy, airway trauma and damage to teeth.[15]

Congenital and Genetic Considerations

Individuals with dwarfism or trisomy 21 may have atlanto-axial instability and may be at risk for spinal cord injury, during attempts at endotracheal intubation. Congenital anomalies, such as Pierre Robin syndrome, Treacher Collins syndrome or Goldenhar syndrome may also present a challenge to airway management due to craniofacial abnormalities.[11]

Acquired Disease Considerations

A dry cough, hoarseness, stridor or wheezing may be suggestive of a tumor, causing intrinsic or extrinsic compression of the trachea or tracheal deviation. Disease states, such as arthritis, cervical disk abnormalities, diabetes mellitus and scleroderma impact on neck and mandibular mobility making it difficult to properly position the patient for intubation. In addition, previous surgery, burns or radiation to the neck may cause scarring and contractures, which may limit tissue mobility. The presence of a tracheostomy stoma or a scar from a previous tracheostomy may be suggestive of subglottic stenosis or an indication of a previous airway complication.

Morbidly obese individuals may have a history of snoring and obstructive sleep apnea due to a short, thick neck and excessive soft tissue of the neck and upper airway, which will consequently complicate endotracheal intubation. Insertion of the laryngoscope may also be more difficult in obese individuals. Pregnancy may also increase the risk of aspiration and bleeding from swollen oral mucosa. Infections in the mouth, salivary glands, tonsils or pharynx may cause pain, swelling or muscle spasms and limit one's ability to easily intubate. Persons with acromegaly may have enlargement of the tongue, epiglottis and vocal cords causing a narrowed glottic opening.[11]

Traumatic Injuries

A history of recent trauma may trigger suspicion of an intracranial injury, a basilar skull fracture or injury to the airway or cervical spine.

Physical Examination

A thorough inspection of the patient's posture, habitus, face, mouth, neck and jaw is essential prior to undergoing endotracheal intubation, if possible. This should be performed by careful examination from the front and side of the patient, with the individual looking forward, mouth open and tongue protruded, followed by mouth closed and neck extended.[16]

Inspection

In 1983, Dr Mallampati devised a trifold classification system of the oropharynx, to predict endotracheal intubation difficulty (Fig. 149.6). The open mouth is examined with the head in neutral position and the tongue protruded. The distance between the base of the tongue to the uvula, soft palate and pharyngeal pillars is rated:[17]

Class I:	Uvula, soft palate and pharyngeal pillars are easily visible
Class II:	Soft palate and pharyngeal pillars are visible
Class III:	Soft palate alone is visible

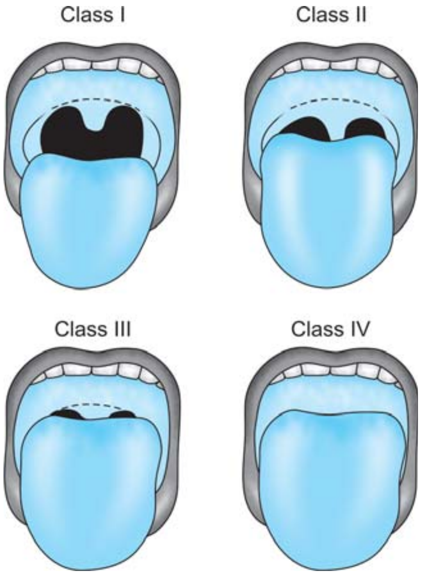


Fig. 149.6: Mallampati classification **(Mallampati)**[12] **(Sampson)**[13]:

Class I: Uvula, soft palate and pharyngeal pillars are easily visible
Class II: Soft palate and pharyngeal pillars are visible
Class III: Soft palate alone is visible
Class IV: Only hard palate is visible

An additional category, Class IV (only hard palate is visible) was later added by Sampson and Young.[18]

In addition to examining the oropharynx, the opening of the mouth and thyromental distance (distance from the mandibular mentum to the superior thyroid notch during neck extension) should be assessed. A mouth opening of less than 2 finger widths and a thyromental distance less than 3 finger widths is suggestive of a difficult airway.[19,20] An alert patient should be able to touch chin to chest, hyperextend their head and turn their head from side to side without pain or paresthesia.[11] Cervicooccipital extension of less than a 160° angle at the hyoid bone limits proper positioning of the mouth and pharynx, to visualize the glottis for endotracheal tube placement. A careful assessment of the mouth should also include evaluation for any prominent or protruding teeth, which may block the view of the glottis. The presence of loose teeth, caps and bridges add to the risk of aspiration from dislodgement or damage to the teeth.[16]

Palpation

The hyoid bone, superior thyroid notch and cricothyroid ligament should be palpated prior to attempting intubation. The neck should also be palpated for evidence of thyroid enlargement or masses, which could potentially obstruct the airway or impede visualization of the glottis.[16]

Auscultation

Auscultation of the neck and chest for stridor or adventitious breath sounds is also an important component of the preintubation assessment. The use of bronchodilators or steroids may be indicated, if airway obstruction is suspected.

Techniques

Airway management may be achieved by definitive or nondefinitive methods.[2] The nondefinite techniques include, utilization of assist devices, such as an oral or nasal airway or the Laryngeal Mask Airway (LMA). The definite methods enable control of ventilation, administration of high levels of oxygen and protection against aspiration. There are three major methods of obtaining a definitive airway: Orotracheal, nasotracheal and the surgical airway.

Bag Valve Mask

Prior to endotracheal intubation, the use of a hand-held bag valve mask to ventilate a patient should be attempted. The bag valve mask is designed to manually provide positive pressure ventilation directly or via an adjunct, such as a pocket mask. The device is capable of self-inflating and drawing in ambient air or oxygen supplied from a tank. After hyperextending the neck, to open the airway or inserting an oropharyngeal airway, the mask is placed over the nose and mouth and held firmly in position with the index finger and thumb. The remaining fingers should keep the jaw tilted upward. The other hand is used to compress the bag once every 5 s. Expert skill and knowledge of the proper use of a bag valve mask is essential.

Oral Airway

An oral airway is an important adjunct tool that may be used prior to intubation, to prevent the tongue from obstructing the airway. There are a variety of oral airways of various sizes to maintain upper airway patency (Fig. 149.7). Insertion of an oral airway is only possible, when the patient does not have a gag reflex due to altered mental status or sedation.[21]

Nasopharyngeal Airway

A nasopharyngeal airway is an alternative airway that may be used when insertion of an oral airway is difficult or impossible. It is a soft plastic or rubber tube (Fig. 149.8) that provides airflow from the nares to the pharynx. Unlike an oral airway, it can be used in conscious patients, who have an intact gag reflex.

Laryngoscopy

The most commonly practiced technique for endotracheal intubation is direct laryngoscopy. A laryngoscope is used to obtain a view of the vocal folds and the glottis. There

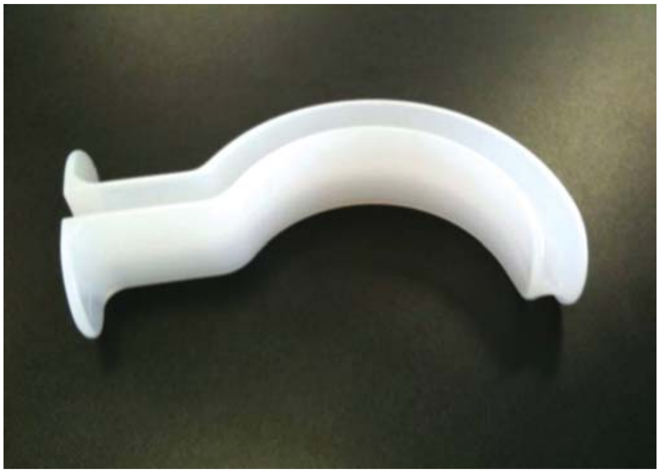


Fig. 149.7: An oral airway

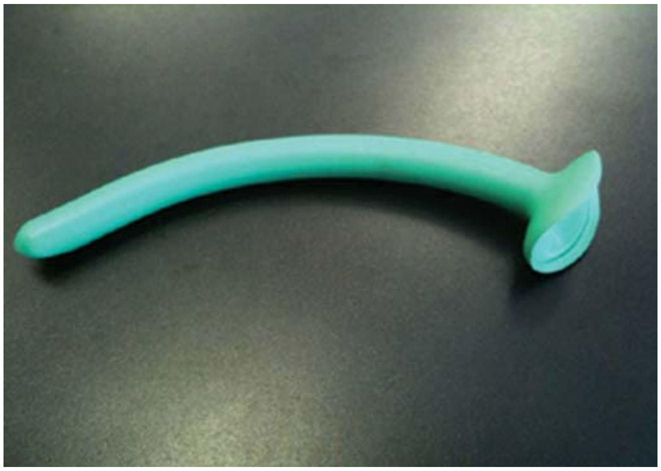


Fig. 149.8: A nasopharyngeal airway

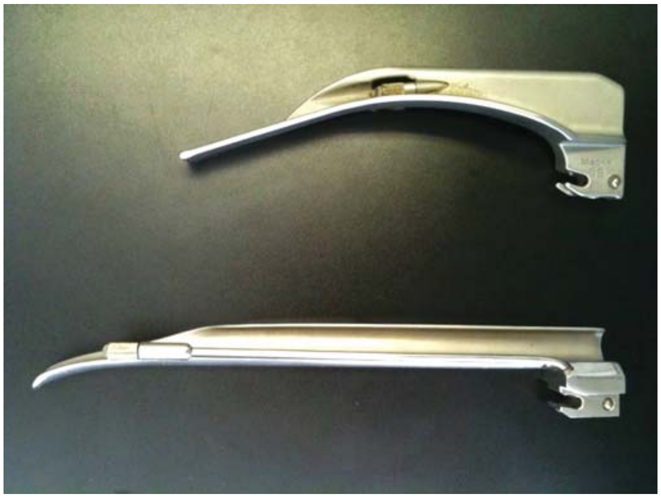


Fig. 149.9: Types of laryngoscope blades. Top: the curved Macintosh. Botttom: the straight Miller blade

are two standard types of laryngoscope blades: The curved Macintosh and the straight Miller blade (Fig. 149.9). The choice of blade shape is a matter of personal preference. The tip of the curved blade is placed in the vallecula. The tip of the straight blade should be placed posterior to the epiglottis, pinning the epiglottis between the base of the tongue and the straight blade. The handle of either laryngoscope should be pulled forward at a 45° angle, to allow visualization of the epiglottis.

The Endotracheal Tube

The standard single-lumen Endotracheal Tube (ETT) (Fig. 149.10) is a sterile tube, made of clear polyvinyl or silicone, to protect the delicate mucosal tissue and allows confirmation of tube placement due to the condensation of expired gases. The distance from the distal tip is indicated in centimeters. A radiopaque stripe or a tip marker is present, to aid in locating the tube on the chest radiograph. Most adult endotracheal tubes have a low pressure cuff system that creates a seal between the endotracheal tube and the trachea, in order to prevent aspiration from the pharynx into the lungs as well as allowing positive pressure ventilation. Ideal cuff pressure is between 18 and 25 mm H_2O when properly inflated. Under inflation of the cuff may result in tube migration, aspiration of upper airway secretions and contribute to ventilator-associated pneumonia.[22] On the other hand, inflation of the cuff above 25 mm H_2O may cause short-term mucosal ischemia and long-term tracheal stenosis due to pressure trauma.[23] Daily confirmation with a bedside cuff pressure gauge is recommended, in order to avoid cuff-related complications.[24]

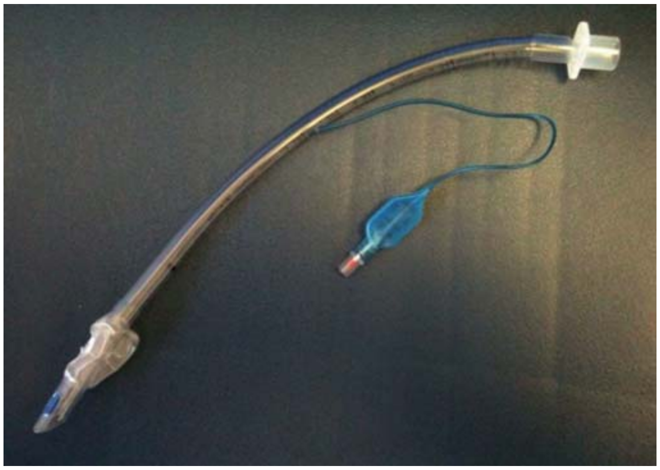


Fig. 149.10: An endotracheal tube

The selection of the endotracheal tube should be approximately 7.0 to 7.5 mm in diameter for an average adult female and 7.5 to 8.0 mm for an average adult male. Complications of endotracheal intubation include trauma, such as perforation or laceration of the pharynx, larynx, trachea or the esophagus. Specific vocal cord injury includes dislocation of the arytenoid cartilages.[25] Malpositioning of the ETT includes mainstem bronchus intubation, causing contralateral lung atelectasis and should be readily identified on physical exam and chest radiograph. Examples of other complications occurring during the peri-intubation period include, aspiration pneumonitis, hypotension, arrhythmias, hypoxia, hypercarbia, laryngeal spasm, bronchospasm and adverse events from anesthesia.[3,19]

Orotracheal Intubation

Orotracheal intubation is the most commonly performed procedure to secure an airway. The approach to the patient without a patent airway begins with removal of possible obstruction. Since the tongue is the most common cause of airway obstruction, relief is attempted by head tilt, chin lift or jaw thrust maneuvers.[25] This will decrease the amount of soft tissue obstruction around the airway. Supplemental oxygen should then be given via facemask or nasal cannula. The patient should be positioned in the sniff position, usually accomplished by placing a small rolled towel underneath the patient's head. The head of the patient should be at the level of the physician's midchest. The oropharynx should be suctioned immediately prior to intubation. The laryngoscope light and the ETT cuff are tested for illumination and proper cuff inflation respectively. The patient's upper incisors should not be used as the fulcrum for the laryngoscope.

The blade of the laryngoscope should be placed in a sweeping motion across the tongue, displacing it to allow the tip of the scope, to advance to the proximal aspect of the epiglottis. When using a Macintosh blade, the tip is placed at the valleculae and a subsequent lifting motion should maximize the view of the glottic opening. The ETT is inserted with the tip visualized going through the glottis without significant resistance. The ETT distance is noted at the level of the teeth and connected to a colorimetric capnography device, to verify appropriate placement in the airway. It is stabilized with tape or a securing device, after auscultation confirms bilateral lung aeration.

Nasotracheal Intubation

Nasotracheal intubation provides another definitive route of securing an airway, particularly in the setting of oral trauma. It may be blindly placed by inserting the tube in the nose, against the nasal septum with the curvature of the tube along the larynx, until it is visualized in the oropharynx. With the aid of a laryngoscope and Magill forceps, the tube is advanced through the glottic opening. Alternatively, the nasal tube may be inserted over an intubating bronchoscope. Nasal intubation is contraindicated in patients with basilar skull fractures and in apneic patients. Complications that can occur with this type of intubation include epistasis, laryngospasm and damage to the turbinates, nasal perforation and sinusitis.[26, 27]

TABLE 149.3: Confirmation of the endotracheal tube (ETT)

Direct visualization of the ETT passing through the vocal cords
Condensation of the expired gases on ETT
End-tidal capnography
Colorimetric detection of carbon dioxide
Observing for bilateral symmetric chest rise
Auscultation for equal breath sounds
Absence of stomach “gurgling”

Confirmation of Tube Placement

It is vitally important to confirm proper tube positioning after endotracheal intubation. Correct ETT placement may be confirmed by several methods, as illustrated in Table 149.3. The most confirmatory test is direct visualization of the ETT passing through the vocal cords. Fogging of the ETT is another sign of tracheal intubation, however, it has been reported to occur with esophageal intubations as well. Capnography and colorimetric detection of carbon dioxide are other commonly used methods for confirmation of endotracheal intubation.[28,29] Colorimetric endtidal carbon dioxide contains a pH-sensitive paper filter that turns from purple to yellow in the presence of carbon dioxide. Capnography can be erroneously positive with gastric intubation, if the patient has been improperly bag valve mask ventilated, causing significant gastric insufflation. Observing the patient for symmetric chest rise, auscultating for equal bilateral breath sounds over the lungs and the absence of a stomach gurgling sound made by air entering the stomach, also verifies tracheal intubation.

Alternative Airway Techniques

It may be difficult to obtain an artificial airway in certain clinical scenarios by conventional techniques. Examples include, cervical and oropharygeal trauma and difficult anatomy, such as excessive supraglottic redundant soft tissue. In order to prepare for such situations, it behooves the intensivist to become skilled in performing alternative techniques. The American Society of Anesthesiologists Task Force on Difficult Airway also incorporates alternative techniques in its recommended algorithm.[1] Various tools and equipment that facilitate alternative techniques include, fiberoptic, video, optical and mechanical methods for better viewing of the larynx, to expedite the passage of an ETT into the trachea. These devices are useful for the management of the difficult or

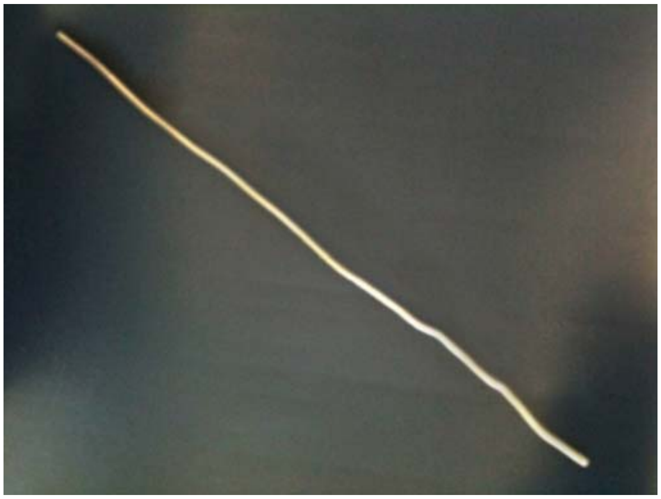


Fig. 149.11: A stylet

failed airway as well as for routine intubations. This section will discuss the types of devices designed to facilitate management of difficult and failed airways.

Stylets

A stylet is a device that can be inserted into the lumen of an ETT, in order to assist with tracheal tube placement (Fig. 149.11). A standard malleable metal stylet lends greater stiffness and adjusts the curvature of the ETT. This allows the tip to be directed through a poorly visualized glottis. The stylet must not project beyond the end of the ETT, in order to avoid potential airway injury. A specialized stylet adapted with advanced optics can provide a better view of the glottis than is obtained with direct laryngoscopy.

Lighted Stylets

A lighted stylet is equipped with a small light bulb at the distal end. Transillumination across the upper airway confirms proper placement, as the brightness will be significantly dimmed or disappear with esophageal intubation. An advantage of lighted stylet intubation includes, less risk of pharyngeal trauma compared to blind attempts when the larynx is not visualized.[30] A potential disadvantage is the need for low ambient lighting that may not be feasible in the critical care setting. A contraindication to the use of a lighted stylet is known abnormal upper airway anatomy.[30]

Intubating Introducer—Gum Elastic Bougie

The intubating introducer consists of a 60 cm stylet with a 30° angle distal tip. The bend allows the operator to direct the tip anteriorly under the epiglottis and through the vocal cords. The introducer is placed blindly into the glottis and advanced approximately 20–24 cm to the level of the teeth. There are two ways to confirm correct placement in the trachea. One way is to feel the clicking sensation, when the stiff stylet tip runs against the tracheal rings. The other sign of airway versus esophageal intubation is sensing resistance to further insertion.[31] The ETT is placed over the proximal end of the catheter and advanced into the glottis. Proper use of the introducer requires practice before introducers can be used successfully.[32] Mechanical trauma to airway structures from intubating stylets are rare.[33]

Fiberoptic Laryngoscope

Rigid fiberoptic laryngoscopes include the Bullard laryngoscope™ (ACMI Circon, Santa Barbara, CA) and the WuScope™ (Achi Corporation, San Jose, CA). Visualization of the larynx is performed, while the patient is in the neutral position, the preferred method, where cervical spine immobility is imperative in the trauma setting.[34,35] An advantage of this device includes, its easy portability. Unfortunately, unfamiliarity and cost of these devices limit their use.

Extraglottic Devices

Extraglottic airway devices for supralaryngeal ventilation can be further divided into cuffed, orally inserted hypopharyngeal airways and cuffed, orally inserted esophageal airways (Combitube ™).

Laryngeal Mask Airway (LMA)

The LMA is a supraglottic device, which consists of a silicone mask designed to fit over the pharynx and allow for gentle ventilation (Fig. 149.12). The advantages of the LMA include rapid, easy insertion, which can be mastered quickly. The entire construct is latex free and available in pediatric and adult sizes. In the setting of a difficult airway, it can be used for awake intubations, blind intubations or intubations combined with fiberoptic bronchoscopy. In addition, the LMA can be used as a conduit to endotracheal intubation.

Before the LMA is used, it should be inspected and tested for leaks. The patient should be positioned in the classic sniffing position and the lubricated LMA cuff is placed facing the patients tongue and advanced posteriorly along the palatopharyngeal curve from oropharynx to hypopharynx. Once resistance is met, the LMA should be pressed along the upper esophageal sphincter. The cuff is inflated with air to approximately

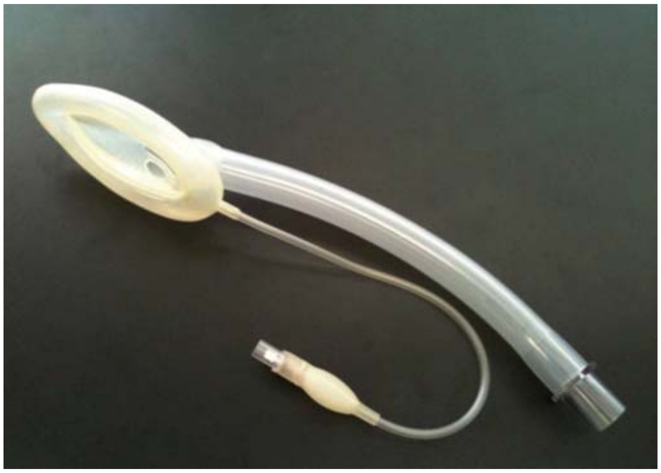


Fig. 149.12: Laryngeal mask airway

60 cm H_2O. The cuff of the LMA lies against the posterior pharyngeal wall and forms a seal. Positive pressure ventilation can be administered through the LMA provided the peak airway pressures do not exceed 20 cm H_2O.

This low-pressure cuff increases the risk of aspiration, if vomiting occurs during ventilation. Contraindications to placement include patients with limited mouth opening, pathologies, such as tumor, abscess, epiglottitis or bleeding at or above the vocal cords and in patients at risk for aspiration. Complications include a higher frequency of gastric sufflation, due to the lower sealing pressure of the cuff in comparison to endotracheal intubation.[36] Coughing and laryngospasm may occur, if the LMA makes contact with the vocal cords. The ProSeal™ LMA has a modified cuff, to provide a more effective seal than the standard LMA. It also comes with a drainage tube for gastric tube placement[36] and therefore, may be safer for use in patients at risk for aspiration. The LMA-Fastrach™ or intubating LMA is a modified standard LMA with a large bore metal tube, a metal handle and an epiglottis elevating bar for endotracheal tube insertion. A high success rate for intubation has been demonstrated with blind and fiberoptic insertion, using the intubating LMA.[37]

Esophageal-Tracheal Combitube™

The Combitube™ is a double lumen tube system with proximal (oropharyngeal) and distal cuffs that can be inserted blindly (Fig. 149.13). The design of the tube allows for ventilation through the distal tube, if properly inserted into the trachea. More commonly however, the distal tube is inserted into the esophagus, in which case, both the proximal (oropharyngeal balloon) and distal cuffs are inflated. The tube is properly placed in the esophagus, if there is no evidence of carbon dioxide detected with ventilation.

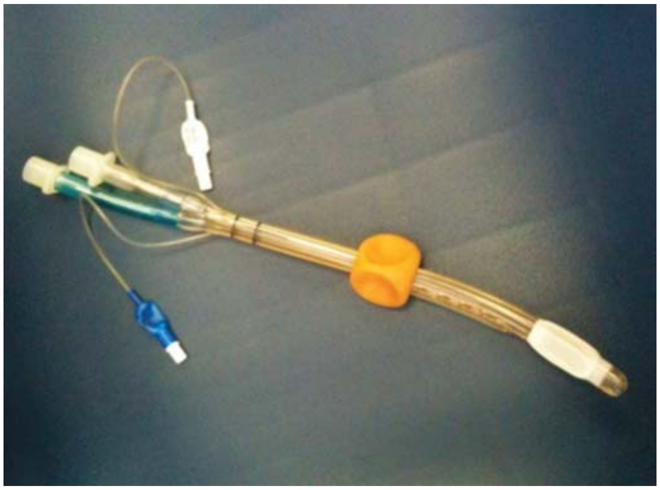


Fig. 149.13: A esophageal-tracheal tube

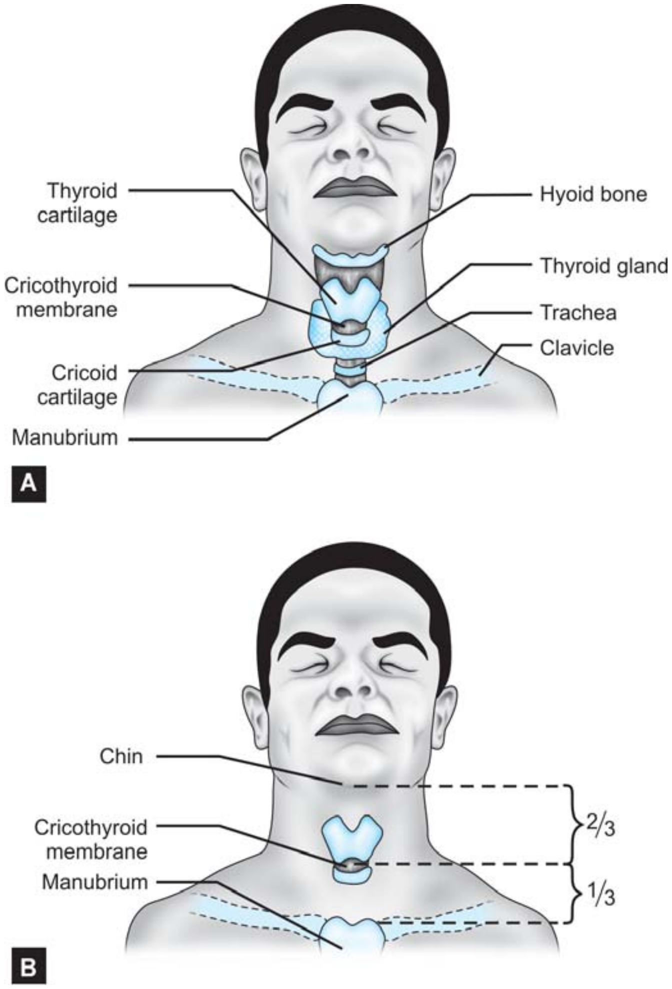
The ventilator is attached to the shorter tube for ventilation into the trachea. If the trachea is intubated, the longer tube is ventilated, which is similar to a conventional endotracheal tube. Drawbacks of the Combitube™ include inability to suction, when the distal tube is placed in the esophagus. The major contraindications of using the Combitube™ are esophageal pathologies, an intact gag reflex and in cases of caustic substance ingestion.[38] Complications of esophageal tracheal Combitube™ include esophageal injury, subcutaneous emphysema and pneumomediastinum.[39,40]

Fiberoptic Bronchoscopy

The use of a bronchoscope can be instrumental in the placement of an ETT in the mouth or the nose.[34] The ETT is placed over the bronchoscope, the scope passed through the glottis for direct visualization of the vocal cords and advanced beyond the vocal cords into the trachea. The ETT is advanced over the bronchoscope into the trachea. Flexible bronchoscopy is a helpful tool for difficult airway intubations in the hands of an experienced practitioner. It is particularly useful when upper airway anatomy has been distorted by tumors, trauma or congenital anomalies. It also allows for awake intubations with topical anesthesia and is particularly useful in patients with cervical injuries, where immobilization is crucial.[41] The bronchoscope may identify causes of acute hypoxia and help to remove secretions or blood in the airway. Limitations include operator inexperience and the need for patient cooperation.

Transtracheal Jet Ventilation

Transtracheal jet ventilation is performed by the placement of a large bore catheter (14-gauge) through the cricothyroid membrane (Figs 149.14A and B) into the trachea (needle cricothyroidotomy). The placement of the catheter is confirmed by aspiration of air before connecting to the ventilation system. High-pressure oxygen can be connected from the wall outlet via a Luer-lock connector. Complications with this technique include aspiration, bleeding and barotraumas, including pneumothorax, pneumomediastinum, subcutaneous emphysema and inadequate ventilation.



Figs 149.14A and B: A. Anatomy of the neck, B. Location of the cricothyroid membrane

Judith E Tintinalli, (Co-Editors), Gabor D Kelen, J Stephan Stapczynski, (Eds). Emergency Medicine: A Comprehensive Study Guide. McGraw-Hill, Medical Publishing Division 2004

Retrograde Intubation

Retrograde intubation involves the placement of a guide wire through a puncture in the cricothyroid membrane into the pharynx in a retrograde fashion. The guide wire is used to aid the placement of an endotracheal tube. An 18-gauge or larger needle attached to a 20 ml syringe partially filled with saline is advanced midline through the cricothyroid membrane. A large volume of air in the syringe will be seen when the trachea is entered. The needle is aimed superiorly and the syringe is removed. A guidewire is threaded through the needle into the oropharynx. The wire tip is retrieved with Magill forceps under direct visualization. An endotracheal tube is advanced down the trachea over the guidewire and the guidewire removed from the oropharynx. Contraindications to retrograde intubation include complete upper airway obstruction, laryngeal trauma, inability to open the mouth to retrieve the wire and urgent intubation, since retrograde intubation may take sometime.[42]

Surgical Airway

A surgical airway is indicated when other means of establishing an airway fail, such as cases of laryngeal trauma and facial injuries or in cases of long-term need of ventilatory support.

Cricothyroidotomy

Cricothyroidotomy (also called cricothyrotomy) establishes an airway, by making an incision in the cricothyroid membrane. Placement of the tracheostomy tube or modified ETT, through the opening establishes an airway for oxygenation and ventilation. This is the preferred method of a surgical airway in situations with supraglottic obstruction and can be lifesaving.

Needle cricothyroidotomy is performed by inserting a 12 or 14-gauge needle catheter through the cricothyroid membrane. The placement of the catheter is confirmed by aspiration of air, once in the tracheal lumen. The needle is withdrawn and the catheter connected to an oxygen supply. This procedure provides a temporary airway to oxygenate a patient in severe respiratory distress, when less invasive techniques (bag-valve-mask ventilation, LMA and ETT insertion) have failed.

A surgical cricothyroidotomy is performed by making a 1 cm transverse incision over the caudal part of the cricothyroid membrane.[43] Once the incision is made, a dilator is inserted to enlarge the incision. A scalpel handle may also be used to dilate the opening, by turning it 90°

to open the airway. Subsequently, an appropriately sized cuffed ETT or tracheostomy tube is inserted, secured with sutures and tied around the neck.

A cricothyroidotomy is absolutely contraindicated, when the patient can be safely orally or nasally intubated. Complications to this technique include bleeding, infection, vocal cord damage, posterior tracheal or esophageal rupture and tracheal stenosis.[44, 45]

Tracheostomy (Percutaneous vs Surgical)

Tracheostomy is a commonly performed procedure for prolonged mechanical ventilation.[46] The timing of tracheostomy should be individualized and based on the likelihood of benefit and predicted need for prolonged ventilation.[47] Early tracheostomy has been advocated in the literature to improve survival and decrease ventilator days.[48] However, recent findings may suggest otherwise.[49] Tracheostomy may be performed by an open surgical approach or by percutaneous dilatation technique.[50,51]

Percutaneous tracheostomy is a common procedure performed at the bedside or in the operating room. Successful performance of the bedside percutaneous procedure is related to the expertise of the operator and ancillary personnel. Percutaneous tracheostomy requires less time to perform and is less expensive than a surgical approach.[52,53] The first or second tracheal interspace is the preferred site for tracheostomy tube placement. The neck is extended to open the tracheal cartilage interspaces and the surgical field prepped and draped with aseptic technique. Local anesthesia is injected subcutaneously at the incision site and a 2 cm skin incision is made over the first or second tracheal interspaces. Hemostats or curved forceps are used to bluntly dissect down to the anterior tracheal wall. A bronchoscope is inserted through the existing ETT and kept just proximal to the end of the tube. The ETT cuff is deflated and the tube retracted to the point above the first tracheal ring for bronchoscopic visualization. The ETT cuff is reinflated and scope position is maintained for bronchoscopic visualization of tracheostomy insertion.

An introducer needle attached to a saline-filled syringe (bevel facing down) is inserted midline through the skin incision and bronchoscopically visualized. The trachea is punctured, confirmed by bubbling in the saline, while visualized by bronchoscopy. The syringe is disconnected and a J-tipped guidewire is advanced through the needle into the trachea and down to the carina. The needle is then removed over the guidewire. Sequentially larger dilators are advanced over the wire, in order to dilate the stoma. Once the incision is dilated, a tracheostomy tube is placed with Seldinger technique and the wire and obturator removed. The bronchoscope is removed from the ETT and inserted into the tracheostomy tube to validate proper placement. After confirmation of correct tracheostomy tube placement, the ETT is removed and the tracheostomy tube is secured.

Disadvantages of percutaneous tracheostomy compared to surgical tracheostomy include an increased risk of anterior tracheal injury and posterior tracheal wall perforation. Contraindications may include uncorrectable bleeding diathesis, gross distortion of the neck from masses (hematoma, tumor and thyromegaly), scarring from previous neck surgery, infection in the soft tissues of the neck and inability to extend the neck. Complications include stoma infections, bleeding, accidental extubation, pneumothorax, tracheal ring fracture and tracheal stenosis, these complications are listed in Table 149.4.[6,54,55]

TABLE 149.4: Complications of tracheostomies
Stoma infection
Bleeding
Tube displacement/extubation
Barotrauma—subcutaneous emphysema, pneumomediastinum, pneumothorax
Recurrent laryngeal nerve injury
Tracheoesophageal fistula
Tracheocutaneous fistula
Tracheal ring fracture
Tracheal stenosis

Surgical tracheostomy is usually performed in the operating room by surgeons under general anesthesia. A 2 cm transverse incision is made 2 cm above the suprasternal notch.[56] Midline dissection of the cervical fascia and underlying neck muscles exposes the thyroid gland. [57] A vertical tracheostomy is created between the second and fourth tracheal ring and the incision is dilated. A tracheostomy tube is placed through the dilated stoma, secured into place and the ETT is removed.[58]

CONCLUSION

Acquiring expert knowledge in securing the airway is a critical step, when caring for patients in the intensive care unit. Understanding the advantages and potential pitfalls for various intubation and airway techniques is essential. A multidisciplinary team approach further improves outcome, given the heterogeneous patient populations that exist in the intensive care setting.

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Analgesia and Sedation in the ICU

Karan Madan, Ritesh Agarwal

INTRODUCTION

Critically ill patients experience a wide variety of stresses in the Intensive Care Unit (ICU) environment. The causes of patient discomfort may be obvious like trauma and invasive procedures or related to prolonged immobility, nursing care and various forms of monitoring and therapy.[1] Pain, presence of catheters or tubes and disruption of sleep are important sources of distress to the patients in the unfamiliar ICU enclosure. Approximately one-third of the ICU patients are mechanically ventilated.[2] These patients usually experience the greatest levels of stress and discomfort in the harsh ICU environment.

Provision of effective and safe care coupled with prevention of patient distress constitutes one of the most important principles in caring for the critically ill. Non-pharmacologic strategies can be tried at optimizing patient comfort but many of critically ill patients, especially those receiving mechanical ventilation, require administration—of analgesic and sedative medications for management at some or the other time during their stay in the ICU. Also, a number of patients in the ICU develop delirium which may be associated with increased long-term mortality and poor psychological outcomes, like post-traumatic stress disorder.[3]

The management of pain, agitation and delirium are extremely critical issues in ICU patient management. Appropriate analgesia and sedative use practice is a neglected field in most ICU’s. Optimal practices are associated with better patient outcomes.

TEAMWORK (MULTIDISCIPLINARY MANAGEMENT) AND PATIENT FOCUSSED CARE

ICU sedation and analgesia practice is one of the prime areas of critical care in which teamwork plays a pivotal role. This involves a continuous interaction between the treating physician, the nursing staff, pharmacists and other members involved in patient care.[4] The clinical pharmacist can inform the treating team regarding the effects of potential drug interactions and the choice of the medication, depending upon the individual patient characteristics.

Every patient requires comprehensive focussed care for optimal outcomes. Based upon the underlying illness and current patient state, decisions need to be taken and frequently reassessed. The choice of medication and the target level of sedation and analgesia need to be individualized. The core principle of patient focussed care is based on the varying need of sedative and analgesic medications in different patients at different times.[5] Higher levels of sedation and even neuromuscular blockade are required when using non-conventional techniques, such as high frequency oscillatory ventilation or positioning the Acute Respiratory Distress Syndrome (ARDS) patient prone.[6,7]

A comprehensive interdisciplinary plan needs to be formulated to provide ideal levels of comfort and also to prevent oversedation. In the resource limited settings and in places with a lack of manpower, the role of the treating physician assumes the prime importance in taking therapeutic decisions, based on individual patient characteristics and guiding the other members of the team in ensuring compliance. Nursing staff play an extremely important role as they interact with the patients most frequently.

INITIAL EVALUATION AND MEDICATION RECONCILIATION

It is extremely important at the time of initial evaluation to carefully assess various factors which contribute to patient discomfort and distress. Underlying medical illness, mechanical ventilation, invasive monitoring, hospital acquired illnesses, various medications and acute medical or surgical illnesses, all contribute to pain, anxiety and delirium in the ICU patients. Initial interventions should be targeted at appropriate management of the predisposing conditions along with sedative, analgesic and antipsychotic medications as deemed appropriate, according to the clinical situation.

Medication reconciliation is the comprehensive evaluation of a patient's medication regimen anytime there is a change in therapy, in an effort to avoid medication errors such as omissions, duplications, dosing errors or drug interactions, as well as to observe compliance and adherence patterns. The concept of medication reconciliation is extremely important when patients move into and out of the ICU. As many as 50% of all medication errors occur at the time of ICU admission or discharge. In approximately 60% of the patients, regular medications are discontinued at the time of admission to the ICU.[8-10]

In the context of sedation and analgesia, omission of medications like antidepressants, anxiolytics, analgesics or antipsychotics can lead to many undesirable consequences.[5] There are also risks of precipitation of withdrawal symptoms.

CONSEQUENCES OF OFF-TARGET SEDATION AND ANALGESIA

Improper assessment and inadequate treatment of pain and agitation in the ICU is associated with a number of adverse consequences (Table 150.1). It is exceedingly important to properly assess pain and agitation in the ICU and provide an adequate level of analgesia and sedation to improve patient outcomes.

TABLE 150.1: Consequences of off-target sedation and analgesia

A. *Consequences of inadequate pain relief and agitation*
  - Self-extubation and removal of other tubes and catheter devices
  - Violent behavior
  - Patient ventilator dys-synchrony
  - Excessive pain leading to increased agitation and anxiety
  - Precipitation of myocardial ischemia in susceptible patients
  - Pain related immunosuppression

B. *Consequences of oversedation*
  - Neural compression leading to pressure nerve palsies
  - Precipitation of delirium
  - Prolonged duration of mechanical ventilation
  - Prolongation of ICU and hospital length of stay (LOS)
  - Breach in skin integrity leading to pressure sores and infections
  - Increased incidence of problems associated with prolongation of mechanical ventilation, e.g. VAP (Ventilator associated pneumonia)

NEED FOR FREQUENT PATIENT ASSESSMENT

A large proportion of ICU patients are oversedated as observed in epidemiological surveys.[11,12] An important finding was the demonstration that during night time, an extremely low proportion of nursing staff perceived their patients to be oversedated. The sleepy state during night time was accepted as the expected state at those hours, thereby contributing to oversedation.[12]

This deliberates a need for more frequent assessment of pain and agitation in the ICU.

ASSESSMENT OF PAIN, SEDATION AND AGITATION IN THE ICU

Assessment of pain, level of consciousness, agitation and cognition are central to patient management. Decisions regarding change in medication can be done accordingly.

USE OF VALIDATED SCALES AND TOOLS

The use of validated assessment methods like sedation scales, pain and delirium assessment tools provides homogeneity of assessment between different caregivers, enhances communication and provides objective measurement and is therefore cardinal to patient focussed care. In addition, the use of scales permits medication titration to desired levels thereby minimizing the risk of oversedation and provision of adequate analgesia.

The use of sedation scales has been associated with a decrease in the duration of oversedation, decreased sedation costs, reduced inotrope use, decreased sedative and analgesic medication use, a decrease in the incidence of nosocomial infections and a reduction in the duration of mechanical ventilation.[13-15]

The society of critical care medicine (SCCM) clinical practice guidelines[1] recommend establishing and regularly redefining a sedation goal for each patient. It is also recommended that a regular assessment should be performed and response to therapy documented.

Assessment of Pain

Experiencing pain is an extremely distressing experience for any individual. The issue of pain control in critically ill patients assumes an even greater magnitude and nearly 90% of the patients have unpleasant memories of their ICU experience, including pain.[16] It should never be forgotten that all critically ill patients have the right to adequate analgesia.[1] Relatively simple procedures that occur frequently in the ICU, such as suctioning and repositioning are usually reported as the greatest source of discomfort to the ICU patients.[17]

Pain Assessment Methods

Communicative Patients

The gold standard for assessment of pain is the patient self report. Patients can be assisted to communicate the pain that they are experiencing, and an attempt should be made to quantify the intensity of pain experienced.

Numeric rating scale (NRS)/Numeric pain scale (NPS): The Numeric rating scale (NRS) or Numeric pain scale (NPS) is recommended by the SCCM to assess pain.[1] It utilizes rating of pain on a 0 to 10 scale with 0 indicating no pain and 10 being the worst pain experienced. It has been successfully used for pain evaluation in critically ill patients who are able to communicate.[17]

A body outline diagram along with the NPS can help in localization of the site of pain. Patients unable to point (including some but not all ventilated patients) can communicate experiencing pain by blinking or squeezing their eyes.[18] In addition, the intensity of pain can be quantified when the observer points to a number on the NPS and the patient nods or blanks in response. Patient cultural and language differences must be kept in mind when assessing pain according to patient self report.[19] Utilization of communication accordingly may be more appropriate.

Non-communicative Patients

Physiologic indicators like hypertension, tachycardia and tachypnea are usually thought to signify the presence of pain but their use has fallen out of favor off late, due to their lack of specificity.[20] A number of scales have been developed, which rely on the patients behavioral and physiologic parameters to signify the presence of pain in the non-communicative adults. Critically ill adults share certain similarities to the pediatric population. They may not be able to communicate the presence of pain like a small child.[21]

The COMFORT scale[22] and the FLACC (Face, Legs, Activity, Cry, Consolability Observational Tool) scale[23] were developed for use in the pediatric population and are not extensively validated for use in the adults. The PAIN (pain assessment, intervention, and notation) algorithm incorporates observation of pain related physiological and behavioral variables but in its original form is too cumbersome for routine ICU use.[24] The Behavioral pain scale (BPS) and the Critical-Care Pain Observation Tool (CPOT) are objective pain assessment scales which can be used in ICU patients during mechanical ventilation. Both have been tested for validity and reliability.

Behavioral Pain Scale (BPS)

Behavioral pain scale[25] is based upon three variables: Facial expression, upper limb movements and compliance with mechanical ventilation (Table 150.2). These variables are thought to signify the presence of pain. Each of these variables can have a value from 1 to 4. The score can range from 3 to 12, which is obtained by adding up the value for each variable. Score of 3 indicates no pain related behavioral response, whereas a score of 12 indicates the maximal pain related behavioral response.

TABLE 150.2: Behavioral pain scale

Item	*Description*	*Score*
Facial expression	Relaxed	1
	Partially tightened (e.g. brow lowering)	2
	Fully tightened (e.g. eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Scores from three domains added up. Total score ranges from 3 to 12.[25]

TABLE 150.3: Critical care pain observational tool[27]

Indicator	*Description*	*Score*
Facial expression	No muscular tension observed Presence of frowning, brow lowering, orbit tightening and levator contraction All of the above facial movements plus eyelid tightly closed	Relaxed, neutral: 0 Tense: 1 Grimacing: 2
Body movements	Does not move at all (does not necessarily mean absence of pain) Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Absence of movements: 0 Protection: 1 Restlessness: 2
Muscle tension	No resistance to passive movements Resistance to passive movements Strong resistance to passive movements, inability to complete them	Relaxed: 0 Tense, rigid: 1 Very tense or rigid: 2
Compliance with the ventilator	Alarms not activated, easy ventilation Alarms stop spontaneously Asynchrony: blocking ventilation, alarms frequently activated	Tolerating ventilator or movement: 0 Coughing but tolerating:1 Fighting ventilator: 2
OR		
Vocalization (Extubated patients)	Talking in normal tone or no sound Sighing, moaning Crying out, sobbing	Talking in normal tone or no sound: 0 Sighing, moaning: 1 Crying out, sobbing: 2
Scores for each of the four domains are added up. Total score of 0 to 8.		

BPS is a scale with demonstrated discriminant validity for the presence of pain.[25] It also possesses fair interobserver reliability.[26] With deepening levels of sedation, patient responsiveness on BPS decreases.[25]

Critical Care Pain Observational Tool (CPOT)

Four behavioral domains are assessed in the CPOT: Facial expression, body movements, muscle tension and compliance with ventilation (Vocalization for extubated patients) (Table 150.3). Each variable can have a score from 0 to 2. The score of individual variables is added-up to obtain the total score which can range from 0 (No pain) to 8 (Maximal pain).

Like the BPS, CPOT has discriminant validity for the presence of pain, also possesses fair inter rater reliability.[27] CPOT was demonstrated to show similar scores with response to painful stimuli in both conscious and unconscious state.[27] However, this might not be true at levels of deep sedation.

Although both BPS and CPOT are seemingly similar, they have certain important differences. CPOT might possess certain advantages over BPS. As only upper limb movements are assessed by the BPS, there is a potential for inaccurate assessment if external equipment hampers the patient's upper limb movements. The ventilation assessment parameters of BPS are not measurable and might contribute to inter rater differences in assessment. CPOT has well defined descriptors of measurement. In addition, CPOT appears to be more logical as a score of 0 in CPOT indicates no pain as compared to a score of 3 in BPS.[19]

Neither of these two instruments have been evaluated for the ability to differentiate responses to pain prior to and after receiving analgesics. However, both BPS and CPOT are reliable and valid instruments for the assessment of pain in the ICU and their use is recommended.

Other Methods for Assessment of Pain[19]

Pain risk profile: It is based on the identification of various individual and environmental factors which may contribute to pain in ICU patients. Early identification of susceptible individuals may allow early initiation of appropriate analgesic therapy.

Surrogate Reporting

This method relies on the information provided by the surrogates, usually family members. An important component of this method is the proper education of the surrogate. The clinician should instruct the family member to consider the actual experiences that the patient might be going through. The surrogate based on the previous experiences of the patient's response to pain of a similar degree can provide valuable information. Although the evidence regarding surrogate assessment of pain remains equivocal, this method may be useful in situations where the patient is unable to self report.

Analgesic Response

This is based on the principle of therapeutic challenge with analgesics. It can be tried when the patient is unable to self report and there is likelihood of presence of pain. In case of no response, alternative causes for the patient's state should be sought.

Assessment of Sedation and Agitation in the ICU

The level of sedation in the ICU is usually assessed using a sedation scale. In one of the earliest works in this regard, it was demonstrated that use of a sedation scale is associated with improved quality of sedation and a statistically significant reduction in the hours of oversedation.[13] An ideal sedation scale should have several important characteristics for an adequate assessment[28] (Table 150.4).

The SCCM guidelines recommend the use of a validated sedation assessment scale. It also recommends that sedation of agitated critically ill patients in the ICU should be started only after providing adequate analgesia and treating reversible physiological causes. Administration of sedatives when the patient's distress is actually due to pain may result in increased agitation.

TABLE 150.4: Characteristics of an ideal sedation scale

- Rigorous multidisciplinary development
- Simple recording and computing of data
- Accurate description of sedation and agitation within well defined categories
- Guides drug titration and thereby management of therapy
- Validity and inter rater reliability in ICU patients
- Ease of administration, recall and interpretation

TABLE 150.5: Various sedation scales

- Ramsay Sedation Scale (RSS)[29]
- Richmond Agitation-Sedation Scale (RASS)[30]
- Sedation Agitation Scale (SAS)[31]
- Motor Activity Assessment Scale (MAAS)[32]
- Adaptation to the Intensive Care Environment (ATICE) instrument[33,34]
- Minnesota Sedation Assessment Tool (MSAT)[34]
- Vancouver interaction and calmness scale (VICS)[35]

A number of scales have been developed (Table 150.5). Some of them have been extensively validated and tested for inter rater reliability in heterogeneous patient populations.

The earliest sedation scale, described nearly 35 years ago was the Ramsay sedation scale.[29] Since then, a number of sedation scales have been developed for clinical and research use which in addition to the levels of sedation, permit the simultaneous evaluation of other parameters like agitation, cognition and patient ventilator dys-synchrony.

These scales have certain differences in structure but share common themes of assessment. They assess the levels of patient sedation based on a common principle of observing response to increasing levels of stimulation. An initial observation is made to see whether the patient is awake. If not, the response to auditory and subsequently more intensive (physical) stimulation is noted. The responses indicate a progressively deepening level of sedation. In addition to sedation, simultaneous assessment of the following parameters can be done:

Cognition

- Cognition refers to the ability to follow commands.
- RASS and ATICE include the simultaneous assessment of cognition.
- RASS additionally permits the assessment of sustainability.

Agitation

Agitation is assessed by many scales. It is measured as a separate subscale in ATICE and VICS. Agitation assessment is incorporated into a single scale in SAS, MAAS and RASS.

RASS is one of the most frequently used sedation scales (Table 150.7). It is performed using a series of steps: Observation of behaviors (score +4 to 0), followed (if necessary) by assessment of response to voice (score -1 to -3), followed (if necessary) by assessment of response

TABLE 150.6: Ramsay sedation scale (RSS)

Sedation level	*Definition*
1	Patient anxious and agitated or restless or both
2	Patient cooperative, orientated, and tranquil
3	Patient responds to commands only
4	Brisk response to a light glabellar tap or loud auditory stimulus
5	Sluggish response to a light glabellar tap or loud auditory stimulus
6	No response to a light glabellar tap or loud auditory stimulus

Awake levels 1 to 3, Asleep levels 4 to 6.[29]

to physical stimulation, such as shaking shoulder and then rubbing sternum if no response to shaking shoulder (score -4 to -5).

With RASS, sedation levels are assigned negative numeric values, whereas agitation levels are denoted by positive numbers thereby enabling sedation and agitation differentiation in a single scale. By using a sedation scale, a target level of sedation can be established and accordingly medication titration can be done. In addition, oversedation can be detected and de-escalation of drugs can be done accordingly.

Light sedation levels - RSS (2-4), RASS (-2 to +1).

Deep sedation levels - RSS (4–6), RASS (-4 or -5), SAS (1 to 2).

RSS, RASS and SAS are the most extensively used and validated scales. However, RSS does not grade agitation.

Objective Measurement of the Cerebral Activity in the ICU

Objective measurement of the brain activity can be done using the cerebral function monitors. These monitors record the EEG signals from the cerebral cortex, process them through various algorithms, in order to yield a dimensionless numeric value which ranges from 0 (complete EEG suppression) to 100 (awake).[21]

The various available systems are the Bispectral index (BIS),[36] Patient State Index (PSI),[37] narcotrend index[38] and the Cerebral State Index (CSI).[39] Their utility in the ICU setting is limited by certain factors, like the Electromyography (EMG) interference or electrical current-related artifact which can lead to erroneous BIS values. Routine use of these tools is not recommended by the SCCM.[1]

Additional approaches for objective monitoring of brain function in the ICU include response entropy and state entropy[40] and auditory-evoked potentials.[41] In certain situations, the use of BIS may be useful like in assessment of consciousness in patients who are paralyzed with neuromuscular blocking agents and patients who are under the influence of deep sedation.[1]

MANAGEMENT OF ANALGESIA AND SEDATION IN THE ICU

Most patients in the ICU require the administration of sedative-analgesic medications for optimizing comfort. The most important group comprises the mechanically ventilated patients, many of whom face the extremes of physiologic stress. In them, sedatives and analgesics are

TABLE 150.7 : Richmond agitation-sedation scale (RASS)[30]

Score	*Term*	*Description*
+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or exhibits aggressive behavior toward staff
+2	Agitated	Frequent non-purposeful movement or patient-ventilator dys-synchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
–1	Drowsy	Not fully alert, but has sustained (>10 seconds) awakening, with eye contact, to voice
–2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
–3	Moderate sedation	Any movement (but no eye contact) to voice
–4	Deep sedation	No response to voice, but any movement to physical stimulation
–5	Unarousable	No response to voice or physical stimulation

TABLE 150.8: Dosing of the selected sedative analgesic medications

Drug	*Loading dose*	*Maintenance dose*
Morphine	2-4 mg IV bolus	0.07-0.5 mg/kg/h
Fentanyl	25-50 mcg IV bolus	0.7-10 mcg/kg/h
Hydromorphone	0.2-0.6 mg IV bolus	7-15 mcg/kg/h
Midazolam	2-5 mg IV bolus	0.04-0.2 mg/kg/h
Lorazepam	2-4 mg IV bolus	0.01-0.1 mg/kg/h
Diazepam	0.03-0.1 mg/kg	-
Propofol	-	5-80 mcg/kg/min
Dexmedetomidine	0.5-1 mcg/kg over 10 min	0.2-0.7 mcg/kg/hr
Remifentanil	1 mcg/kg over 1 min	0.6-15 mcg/kg/hr

required to improve patient ventilator synchrony and oxygenation.[42]

Intravenous route is the preferred route of administration, as it allows better dose titration, has a faster onset of action and higher bioavailability than other routes (Table 150.8). Intermittent therapy should be used wherever possible and continuous infusions should be avoided since continuous IV sedation is associated with prolonged duration of mechanical ventilation and increased Length of Stay (LOS) in the ICU.[43]

Analgesic Medications

It is recommended by the SCCM to establish a therapeutic plan and goal of analgesia for each patient which should be communicated to all caregivers to ensure consistent analgesic therapy.[1] Pharmacotherapy with opioid analgesic agents is the mainstay of provision of analgesia to patients in the ICU. Acetaminophen and the nonsteroidal anti-inflammatory agents (NSAIDs) possess weak analgesic activity and may lead to adverse effects in patients who are critically ill. Acetaminophen has a limited role in critically ill patients in provision of relief from mild to moderate pain or discomfort and use as an antipyretic agent.[1]

Opioid Analgesics

Mechanism of action of opioids: Opioids act through stimulation of opioid receptors. The opioid receptors are the μ, κ, and δ opioid receptors, which are widely distributed throughout the peripheral tissues and the central nervous system.[44] The μ receptor is the main opioid receptor, subdivided into the μ1 and the μ2 subtypes. μ1 receptors are responsible for the mediation of analgesia, whereas μ2 receptor binding leads to constipation, nausea and respiratory depression. κ receptor binding mediates spinal analgesia, pupillary constriction and the sedative effects of opioids.

It is important to note that although opioid administration may lead to mild to moderate anxiolytic effect, they do not produce amnesia. Opioids have an excellent cough suppressant action. In addition, they provide a marked relief in the subjective sense of dyspnea. By a combination of these two effects, they may be particularly helpful in mechanically ventilated patients.[45]

Morphine, Fentanyl and Hydromorphone are the most commonly used opioid analgesic agents in the ICU. *Morphine:* Morphine is a μ receptor agonist, possesses weak κ and δ receptor agonistic activity. It has poor lipid solubility, therefore has a relatively slow onset of action (5 to 10 minutes). It is primarily metabolized by glucuronidation in the liver, which leads to the generation of morphine 6 glucuronide and 3 glucuronide. Morphine 6 glucuronide has an activity of nearly 20 times that of morphine.[46] The excretion of both morphine and the active metabolites occur through the kidney. Morphine should therefore be avoided in patients with renal insufficiency, as it can accumulate and lead to prolonged drug effects.

Fentanyl: Fentanyl is a μ receptor agonist which has high lipid solubility, therefore has a rapid onset of action (< 1 min). Fentanyl is metabolized to inactive metabolites in the liver which undergo renal excretion. Fentanyl is preferred in patients with renal insufficiency. Cautious use should be done in patients with endstage renal disease, as fentanyl itself may accumulate at high doses. Owing to its high lipophilicity, repeated dosing or infusion can lead to a prolonged duration of effect, as the drug re-enters the plasma after discontinuation.[45] In acutely distressed patients, Fentanyl is the preferred agent for rapid onset of analgesia.

Hydromorphone: Hydromorphone is a μ receptor agonist with a duration of action and half-life nearly similar to morphine. However, its hepatic metabolism (by glucuronidation) leads to inactive metabolites (hydromorphone-3 glucuronide) making hydromorphone the opioid of choice in patients with endstage renal disease.[42]

Remifentanil

Remifentanil, an ultrashort acting selective μ receptor agonist is emerging as a promising opioid analgesic for use in the critically ill patients. The drug has unique pharmacokinetics in that it undergoes rapid metabolism by nonspecific blood and tissue esterases to an inactive metabolite, remifentanil acid. The drug is intensely lipophilic (onset of action < 1 min) and approximately 250 times more potent than morphine.[47] The terminal half life of the drug is approximately 10 to 20 minutes.

Because of the short duration of action, remifentanil may be preferable for analgesia in patients requiring frequent neurological assessments. Although the ultrashort action is beneficial in avoidance of prolonged drug effects, pain may rapidly emerge after drug discontinuation and longer acting agents may need to be administered to patients with ongoing pain.

Other agents: Meperidine with an onset of action and half-life similar to morphine should not be routinely used for analgesia in the ICU.[48] It has an active metabolite, normeperidine, a CNS stimulant which can cause neuroexcitation, manifested as tremors and seizures.[49]

Side Effects of Opioids

- *Respiratory depression:* Opioids lead to dose dependent, centrally mediated respiratory depression with respiratory rate decreased initially with preserved tidal volumes. As the dosage increases, tidal volume also is reduced and ventilatory response to hypoxia is obtunded.[45]
- *Hypotension:* Opioid induced hypotension is of particular concern in hypovolemic and hemodynamically unstable patients[50] and can occur in euvolemic patients also. By blunting the sympathetic tone, vagally mediated bradycardia, histamine release and increase in systemic venous capacitance, opioids can cause a precipitous fall in blood pressure.[51]
- *Gastric retention and ileus:* Routine use of stool softeners and stimulant laxatives may minimize opioid induced constipation but is often ineffective. Because of gastric hypomotility, small bowel intubation for feeding may be required.
- *Other side effects:* Muscle rigidity, urinary retention, nausea and pruritus.

Sedative Medications

Benzodiazepines

This class of drugs, which act by potentiating the Gamma-Aminobutyric Acid (GABA) receptor complex activity are the most commonly used sedative agents in intensive care. Benzodiazepines possess anxiolytic and anticonvulsant properties. They are potent inducers of anterograde amnesia but do not cause retrograde amnesia.[42] The pharmacologic effect depends on the degree of GABA receptor binding. Approximately 20% binding is associated with anxiolysis, 30–50% with sedation, and 60% with hypnosis.[52]

Benzodiazepines are associated with a dose dependent respiratory depression which is particularly marked when co-administration is done with opioids.[45] They can lead to hypotension particularly in hypovolemic patients. They can modulate the anticipatory pain response thereby can lead to reduction in the dose of opioids administered (opioid sparing effect).[53]

Midazolam

Midazolam is a rapidly acting, water soluble benzodiazepine (onset of action within 5 minutes) which has a short duration of action. It is oxidized by the cytochrome P450 (CYP 3A4) enzyme system in the liver leading to the production of water soluble hydroxylated metabolites. The primary metabolite is 1-hydroxymidazolam glucuronide, a CNS depressant which can cause prolonged sedation especially if kidney failure is present, as it is renally excreted. Obese patients and patients with hypoalbuminemia can also have prolonged sedation after midazolam administration.[54] CYP 3A4 inhibiting drugs like ketoconazole, itraconazole and erythromycin can lead to prolongation of sedative effects of midazolam.[42]

Because of unpredictable awakening and time to extubation when midazolam infusions continue longer than 48–72 hours, it is recommended for short-term use only. Midazolam is a preferred agent for rapid sedation of acutely agitated patients.

Lorazepam

Lorazepam has an onset of action within 5 to 20 minutes and the effect lasts for up to 6 to 8 hours. Unlike midazolam, hepatic metabolism of lorazepam leads to production of inactive metabolites which are excreted by the kidney.[45] An important concern with lorazepam administration is propylene glycol toxicity. Propylene glycol is used as a solubility enhancer of the drug for intravenous preparations. The toxicity may manifest as hyperosmolar states, worsening metabolic acidosis and acute tubular necrosis.[42] Monitoring of serum Osmolal gap should be done in patients receiving 50 mg per day and greater or > 1 mg/kg of lorazepam per day. An osmolal gap greater than 10 to 15 indicates significant accumulation of propylene glycol.[55] Treatment involves discontinuation of lorazepam infusion. In severe cases, hemodialysis provides effective removal of propylene glycol.[56]

Only a few randomized trials have compared midazolam with lorazepam for prolonged infusions. No significant difference in time to awakening was demonstrated in two studies. However, a double blind randomized controlled trial reported significant delays in emergence with lorazepam (31.1 hours for lorazepam vs 14.9 hours for midazolam for deep sedation after 72 hours infusion), as compared to midazolam.[57–59]

Lorazepam use in the ICU was found to be an independent risk factor for transition to delirium, even after adjusting for covariates.[60] Fenatanyl, propofol and morphine were also associated with higher odds ratio but not reaching statistical significance, in the same study.

Although lorazepam is recommended for the sedation of most patients via intermittent IV administration or continuous infusion,[1] in view of the possible concerns regarding prolonged emergence times, risk of propylene glycol toxicity and possible increased risk of delirium, prolonged infusions of lorazepam should be used cautiously. Midazolam is a better option in patients with normal renal and liver function parameters.

Propofol

Propofol (2,6 diisopropylphenol) is a widely used ICU sedative. Like the benzodiazepines, it possesses sedative and hypnotic properties and provides amnesia.[61] However, its site of binding on the GABA receptor is different from that of the benzodiazepines. It lacks analgesic properties therefore patients may require a greater dose of opioids for pain relief if receiving propofol rather than benzodiazepines.[62]

It is profoundly lipophilic, therefore crosses the blood-brain barrier, and rapid redistribution after infusion discontinuation leads to quick emergence times.[45] SCCM guidelines recommend propofol as the preferred sedative agent, when rapid awakening is important like in neurological assessment. Propofol reduces cerebral blood flow and metabolism and decreases the intracranial pressure.

Although propofol is metabolized in the liver by conjugation to metabolically inactive metabolites, clearance apparently is not significantly altered by hepatic or renal disease.[63] Clearance of the drug is slowed down in the elderly patients. Propofol causes profound respiratory depression, can also cause hypotension, especially in hypovolemic patients. Airway should be secured or intubation should be at standby whenever administering propofol.[45]

Propofol is a caloric source and provides 1.1 kcal/ml from fat.[42] Prolonged infusions may be associated with hypertriglyceridemia and also pancreatitis, therefore serum triglyceride levels should be monitored.[64] It is recommended to monitor triglyceride concentrations after two days of propofol infusion and also to include the total caloric intake from lipids in the nutrition support prescription.[1]

A number of randomized controlled trials have compared propofol with midazolam for sedation in the ICU. In a systematic review of 27 RCTs,[65] propofol use was associated with more effective sedation (longer duration of adequate sedation) and shorter weaning time for short-term infusions (<36 hours) but was associated higher adverse event (arterial hypotension and hypertriglyceridemia) rates. When daily interruption of sedation (DIS) was routinely used with both drugs, the duration of mechanical ventilation was similar.[66] In a trial comparing propofol infusion and DIS with intermittent lorazepam, duration of MV was significantly reduced with propofol and DIS.[67]

Propofol infusion syndrome (PRIS): Propofol infusion syndrome is a rare complication seen with infusion of propofol.[68] It is characterized by acute refractory bradycardia leading to asystole in the presence of one or more of the following: Metabolic acidosis (base deficit >10 mmol.l^{-1}), rhabdomyolysis, hyperlipidemia and enlarged or fatty liver. This potentially fatal condition is typically associated with propofol infusions at doses higher than 4 mg/$kg^{-1}.h^{-1}$ for greater than 48 hours duration. This is likely to occur from mitochondrial respiratory chain inhibition or impaired mitochondrial fatty acid metabolism mediated by propofol. Treatment involves immediate discontinuation of propofol and supportive treatment with hemodialysis or hemoperfusion, as the clinical setting dictates.

Dexmedetomidine

Dexmedetomidine is the dextro enantiomer of medetomidine which is the methylated derivative of etomidine. It is a highly specific alpha-2 receptor agonist with a specificity for the alpha-2 receptor seven times that of clonidine and an alpha-2/alpha-1 binding affinity ratio of 1620:1.[69] The drug possesses anxiolytic, sedative and analgesic properties. The mechanism of action is multipronged with sedation and anxiolysis via receptors within the locus ceruleus and analgesia via receptors in the spinal cord.[70] The drug does not produce any significant respiratory depression. There is also mounting evidence that dexmedetomidine has protective effects against ischemic and hypoxic injury.[47]

The onset of action occurs after approximately 15 minutes of IV injection, the drug distribution occurs rapidly from the brain, leading to a short terminal half-life. Hepatic metabolism by glucuronidation leads to production of inactive metabolites. Dose reductions are required in the presence of both renal and liver disease.[47] The drug is apparently remarkably safe when administered as the sole agent, with oversedation which spontaneously recovers on drug discontinuation being the only reported adverse event on accidental infusion of large doses.[71] However, on coadministration with sympatholytic or cholinergic agents in the settings of vagal stimulation, there is a risk for excessive bradycardia and even sinus arrest.[47]

Dexmedetomidine can provide excellent sedation without respiratory depression during fiberoptic intubation or other difficult airway procedures. In these settings, it has added benefits of decreasing saliva production and airway secretions.[72–74] In high infusion doses, it has been used as a sole agent to anesthetize patients with tracheal stenosis, as it preserves spontaneous ventilation.[74] Currently, the drug is approved by the United States Food and Drug Administration (US-FDA) for use up to 24 hours in mechanically ventilated patients. Recent studies have indicated dexmedetomidine may be safely used as infusion with durations exceeding 24 hours.[70,75,76]

In a recently published prospective,multicenter, randomized double blind trial comparing midazolam and dexmedetomidine, patients in the dexmedetomidine group had a significantly lesser duration of mechanical ventilation and had significantly lesser prevalence of delirium during treatment. The time within the target sedation levels was comparable between the groups. The most important treatment related adverse effect of dexmedetomidine was bradycardia.[70]

Dexmedetomidine may be preferred sedative agent for ICU patients, because of its beneficial effects. If patient has bradycardia, LV dysfunction or in settings when deep sedation is required, other agents may be more appropriate.

Volatile Anesthetic Sedation

Volatile anesthetic agents offer the advantage of quick onset and offset of action and ease of titration of effect. The route of delivery and elimination are primarily the lungs, therefore hepatic or renal dysfunction has little impact on the duration of effect and emergence times. Excellent control of the drug effect can be done by monitoring the end-tidal concentration or fraction. Adverse effects can be immediately reversed by decreasing the inspired concentration of the agent. Isoflurane, desflurane and sevoflurane have been used for ICU sedation. The major obstacles to the use of volatile anesthetics for ICU sedation are cost, concerns for environmental pollution and the need of anesthetic expertise. The requirement of a cumbersome circuit for delivery hinders their use.

Recent technological advances like a new and fairly simple device, the ‘‘Anesthetic Conserving Device’’ (AnaConDa, Hudson RCI, Uppslands Vasby, Sweden) allow the infusion of liquid volatile anesthetic through the breathing circuit of a standard ICU ventilator. A semi-closed rebreathing circuit is created which retains 90% of the inhaled anesthetic.[47]

The use of volatile anesthetic sedation has demonstrated shorter emergence times (isoflurane vs midazolam or propofol), shorter times to extubation and hospital LOS postcardiac surgery (sevoflurane vs propofol), better cognitive functions after emergence (desflurane vs propofol) and a trend towards lesser propensity to develop delirium (isoflurane vs midazolam).[77–82] Volatile anesthetic sedation may become an attractive alternative to routine use of IV sedative agents in the ICU in future.

Peripherally Acting Mu-opioid Receptor (PAM-OR) Antagonists

Opioid use in the ICU is associated with a number of gastrointestinal side effects like constipation, ileus and delayed gastric emptying. PAMORAs are a novel class of drugs which do not cross the blood-brain barrier to antagonize the central effects of opioids, thereby preserving the analgesic effects. They antagonize the peripheral side effects of opioids, importantly constipation and ileus.[47]

Methylnaltrexone and Alvimopan are currently the FDA approved PAMORAs. Subcutaneous methylnaltrexone is approved for the relief of opioid-induced constipation and oral alvimopan, to facilitate the return of gut dysfunction after anastomotic bowel surgery. This class of drugs may prove to be of great therapeutic potential in the management of patients in the ICU particularly in those requiring frequent and prolonged administration of opioids.

Use of Patient Targeted Sedation—Analgesia Protocols and Daily Interruption of Sedation

Use of Sedation Protocols or Algorithms

Use of protocols for ICU sedation and analgesia involves assessment of pain and levels of sedation, using validated assessment tools and integration of the same into an algorithm according to which changes in the medication dosage are done.[83] Patient management regarding ICU sedation and analgesia is multidisciplinary; therefore, this area is particularly well suited to a protocolized and structured approach.

The primary aim of these approaches is to avoid accumulation of medications and their active metabolites which can be associated with a slower rate of recovery from critical illness. Critically ill patients are susceptible to prolonged effects of sedative analgesic medications, owing to a number of factors like alterations in volume and protein binding status and presence of renal or hepatic dysfunction and other factors.[84] Use of protocols has also been associated with reduction in diagnostic studies for unexplained changes in mental status, a reduction in the side effect of medications and reduction in hospitalization costs.[66] Less patient ventilator dys-synchrony and decreased incidence of VAP have also been found to be associated with the use of a sedation algorithm or protocol.[85,86]

The development and design of the protocol should be multidisciplinary, so should be the implementation.[87] Treatment goals should be established and frequent assessments done. Validated scales should be used for the assessment of pain and agitation. Evidence based selection of medication and patient focussed approach should be used. The protocol should be robust enough to effectively control pain and agitation, but avoid oversedation. Finally, multidisciplinary acceptance of the protocol and its integration into routine care should be achieved.

In most algorithms, it is the bedside nurse who is actually responsible for the implementation of the protocol interventions. The availability of a clinical pharmacist to ensure adherence is not possible at all centers. The addition of a daily intervention of involving a clinical pharmacist to ensure sedation protocol adherence led to a significant reduction in the duration of mechanical ventilation in one study.[88]

Most algorithms incorporate the management of pain and agitation within a single algorithm. First focus is towards the detection of pain and adequate analgesia, followed by sedative therapy as required. This strategy has been termed as ‘‘analgesia-first’’ or “A1” approach by some authors in which sedatives are administered only after aggressive analgesic strategies.[89]

The protocols used in the various published studies range from simple to complex algorithms. The simpler protocols make use of a sedation scale to make objective assessment and simple instructions regarding medication selection and dose of administration. Complex protocols have targeted a number of domains, like the assessment of the intensity of pain, sedation, patient ventilator dys-synchrony and delirium.[87]

Analgesia Based Sedation Protocols/Co-sedation

Recently, there has been interest in strategies that focus primarily on provision of analgesia, with addition of a sedative/hypnotic agent as and when required - termed as “analgesia based” or “co-sedation” strategies. Two approaches have been used in trials. In one, initially titration of analgesic infusion is done prior to the addition of a sedative drug. In the other approach, co-infusion of both the sedative and analgesic drug has been done.

Analgesia based strategies have been demonstrated to reduce the duration of mechanical ventilation,[90] lead to better sedation with more “on-target” sedation,[85] less patient ventilator asynchrony[85] and faster awakening for neurological assessment in neurotrauma patients.[91]

Analgesia-Delirium-Sedation Protocols

A shorter duration of mechanical ventilation was observed when pain (visual scale), agitation (RASS) and delirium (CAM-ICU) were assessed as a part of the single protocol.[92]

Numerous controlled trials comparing protocols with usual care have supported the use of structured approaches. However, the ideal structure of the approach is not clear, as a multitude of approaches have been used. The common principle however remains to reduce oversedation.

A longer ICU LOS has been reported following the use of a sedation algorithm.[93] However, such reports are scarce and the benefits of using sedation protocols or algorithms have been consistently reported. Centers can have their own approaches according to the available infrastructure, with a common goal of the approach being drug administration reduction of oversedation and using an intermittent strategy vs continuous infusion. Also, the algorithm should be easy to understand and implement.

Daily interruption of sedation (DIS): The underlying principle of this strategy is to provide a daily drug free period to minimize the chances of drug accumulation and allow the patient to awaken. A reassessment can be done of the actual level of pain, level of agitation and the readiness of the patient to tolerate spontaneous breathing. The strategy incorporating daily interruption of sedative (midazolam or propofol) and analgesic (morphine) medications until the patient was agitated or able to follow simple tasks, led to significant reductions in the duration of mechanical ventilation, use of less number of diagnostic tests for unexplained altered level of consciousness and a shorter ICU LOS.[66]

DIS has also been associated with a reduction in the risk of several well known complications of critical illness like ventilator-associated pneumonia, upper GI bleed, bacteremia, cholestasis, barotraumas, venous thromboembolism and sinusitis requiring surgical intervention.[94] A careful clinical observation is required while practicing the DIS strategy. If the patient develops signs of increasing distress and agitation, a bolus administration of the drugs can be done and infusions restarted at half the previous rates. Patients who after the daily interruption of medications, do not develop signs of increased agitation and are awake, should have their drugs restarted only when needed, not routinely.

Combining DIS with SBT (Spontaneous breathing trials): A low MIP was found to be independently associated with deeper levels of sedation in mechanically ventilated patients.[95] It is therefore possible that improved levels of consciousness may be associated with greater chances of tolerating spontaneous breathing and consequent liberation from mechanical ventilation.[96]

Concerns with DIS Implementation: Because of the abrupt awakenings which occur in patients with DIS, there have been a few practical concerns such as a rebound increase in agitation when the medications are stopped, with possible related events like self removal of catheters, violent behavior and patient ventilator asynchrony.[66, 67, 96]

Another concern has been the adverse neuropsychiatric impact of daily interruption of sedation, leading to abrupt awakenings in the critically ill individuals. However, DIS has been shown to be associated with no adverse neuropsychiatric outcomes and has demonstrated a trend towards a reduced occurrence of post-traumatic stress disorder (PTSD) at 1 year.[97]

Awakenings during DIS are associated with an adrenergic surge, with consequent increases in heart rate, blood pressure and levels of circulating catecholamines, raising concerns regarding the implementation of this strategy in patients with an underlying risk of coronary artery disease (CAD). In an observational study, DIS was not shown to increase the number of cardiac ischemic events in patients with underlying risk factors for CAD.[98]

Although DIS appears to be a relatively safe and effective strategy, extreme caution should be exercised in certain group of individuals like those with a history of alcohol or substance abuse as precipitation of withdrawal in them can lead to undesirable consequences.[5, 45] Caution should also be exerted in patients with conditions like hypertensive emergencies and status asthmaticus, in whom the stress response may have detrimental consequences.[5]

Recent Developments and Novel Approaches

"No Sedation" Protocols

The no sedation protocol in a recent single center trial, on 140 critically ill adult patients relied on the intermittent administration of morphine without any continuous infusion of sedative or analgesic agents.[99] Protocol violation with administration of sedative agents was required in 10 patients mostly to permit adequate ventilation in ARDS.[100] Complications did not differ between the groups but delirium was more frequent in the no sedation group (DSM-IV criteria) and there was a need for an extra person at the bedside to comfort and reassure patients more often in the intervention group than in the control group (20% *vs* 5%).

This strategy appears promising but findings will need to be confirmed in large, multicenter trials, before it can be widely adopted. Nonetheless, this approach may provide a shift in paradigm for the future research trials to using as less sedation in the ICU as possible.

Patient Controlled Sedation (PCS) for Mechanical Ventilation

Based on the demonstration that patients who self-administer analgesics, i.e. patient controlled analgesia (PCA), eventually have lesser drug requirements and achieve better symptom control, it was hypothesized that PCS in mechanically ventilated patients, an untested approach till now, might lead to reduced sedative requirements, and eventually may be associated with better clinical outcomes. The safety and adequacy of this novel approach was tested in a recent single center pilot study, using dexmedetomidine given as a basal infusion coupled with patient triggered boluses, for 24 hours.[101] In a small sample size of 17 mechanically ventilated patients who had stable or improving pulmonary status, PCS was rated favorably for self-management of anxiety. The level of relaxation obtained and comfort in self-administration of sedative medication were acceptable.

This study demonstrated the feasibility of PCS using dexmedetomidine in mechanically ventilated patients with improving pulmonary status, those who have minimal sedative requirements and able to comprehend the instructions for pump use.

Sedation and Immunity

Available evidence links benzodiazepine and propofol use with suppression of the innate immune response and an unclear effect on the adaptive immune response.[102]

Opioids on the other hand, lead to suppression of both innate and adaptive immune responses. Chronic use of morphine leads to a shift to Th2 cytokine predominance.[103] Such a shift has also been observed in the later stages of sepsis and therefore opioids may contribute to increased incidence of infections and immunosuppression in the critically ill patients.

Dexmedetomidine may have particularly beneficial immunologic effects as an ICU sedative agent. As compared to other sedatives, Dexmedetomidine has superior anti-inflammatory effects, improves macrophage function and has antiapoptotic effects.[102, 104] There also are indications that the choice of sedative may be of great importance in patients with sepsis. In a subgroup analysis of the MENDS study, dexmedetomidine demonstrated a 70% mortality benefit at 28 days, as compared to lorazepam based sedation with a lesser duration of mechanical ventilation and more delirium free days in dexmedetomidine treated patients.[75]

Global Use of Sedation Scales and Protocols

Surveys done prior to the SCCM "Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult" in 2002 revealed that sedation assessment was performed in less than 50 % of ICU's all over the globe.[21] Even after the publication of SCCM guidelines, use of sedation scales for objective assessment in the ICU's remains disappointingly low.

In a study of 1381 patients in 44 French ICU's in 2004, a sedation protocol was being used in 36% ICU's and a sedation or pain assessment scale in approximately 50% of the patients receiving sedative analgesic medications. Procedural pain was specifically managed in less than 25% of the patients. DIS was not being used in any of the ICU'S. 40 to 50% of the assessed patients were under deep sedation.[11]

Widespread implementation of sedation and delirium assessment tools is achievable but there are several practical issues like implementation by the nursing staff-lack of time concerns and lack of confidence.[105]

Sedation and Analgesia Withdrawal

Symptoms of acute withdrawal syndrome can occur following prolonged administration of these agents in the ICU. Also, frank withdrawal symptoms may not be obvious all the time, patient may manifest clinical signs only. Withdrawal symptoms and even physical dependency have been documented, particularly in critically ill pediatric population with almost any agent.[106,107] In a retrospective study of patients in an adult trauma/surgical ICU, 32% of the patients requiring more than 7 days of ICU care developed acute withdrawal syndrome, with administration of sedative and analgesic medications potentially implicated for the same.[108]

Development of withdrawal syndrome may have potential deleterious consequences and has also been linked to the development of ICU delirium.[5] SCCM guidelines recommend considering the potential for opioid, benzodiazepine and propofol withdrawal after high doses or more than approximately seven days of continuous therapy and systematic tapering, to prevent withdrawal symptoms. During the period of recovery from critical illness, a careful watch should be kept for signs and symptoms, which may be nonspecific indicators of withdrawal like hypertension, tachycardia, fever, nausea, insomania, delirium, agitation and diaphoresis. Gradual reduction of sedative and analgesic medications should be considered in patients thought to be at high risk, particularly the pediatric patients.

Delirium in the ICU

Delirium is characterized by an acutely changing or fluctuating mental status, inattention, disorganized thinking and an alteration in the level of consciousness. Agitation may or may not be there. Delirium occurs in approximately 35 to 80% of the ICU patients, is independently associated with a longer hospital LOS, increased mortality and greater economic costs.[3,109,110] Delirium assessment using validated assessment tools is seldom performed in the ICU's.[111]

Delirium can be classified into three subtypes: hypoactive, hyperactive, or mixed.[112] Hypoactive delirium is associated with the worst prognosis. It is characterized by psychomotor retardation, difficult to detect unlike hyperactive delirium which is easily recognized.

Assessment of Delirium in the ICU

Routine assessment of delirium in critically ill patients is recommended even in those who are calm and apparently not agitated. The gold standard criteria for the diagnosis of delirium is the clinical history and examination. This method of assessment is usually not possible in critically ill and ventilated subjects because of the inability to speak and write and therefore other tools for assessment of ICU delirium have been developed (Table 150.9). These tools can be used for delirium assessment by trained ICU staff and not necessarily by psychiatrists.

TABLE 150.9: Delirium assessment tools in the ICU

- Confusion assessment method for the intensive care unit (CAM-ICU)[113]
- Intensive care delirium screening checklist (ICDSC)[114]
- Cognitive test for delirium[115]
- Cognitive test for delirium – abbreviated version[116]
- Neelon and champagne confusion scale[117,118]
- Delirium detection score[119]
- Nursing rating scale for ICU delirium

The confusion assessment method for the intensive care unit (CAM-ICU) and cognitive test for delirium are interventional tools based on direct testing of the patient's state by the rater, whereas ICDSC and Nursing scale for delirium are observational tools based on the observation of certain patient behaviors by the rater.[5]

The CAM-ICU and ICDSC have been extensively validated. The ICDSC also offers an advantage of detection of "subsyndromal" delirium which over the course of time may progress to overt delirium.[5, 120] In subsyndromal delirium, patients exhibit one or more delirium symptoms without meeting the criteria for full-blown clinical delirium. SCCM guidelines[1] mention CAM-ICU as a promising tool for the assessment of delirium in ICU patients. The components of CAM-ICU include the observation of an acute onset of mental status change or a fluctuating mental status, inattention, disorganized thinking and an altered level of consciousness. The tool on an average takes approximately 2 minutes to complete and is easy to use.

Prevention and Treatment of Delirium

Delirium prevention in ICU: The strategies for prevention of delirium may be divided into nonpharmacologic, pharmacologic and combined approaches.[109] Use of certain nonpharmacologic approaches have demonstrated favorable outcomes in non ICU patients.[121,122] These strategies based on the underlying principles of reorientation, communication, mobilization and minimization of drug exposure may be used in ICU subjects too. Pharmacologic approaches to reduce delirium in the ICU have not been evaluated extensively. No studies have been done to assess the role of prophylactic haloperidol in the ICU patients. Dexmedetomidine appears to be a promising drug which may assume an important role in ICU delirium management. In a recent RCT, the prevalence of delirium was significantly lower in dexmedetomidine-treated patients: 54% versus 76.6% in midazolam-treated subjects ([95% CI, 14%–33%]; p<.001).[70]

A combined approach using both pharmacologic and nonpharmacologic methods has been tried, with a reduction in subsyndromal delirium.[123] These strategies are difficult to implement, may not be appropriate for use in all patients.

Treatment of delirium: Pharmacologic therapy remains the mainstay of management of delirium in the ICU. Attention should first be paid to the recognition of an underlying correctable cause. Antipsychotic agents are the most commonly used and recommended drugs for the management of delirium. Both conventional and atypical antipsychotic agents are apparently effective.

Haloperidol, olanzapine and quetiapine have been used in the management. Studies evaluating the use of antipsychotics in ICU are limited. In a small prospective trial, both olanzapine and haloperidol were found to be equally efficacious in controlling delirium. Olanzapine, however was associated with lesser extrapyramidal side effects.[124]

According to the SCCM guidelines, Haloperidol is the preferred agent for the treatment of delirium in critically ill patients. There is however no consensus on the optimal dosing and the treatment regimen of haloperidol. Haloperidol is usually administered by intermittent IV injections. Initially, a starting dose of 2 mg IV can be administered followed by repeated doses (doubling the previous dose) every 15–20 min. The loading dose is administered till the control of acute agitation.[1, 125] After the control of acute agitation, scheduled intermittent doses (25% of the loading dose) may be administered 6 hourly and then gradually tapered off.

Monitoring should be done for electrocardiographic changes (QT interval prolongation and arrhythmias) when receiving haloperidol.[1] Development of Extra-Pyramidal Syndrome (EPS) is another known complication of administration of neuroleptic agents. If EPS develops, haloperidol should be stopped and a trial of diphenhydramine or benztropine should be given.

Prior to hospital discharge, cognitive function assessment is preferable in all the patients with proper neuropsychiatric advise and rehabilitation during follow-up, if required.

In conclusion, teamwork and patient focussed care play a key role in the management. Adequate pain relief should always take priority oversedative administration and adequacy of analgesia should be determined using patient self report, if possible. Consequences of inappropriate sedation and pain relief have been well recognized, thereby necessitating frequent and structured assessment of pain and agitation in the ICU patients using validated assessment instruments. The choice of sedative and analgesic agent should be done keeping the individual patient clinical characteristics in focus. Protocol based sedation and DIS are strategies which are backed up with good quality evidence to be associated with better patient outcomes. Institutions should devise protocols, depending on the feasibility and ease of use according to the available resources. Delirium assessment using validated delirium assessment tools should be included as a part of the patient assessment and delirium should be appropriately managed.

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Weaning from Mechanical Ventilation

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INTRODUCTION

Patients require mechanical ventilatory support when the ventilatory and/or gas exchange capabilities of their respiratory system fail as a result of processes both within the lung as well as in other organ systems. Once the cause of respiratory failure starts improving, then the ventilatory support needs to be discontinued either gradually or abruptly. Weaning is a process of abruptly or gradually withdrawing ventilatory support, and includes discontinuation of Mechanical Ventilation (MV) and removal of artificial airway if any. Difficulty and complexity in weaning can be estimated by the time spent in the weaning process which represents 40 to 50% of the total duration of mechanical ventilation.[1] In patients with more slowly resolving lung disease, time spent in the weaning process is likely to be much higher. Approximately 70 to 75% of mechanically ventilated patients whose underlying cause of respiratory failure has either improved or resolved can be discontinued abruptly from mechanical ventilation.[2,3] The remaining patients will need gradual and progressive withdrawal from mechanical ventilation.

The determinants of assessing a patient's readability to wean and the best weaning technique currently remain unclear. The process of weaning begins when the patient has started recovering from acute respiratory failure. Thereafter, clinical, biochemical and respiratory assessments are frequently performed to determine the patient's readiness for discontinuation of ventilator support and extubation. The assessment for weaning generally begins from the first day of ventilation, and Fig. 151.1 shows the stages of weaning process. Not only delayed weaning is associated with increased costs of ICU care but the risks of nosocomial pneumonia, cardiac morbidity and death is also increased. On the other hand, a premature weaning attempt carries the risk of compromised gas exchange, high incidence of nosocomial pneumonia, difficulty in re-establishing the airway and 6–12 fold increased risk of mortality.[4]

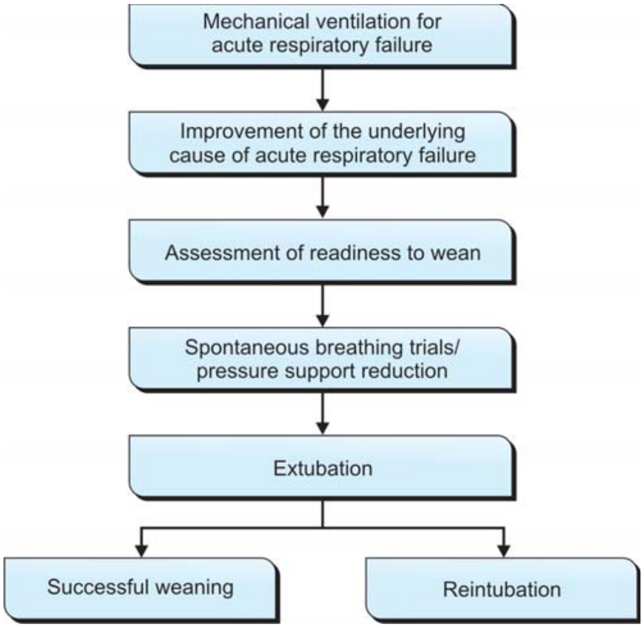
Mechanical ventilation for acute respiratory failure
Improvement of the underlying cause of acute respiratory failure
Assessment of readiness to wean
Spontaneous breathing trials/ pressure support reduction
Extubation
Successful weaning
Reintubation

Fig. 151.1: Stages in weaning from ventilation

Weaning can further be classified as: (a) Simple weaning: Initiation of weaning to successful extubation on the first attempt without difficulty is simple weaning. It carries a good prognosis with an ICU and in-hospital mortality of approximately 5% and 12%, respectively;[5,6] (b) Difficult weaning: Failure to tolerate initial

Spontaneous Breathing Trial (SBT) successful weaning requiring up to three SBTs or up to 7 days from first SBT and (c) Prolonged weaning: Failure of at least three SBT or takes more than 7 days after the first SBT is prolonged weaning. Both difficult and prolonged weaning increases duration of hospital stay and consequently carries an ICU mortality of approximately 25%.

PATHOPHYSIOLOGY OF WEANING

In a patient being mechanically ventilated, a complex interaction of the control of breathing, lung and chest wall mechanics, respiratory muscles, gas exchange properties of the lung and the cardiovascular hemodynamics determines the process and timing of weaning. Disturbance at any level can potentially lead to weaning failure.

Altered Control of Breathing

Central drive may be impeded by metabolic alkalosis, MV itself or the use of sedative/hypnotic medications. Failure of breathing control leading to weaning failure can occur due to either structural lesion like brainstem strokes or central apneas or metabolic factors such as electrolyte disturbances or sedation/narcotic usage.[7–9] Additionally, structural or metabolic abnormalities including drugs affecting the peripheral nerves will also result in altered afferent or efferent output and ventilator dependence.[10, 11]

Altered Respiratory Mechanics

Physiological variables most commonly altered during weaning process are the resistance, elastance and air trapping. Four factors account for the increase in resistance, and these are increased inspiratory flow, decrease in lung volume, accumulation of secretions and bronchoconstriction.[12–14] Low respiratory system compliance occurs due to stiff chest wall, stiff lungs, flooded or atelectatic alveoli. The presence of auto-Positive End Expiratory Pressure (auto-PEEP) increases the pressure gradient needed to inspire irrespective of whether patient is triggering the ventilator or spontaneously breathing.[15, 16] This increase in inspiratory threshold raises the work of breathing and leads to weaning failure.[17]

Respiratory Muscle Dysfunction

Respiratory muscles weakness occurs commonly in the critically ill patients as a consequence of:

- Atrophy and remodeling from inactivity[18]
- Critical illness neuropathy and myopathy[19,20]
- Drugs (neuromuscular blockers, aminoglycosides and corticosteroids)[21–23]
- Metabolic factors like nutrition, electrolytes and hormones
- Imbalance between respiratory muscle capacity and the load[24-26]

The load on the ventilatory muscles depends on the ventilation demands and respiratory system mechanics (i.e. primarily compliance and resistance). Ventilatory demands are increased as a consequence of increased oxygen demands during sepsis, anemia, pulmonary embolism and increased dead space in patients with obstructive defects. Likewise, compliance worsening due to lung edema, infection, inflammation, fibrosis and chest wall abnormalities such as edema or surgical dressings or increased resistance secondary to bronchoconstriction and airway inflammation and secretions will alter the lung mechanics and consequently increase the respiratory load. Additional load also can be imposed by narrow endotracheal tubes and by insensitive or poorly responsive ventilator demand valves.

Inadequate nutrition causes increased protein catabolism leading to a loss of muscle performance.[27, 28] Similarly, in semi-starvation conditions, normal hypoxic ventilatory response and the hypercapnic ventilatory response deteriorate.[29] In contrast overfeeding leads to excess CO_2 production that may impair the ventilator withdrawal process by further increasing the ventilation loads on ventilatory muscles.[30,31]

Electrolyte imbalance most importantly deficiency of phosphate and magnesium has also been shown to impair ventilatory muscle function.[32–35] Severe hypothyroidism and myxedema directly impair diaphragmatic function and blunt ventilatory responses to hypercapnia and hypoxia.[36,37] Beside thyroid hormone, insulin/glucagon and adrenal corticosteroids are also important for optimal muscle function and deficiency of any of them may cause respiratory muscle dysfunction.

Cardiovascular Performance

All the ventilatory work during respiration is performed by respiratory muscle without getting fatigue. Thus they depend on an efficient transport of oxygen by the cardiovascular system. Several groups of investigators have drawn attention toward the potential for weaning process to induce ischemia or heart failure in susceptible individuals with limited cardiac reserve.[38–42] These cardiovascular dysfunction during the transition from MV to spontaneous breathing occurs due to increased metabolic and circulatory demands, increased venous return due to displacement of blood from the abdomen to thorax by contracting diaphragm and increased left ventricular afterload imposed by negative pleural pressure swings.

OUTCOME OF WEANING

Weaning failure is defined as either the failure of the weaning process or intolerance to the SBT or the need for reintubation within 48 hours following extubation. *Intolerance to SBT* is defined by objective indices of failure, such as tachypnea, tachycardia, hypertension, hypotension, hypoxemia or acidosis, arrhythmia and subjective indices, such as agitation or distress, depressed mental status, diaphoresis and evidence of increasing effort.[2, 3, 5, 43]

ASSESSMENT FOR WEANING

The evaluation of patients' readiness for weaning begins with the resolution of respiratory failure and/or the disease entity that prompted the initiation of MV as well as the presence of a basic level of physiological readiness like intact airway reflexes, afebrile and cardiovascular stability. The patient's capacity to breathe spontaneously is often underestimated by the subjective criteria and clinical judgment. Stroetz et al. showed, intensivists could not accurately predict patient tolerance of a 1-hour period on minimal pressure support.[44] Similarly, Afessa and colleagues reported that practitioners in the critical care failed to accurately forecast 3-day and 7-day weaning outcome for mechanically ventilated patients in a medical Intensive Care Unit (ICU). [45]Thus, there is an obvious rationale that predicting readiness of successful weaning from MV needs to be based on objective predictors that can be applied in clinical decision making. To facilitate the process of assessment, various objective criteria have been established. Nevertheless, the objective criteria only needs to assist physician's clinical judgment and many patients may be weaned even if they do not fulfill these criteria. These criteria are broadly described in Table 151.1.

Indices to Predict Weaning Success Prior to SBT

Even prior to the implementation of an SBT, there are certain simple indices that are used to predict the outcome of the weaning trial.

TABLE 151.1: Objective criteria to facilitate assessment of weaning

A. Patient parameters

1. Improvement of the basic underlying cause
2. Awake, alert and cooperative
3. Hemodynamically stable
4. Respiratory rate <30/minute
5. No effect of sedation/neuromuscular blockade
6. Minimal secretions (generally less than 2 hourly suctioning requirement)
7. Good nutritional status

B. Ventilator parameters

1. Spontaneous tidal volume (TV) >5–8 ml/kg
2. Vital capacity (VC) >10-15 ml/kg
3. PEEP requirement <5 cm of H_2O
4. Static compliance >30 ml/cm of H_2O
5. Minute ventilation <10 L
6. Ratio of dead space volume to tidal volume (VD/VT) <60%
7. Maximal Inspiratory Pressure (MIP/Pimax)
8. Negative inspiratory force

C. Oxygenation criteria

1. $PaCO_2$ <50 mm Hg with normal pH
2. PaO_2 >60 at FiO_2 0.4 or less
3. SaO_2 >90% at FiO_2 0.4 or less
4. PaO_2/FiO_2 >200
5. $P(A\text{-}a)O_2$ <35 mm Hg at FiO_2 of 1.0

Simplified Weaning Index (SWI)[46]

$$\text{SWI} = \frac{F_V \times (\text{IP} - \text{PEEP})}{\text{MIP} \times 40} \times PaCO_2$$

A SWI less than 9 per minute is 93% predictive of successful weaning in the patient whereas a SWI greater than 11 per minute is 95% predictive of weaning failure.

CROP Index (Compliance, Rate, Oxygenation, Pressure)

The CROP index is an integrative index incorporating several measures of readiness for liberation from mechanical ventilation, such as dynamic respiratory system compliance (Crs), spontaneous breathing frequency (f), arterial to alveolar oxygenation [partial pressure of arterial oxygen (PaO_2)/partial pressure of alveolar oxygen (PaO_2)], and PImax in the following relationship:

$$\text{CROP Index} = \frac{C_{dyn} \times \text{MIP}}{f} \times (PaCO_2 / PACO_2)$$

CROP index assesses the relationship between the demands placed on the respiratory system and the ability of the respiratory muscles to handle them.[47] A CROP Index greater than 13 ml per breaths per minute is predictive of weaning success.[47]

Rapid Shallow Breathing Index (RSBI)

Tobin and colleagues[30] first noted that patients with weaning failure developed significantly more rapid and shallow breathing than those who succeeded.[48] Subsequently, the same authors in a prospective study demonstrated that the ratio of frequency to tidal volume [Rapid Shallow Breathing Index (RSBI)] obtained during the first minute of a T-piece trial and at a threshold value of ≤105 breaths/minute/l was a significantly better predictor of weaning outcomes than other 'classic' and commonly used parameters.[47] It has a sensitivity and specificity of 97% and 65% respectively.[47] However, in later studies it was noted that RSBI has certain shortcomings, like it can produce excessive false positive predictions and has a less predictive power in COPD, elderly and in patients who needs ventilatory support for more than 8 days.[40, 49–51] One option to overcome this discrepancy is to use a SBT of 30–120 minutes in a patient who has RSBI of ≤ 105 breaths/minute/l to further assess patient readiness for liberation from mechanical ventilation.

Another important limitation RSBI is that the RSBI threshold can be influenced by the ventilatory support settings, the experimental conditions, and the patient population. When measured during trials of Pressure Support Ventilation (PSV), the RSBI has a limited value in predicting weaning outcome.[44] El-Khatib et al. reported that in the same patient's population, different ventilatory support settings can have a significant influence on the RSBI values. They showed there was a significant decrease in RSBI during a trial of PSV, Continuous Positive Airway Pressure (CPAP) on 40% oxygen and CPAP on room air as compared to a trial of T-piece for 1 minute in a spontaneously breathing patient at room air.[52,53] Thus, RSBI should only be adapted if the determination of the index is performed where patients were disconnected from the ventilator and spontaneously breathed room air for one minute because it can easily be applied at the bedside, and can be readily utilized to identify patients who are candidates for SBT.

Muscle load indices: These require more sophisticated measurements such as pleural pressure (estimated from esophageal pressure) to calculate the Pressure Time Product (PTP) and Pressure Time Index (PTI).[54] PTI can be a useful predictor of fatigue when it is more than 0.1.

TECHNIQUES OF WEANING

Once the patient has passed the predictor test they can immediately be extubated, however, because of the high rates of post-extubation distress and reintubation rates of approximately 40%, this approach is not recommended and there is need for a formal weaning trial before extubation.[55] Weaning trials also improves the patient's likelihood of tolerating extubation because of the improved reconditioning of the respiratory muscles. The major techniques used for weaning from MV is simply to initiate a trial of unassisted spontaneous breathing in the form of either a T-piece trial, low level CPAP trial, SIMV trial, PSV trial or a combination of these trials. As long as the principle of "Do Not Exhaust" is followed, the decision on which trial to use remains largely a matter of physician preference and the local protocols. SBTs are used to test readiness for weaning as well as to implement a weaning protocol that involves increasing periods of unsupported spontaneous breathing interspersed with periods of full ventilatory support.

Spontaneous Breathing Trails (SBTs)

The SBT is the oldest weaning technique wherein the patient is directly removed from the ventilator and put on T-piece with supplemental oxygen. It is mainly used for the assessment of readiness for extubation but it can also be used for weaning in which the length of the each SBT is gradually increased with alternating period of gradually decreasing ventilatory support. The SBT can be conducted without removing the patient from the ventilator which has the added advantage of quickly reinstitution of the ventilatory support in the face of SBT failure. It can be performed with no positive pressure applied to the airway with a low level of CPAP (5 cm H_2O) or PS (7 cm H_2O). Optimal SBT duration has been examined in two studies suggesting that 30 minutes is equivalent to 120 minutes with either T-piece or PSV.[6, 56] Optimal SBT duration may depend upon the duration of ventilation or the underlying cause for respiratory failure. An investigation of 75 patients with Chronic Obstructive Pulmonary Disease (COPD), ventilated for 15 or more days, found a median time to trial failure of 120 minutes.[57] Therefore, in some patients the SBT should be extended to at least 120 minutes. However, we generally use an SBT of at least 60 minutes.

A potential concern about the SBT is safety. Although unnecessary prolongation of a failing SBT may precipitate muscle fatigue, hemodynamic instability, discomfort or worsened gas exchange, however, there are no data showing that SBTs contribute to any adverse outcomes if terminated promptly when failure is recognized.[25, 58–60] The detrimental effects of ventilatory muscle overload during failing SBT often occurs early, thus, the initial few minutes of an SBT should be monitored closely and judiciously before continuing the SBT.[43,47,61] Thereafter, SBT can be continued for at least 30 minutes but not greater 120 minutes to assure maximal sensitivity and safety.

Failure of SBT is defined by the presence of tachypnea, tachycardia, arrhythmia, hypertension, hypotension, hypoxemia or the subjective evidence of agitation or distress, depressed mental status and diaphoresis.[2,3,5] A failed SBT should prompt a search for other causes or complicating factors and once the medical management is optimized further SBTs over a day is not expected to be helpful. Since failed SBTs are often due to persistent mechanical abnormalities of the respiratory system especially muscle fatigue that are unlikely to reverse rapidly.[58,59,62] Esteban et al. specifically addressed this issue and provided strong evidence that twice-daily SBTs offer no advantage over a single SBT and thus next SBT should be given after 24 hours only.[3]

Pressure Support Ventilation

Gradual reduction of PS is commonly utilized and is the sole mode of MV used during the weaning process in 21% of patients.[63] It is a pressure limited ventilation that recognizes the patient's inspiratory effort, ensures appropriate delivery at the time of inspiration and cycles to the expiratory phase without need for active patient exhalation. During PSV, breath is flow cycled to the expiratory phase when the flow decelerates to the 5 L/min or 25% of the peak inspiratory flow. The disadvantage is that flow deceleration is determined by resistance and compliance of the respiratory system. In patients with airflow obstruction, flow decelerates slowly. The flow needed to cycle may not be reached, stimulating active exhalation. During weaning, PSV is started at around 10–20 cm of H_2O and reduced by 2–4 cm H_2O at least twice daily till very low values can be tolerated. PSV is useful to counteract the extra work imposed by breathing through an endotracheal tube.

Synchronized Intermittent Mandatory Ventilation (SIMV)

Breathing during the SIMV mode is either mandatory ventilator controlled or spontaneous. Mandatory breaths are synchronized with the patient's effort that is either volume or pressure controlled. Spontaneous breathing is pressure supported. Weaning by SIMV is achieved by gradually decreasing the mandatory breathing rate by 2–4 breaths per minute and allowing the patient for spontaneous breathing effort to maintain the minute ventilation. As traditionally believed, respiratory muscle rest does not occur during mandatory breath of SIMV. In fact, respiratory center output and respiratory muscle activity is as great during the mandatory breaths as the spontaneous breaths.[64, 65] A comparative chart of different modes of weaning is given in Table 151.2.

TABLE 151.2: Comparative analysis of three commonly used modes for weaning

	T-piece	*SIMV*	*PSV*
Work quantity	All or none	Adjusted by no. of mandatory breaths	Adjusted by level of given pressure
Tidal volume	Determined by patient	Set by clinician	Patient interacts with applied pressure
Minimum minute ventilation	Not assured	Assured	Not assured
Synchrony	Regular periods of irregular load	Regular load	Constant
Patient comfort	Least	Intermediate	Most
Equipment complexity	Simple	Intermediate	Maximum

Continuous Positive Airway Pressure (CPAP)

The CPAP by itself is not a mode as it does not provide any inspiratory support. However, CPAP when applied during spontaneous breathing in patients with acute respiratory insufficiency reduces mean intrathoracic pressure has beneficial effects on right and left ventricular performance improves oxygenation and reduces the work of breathing.[66, 67] Bailey et al. randomized patients to receive CPAP or T-piece trials prior to extubation and observed no significant difference in oxygenation or time spent on mechanical ventilation.[68] Squadrone et al., in a multicenter randomized controlled trial, observed that CPAP compared to oxygen supplementation substantially reduced the reintubation rate.[69] Although combinations of CPAP and PSV are commonly applied during the weaning period, there is also a lack of prospective randomized controlled trials to suggest that CPAP is superior to other techniques such as PSV alone or T-tube in the process of weaning from invasive mechanical ventilation.

Role of Noninvasive Ventilation (NIV) in Weaning

Mechanical ventilation once instituted can be withdrawn abruptly in majority of the patients. However, approximately one third of the patients still require gradual weaning.[2,3] Among them 13 to 19% needs reintubation because of post-extubation respiratory failure.[43,70] Although the need for reintubation may be a marker of increased severity of illness, it is an independent predictor of mortality.[71,72] Therefore, any strategy that prevents the development of respiratory failure after extubation and subsequent reintubation are needed. One such strategy is the application of NIV that has been applied in patients with difficult weaning as well as used for the prevention and treatment of post-extubation respiratory failure. In patients with chronic respiratory failure especially those due to COPD, the application of NIV has been shown to decrease endotracheal and MV duration, the ICU and hospital stays, the incidence of nosocomial pneumonia, the need for tracheotomy to facilitate weaning, as well as an improvement in survival, both in the ICU and at 90 days.[66,73,74] Burn et al. in a meta-analysis on the use of NIV during weaning reported that NIV can facilitate weaning in mechanically ventilated patients, especially in the subgroup of patients with COPD.[75] Despite a beneficial effect of NIV in hypercapnic respiratory failure, no benefits could be demonstrated from NIV in avoiding reintubation in patients who developed respiratory failure after extubation.[76,77] Because longer time from extubation to reintubation is associated with worse outcome, the delay in reintubation correlates with worse survival rates in patients who received NIV for established post-extubation respiratory failure in these studies.[71,76,77] Subsequently, a strategy based on the early use of NIV during the initial periods after extubation in order to avert respiratory failure after extubation in patients at risk for this complication were explored. Use of NIV following extubation, compared to standard therapy, decreased the reintubation rate and ICU mortality, but not hospital mortality in two randomized trial and this was reemphasized in a recent meta-analysis.[78–80] In conclusion, NIV is definitely useful in facilitating weaning in hypercapnic respiratory failure as well as in the prevention of post-extubation respiratory failure in high-risk patients. Criteria to define patients at high risk for post-extubation respiratory failure are shown in Table 151.3.

Role of Tracheostomy

Tracheostomy is commonly performed to provide long-term airway access in patients who require prolonged mechanical ventilation. The conceptual advantages of tracheostomy includes improved patient comfort, more effective airway suctioning, decreased airway resistance, enhanced patient mobility and more secure airways. These benefits are associated with fewer ventilator complications and accelerated weaning from mechanical ventilation. Thus tracheostomies are more comfortable and impose less breathing work and may decrease the sedation needs.[81] When compared to standard endotracheal tubes, the small radius of curvature of tracheostomy tubes increases turbulent airflow and airway resistance while the short length of tracheostomy tubes reduces overall airway resistance.[82–85] In a randomized trial, early-tracheostomy strategy resulted in lower mortality, fewer cases of pneumonia, fewer accidental extubations and less time spent on a mechanical ventilator in the ICU than a late-tracheostomy strategy.[86] We generally perform tracheostomy in all patients with anticipated ventilatory requirements of more than 7 to 14 days.

TABLE 151.3: Choice of patients to prevent postextubation respiratory failure

1. Elderly patients (age >65 years)
2. More than one consecutive failure of weaning trial
3. Chronic heart failure
4. $PaCO_2$ >45 mm Hg after extubation
5. More than one medical/surgical comorbid illness
6. Poor cough reflex
7. Upper-airways stridor at extubation that does not require immediate reintubation
8. APACHE II score >12 on the day of extubation

Weaning Failure

In patients requiring mechanical ventilation, weaning failure is relatively common, with an estimated prevalence of 31% and a range 26 to 42%.[2,3,6,43] When initial attempts at spontaneous breathing fail to achieve the goal of liberation from mechanical ventilation, clinicians must choose appropriate mode(s) of ventilatory support which maintain a favorable balance between respiratory system capacity and load, attempt to avoid diaphragm muscle atrophy and aid in the weaning process. It is advisable to wait for 24 hours before attempting a new trial of spontaneous breathing. Jubran et al. showed that failures are often due to persistent mechanical alterations in the respiratory system that are unlikely to rapidly reverse.[87] A failed trial can precipitate respiratory muscle fatigue[62] and studies in healthy subjects suggest that complete recovery from fatigue can take longer than 24 hours. In addition, Esteban et al.

showed that multiple daily breathing trials offer no advantage over a once-daily trial.[3] Pressure support or assist-control ventilation modes should be favored in patients failing initial trial/trials. We generally use gradual reduction of PS in these patients with PS reduced by 2 cm H_2O on every six hours.

CONCLUSION

The weaning process is a critical component of ICU care. Both disease factors and management factors may lead to difficult weaning that requires a good assessment for the readiness of weaning. The SBTs in those patients passing the screen is the "gold standard" for ventilator withdrawal assessment should be performed in virtually all patients who are recovering from respiratory failure. Decision to extubate in successful SBT requires further assessments of the patient's ability to protect the airway. In selected patient population especially with hypercapnic respiratory failure, NIV trial to facilitate weaning is warranted.

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Extracorporeal Life Support for Severe Acute Respiratory Failure

Steven A Conrad

INTRODUCTION

Acute respiratory failure resulting from Acute Respiratory Distress Syndrome (ARDS) is associated with a mortality rate of 40–50%,[1] and may be even higher at the more severe end of the spectrum. Attempts to maintain gas exchange through the native lungs in this setting often requires application of positive pressure ventilation at levels known to induce lung injury, resulting in Ventilator-Associated Lung Injury (VALI).

Extracorporeal Life Support (ECLS) is a family of extracorporeal cardiopulmonary support techniques, with Extracorporeal Membrane Oxygenation (ECMO) being the most widely applied. During ECMO blood is drained from the central venous system through a vascular cannula, pumped through an artificial membrane lung, and returned to the patient's arterial (venoarterial ECMO) or central venous system (venovenous ECMO). Blood flow through the circuit is high enough to provide full exchange of oxygen and carbon dioxide. Venoarterial (VA) ECMO provides cardiac support by virtue of its provision of Cardiopulmonary Bypass (CPB). Venovenous (VV) ECMO provides no direct cardiac support, but is the support mode of choice in the vast majority of respiratory failure cases.

ECMO is the translation of CPB techniques, used for cardiopulmonary support for several hours during cardiovascular surgical procedures, to prolonged support in the intensive care unit for periods lasting from several days to several weeks. Despite its origin in CPB, ECMO differs from CPB in a number of important ways, including differences in circuit construction, approach to anticoagulation, vascular access, blood flow and temperature management. Although ECMO is used for support of cardiac failure, such as failure to wean from CPB, this chapter will focus on its use in respiratory failure.

Other extracorporeal techniques in common use for respiratory failure include extracorporeal carbon dioxide removal (ECCO$_2$R) and arteriovenous carbon dioxide removal (AVCO$_2$R). ECCO$_2$R is venovenous extracorporeal support utilizing low blood flow (20–25% of cardiac output) for the primary purpose of carbon dioxide removal.[2] This amount of blood flow is sufficient for elimination of carbon dioxide in the management of hypercapnic respiratory failure and as an aid in achieving low tidal volume ventilation. It does not, however, provide sufficient oxygen transfer to support patients with severe hypoxemic respiratory failure, although at higher blood flow partial oxygenation support is achievable. AVCO$_2$R is carbon dioxide removal using a pumpless circuit in which arterial pressure drives blood flow through the oxygenator.[3] This greatly simplifies circuit-reduced resources needed for CO$_2$ removal, but does require cannulation of a peripheral artery, most commonly the femoral artery. In some centers AVCO$_2$R has replaced ECCO$_2$R for the management of hypercapnia.

CLINICAL TRIALS OF EXTRACORPOREAL SUPPORT

Following a report of successful application of VA ECMO in a young adult with post-traumatic ARDS in 1971,[4] VA

ECMO became more widely used in the United States for adult respiratory failure, without standardization of criteria or techniques, and often with little experience on the part of the institution. To address the role of ECMO in the management of severe respiratory failure, a multicenter randomized trial of standard care compared to standard care plus management with VA ECMO was conducted between 1975 and 1978.[5] This trial demonstrated no survival benefit with the use of VA ECMO, with survival approximately 10% in both the control and the ECMO groups. Several factors may have contributed to the observed lack of benefit, including the lack of lung rest (not practiced at that time), high anticoagulation levels and bleeding complications, and the use of venoarterial bypass as opposed to venovenous support.

Gattinoni and colleagues[6] identified the relationship of VALI with poor outcome, and conducted a historical controlled trial of $ECCO_2R$ using low flow venovenous support that suggested a role for this mode of ECLS in acute respiratory failure. Morris et al.[7] sought to duplicate these results with a single center trial of $ECCO_2R$ conducted between 1987 and 1991, in which the ventilator management was directed by a computer-driven protocol. No difference in outcome was found in this trial, but several factors may have contributed to this observed lack of benefit. The $ECCO_2R$ subjects did not receive adequate lung rest, which may have resulted from the enrollment of subjects with severe hypoxemia that could not be oxygenated adequately using lower levels of ventilator support. Bleeding complications were substantial, and large volume transfusions were necessary. This study has often been used as evidence that ECMO does not provide benefit in adult respiratory failure, but this study used $ECCO_2R$, which must be distinguished from ECMO that is capable of providing full oxygen delivery.

A number of clinical and technological advancements in extracorporeal support have been made in the last 20 years that have improved the current practice of extracorporeal support. Recognizing these improvements, Peek and colleagues conducted a national trial of ECMO in the United Kingdom comparing conventional management with conventional management plus ECMO in adults with severe acute respiratory failure (CESAR, Conventional ventilation or ECMO for severe adult respiratory failure).[8] This trial showed that the incorporation of extracorporeal support as part of the management protocol for severe acute respiratory failure resulted in an improved survival without major disability at six months following onset of illness. In addition, the use of extracorporeal support was economical with respect to use of resources.

PRE-ECMO MANAGEMENT

The ECMO is resource intensive and is associated with potential complications; its introduction into the care of a patient should come after conventional measures have failed to provide adequate gas exchange in the setting of lung rest, and in the absence of hemodynamic compromise.

The primary goal of lung protective strategy in mechanical ventilation is to reduce applied mechanical stress to the lungs, with gas exchange a second, albeit important, goal. Ventilator support targets a distending pressure to support oxygenation while minimizing tidal ventilation to reduce the risk of volutrauma. Positive End-Expiratory Pressure (PEEP) should be set above the lower inflection point of a static or slow dynamic compliance curve. In severe ARDS, compliance measurements may not be feasible or interpretable, in which case PEEP in the range of 16–20 cm H_2O can be targeted. Tidal ventilation should be limited to maintain end-inspiratory inflation pressure to less than 30 cm H_2O, and preferably less than 25 cm H_2O. When controlled ventilation is required, pressure control ventilation is preferred over volume ventilation as it provides a larger mean tidal volume for the same end-inspiratory pressure with improved distribution of ventilation. Supported spontaneous ventilation, however, offers several advantages over controlled ventilation, including improved hemodynamic function, minimal to absent sedation requirements, better ventilator synchrony, and preserved cough and ability to clear secretions. With tidal volume determined by the patient and not the ventilator, risk of VALI may be decreased, and this mode can be used as the primary mode of ventilation in ARDS.

Volume overload contributes to impaired gas exchange and higher mortality,[9] and is usually the result of the combination of excessive fluid administration and secondary hypoproteinemia. Careful goal-directed fluid resuscitation with maintenance of plasma colloid oncotic pressure can usually prevent fluid overload. When present, it must be aggressively treated with diuresis or ultrafiltration. Continuous ultrafiltration may be better tolerated.

Prone ventilation improves ventilation-perfusion matching, primarily through improved gas distribution,[10,11] in many patients with severe acute respiratory failure, in particular those with type II ARDS. The resulting improvement in gas exchange and pulmonary mechanics may facilitate the application of lung protective strategies and reduce the need for ECMO. In a randomized trial of prone positioning in ARDS, a subgroup analysis of the quartiles with lowest PaO_2:FiO_2 ratio and highest acute physiology scores.[12]

PATIENT SELECTION

Failure of the above management techniques to achieve adequate unloading of cardiopulmonary support in the setting of potentially reversible pulmonary disease should prompt consideration for ECMO. Selection criteria for initiation of ECMO vary somewhat among ECMO programs, but are generally based on consideration of four components: (1) oxygenation impairment, (2) level of mechanical ventilation support, (3) pulmonary compliance and (4) the extent of pulmonary involvement. Typically patients with a PaO_2/FiO_2 ratio less than 100 (measured on FiO_2 of 1.0), PEEP greater than 15 or mean airway pressure greater than 25, pulmonary compliance less than 20 ml/cm H_2O and bilateral pulmonary involvement will receive extracorporeal support.

The Murray score,[13] which includes all four of these components, has been validated as a marker of severity of ARDS in adults, and was used as one of the main entry criteria in the CESAR trial of adult ECMO.[8] The Murray inclusion score in the CESAR trial was 3 or greater, although the average Murray score of enrolled subjects was higher (3.5) with a PaO_2/FiO_2 ratio of 75, due at least in part to the dependence of enrollment on referrals from outlying institutions. Based on these observations, a Murray score of 3 or greater could be considered a criterion for extracorporeal support.

Other factors may require consideration independent of the above criteria. Severe hypercapnia resulting in respiratory acidosis or requiring high levels of ventilator support, cardiovascular dysfunction secondary to or complicating mechanical ventilator support, and support during procedures with risk of hypoxemia are additional reasons ECMO has been used.

Many centers providing pediatric extracorporeal support have relied on the Oxygenation Index (OI) to guide decisions to provide ECMO. This score considers both the impairment of oxygenation and level of applied support:

$$OI = \frac{FIO_2\ (\%)}{PaO_2} \times MAP$$

A value of approximately 30 and greater is frequently used as a criterion for initiation of extracorporeal support in infants and small children,[14,15] but could also be used in adults.

TECHNIQUES OF ECLS

Extracorporeal Circuit

ECMO employs an extracorporeal circuit that consists of a drainage cannula, a blood reservoir or bladder, a blood pump, an artificial lung (also called an oxygenator), a heat exchanger and return cannula connected by polyethylene tubing (Fig. 152.1). Cannulas are discussed in further detail below:

The bladder is a collapsible chamber that fills with blood draining from the drainage cannula, and provides a reservoir at the inlet to the pump, allowing visual determination of the adequacy of venous drainage. Inadequate drainage can lead to hemolysis and must be avoided. The traditional bladder design is open to the atmosphere, and does not support active suction. It depends on gravity drainage alone, and may require elevation of the patient to achieve adequate venous drainage. A newer bladder design incorporates a rigid housing that can optionally be sealed from the atmosphere, allowing active suction (when required) while serving as a method to monitor inlet pressure and to act as a compliance chamber.

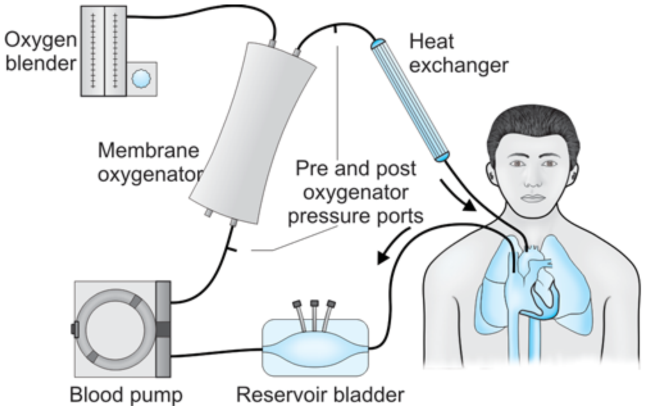

Fig. 152.1: The typical components of an extracorporeal circuit. Vascular cannulas are placed to drain from and return blood to the circulation. Blood drained from the circulation flows into a reservoir (bladder) that serves to maintain blood inflow to the pump. From the pump blood flows through the artificial lung (membrane oxygenator) for gas exchange, then through a heat exchanger to prevent heat loss or control the patient's temperature. Reproduced with permission from Nichols DG, Kochanek PM, Ackerman AD, Singhi SC, Argent AC (Eds). Rogers' Textbook of Pediatric Intensive Care, 4th edition. Lippincott Williams & Wilkins; 2008

The blood pump is capable of pumping up to about 10 l/min, although most patients require 4–5 liters per minute. The two types of pumps available are roller pumps and rotary (centrifugal) pumps. A roller pump is an occlusive pump that employs a rotating head within a fixed housing between which tubing is squeezed as it rotates, forcing blood through the circuit. These have been the mainstay of most ECMO programs for many years, but require continuous monitoring due to the risk of tubing rupture. While older rotary pumps were not well suited for prolonged use, more recent designs have resulted in pumps with desirable features, performance and extended life. A rotary pump uses centrifugal action of a rotating head within a rigid housing to draw blood in under negative pressure into the center, discharging it at the periphery. They are nonocclusive, do not run the risk of circuit tubing rupture, and as a result are rapidly becoming the preferred pump for extracorporeal support.

The artificial lung or oxygenator provides for exchange of oxygen and carbon dioxide between the blood and a gas phase (sweep gas). Artificial lungs are of several types, but only the membrane oxygenator design that prevents contact of the blood and gas phases is suitable for long-term support. The traditional design was that of a flat solid silicone membrane, and could function for days to weeks. The alternative design is the hollow fiber, in which the membrane is tubular in design with a diameter of about 250 micrometers. The sweep gas is delivered inside of the hollow fibers and blood on the outside. Several thousand fibers provide sufficient surface area to support gas exchange in an adult. Although the hollow fiber design is far more efficient than the silicone membrane, the material used in early hollow fiber devices (e.g. microporous polypropylene or PE) was not suitable for long-term support. More recent materials (e.g. polymethylpentene or PMP) have been developed that are suitable for long duration,[16] and are becoming the preferred technology for gas exchange.

The final component of the circuit is the heat exchanger. The high flow rates associated with extracorporeal support, especially in infants and children, can result in loss of heat sufficient to cause hypothermia. The heat exchanger employs circulating water from a temperature control unit to maintain normothermia, or induce mild hypothermia if clinically indicated.

Venovenous ECMO

Venovenous support involves drainage of blood from the central venous system, using the system described above, and returning back into the central venous system (Fig. 152.2). This approach provides only support of gas exchange, as the patient's cardiac output is provided by the cardiovascular system. Since blood is returned into the same vascular bed from which it is withdrawn, leading to recirculation and incomplete mixing, venous blood entering the right heart is never fully saturated with oxygen. Oxygen saturation values on VV ECMO typically run 80–85%, but can be as low as 75%. With the newer dual lumen cannulas that reduce recirculation, values of 85–90% or even higher may be seen. Although diminished, these values are able to provide adequate oxygen delivery if cardiac output is maintained and hemoglobin levels are in the normal range (14–15 gm/dl). The use of inotropic and/or vasopressor agents in low doses is often required, but dose requirements are usually much lower once ventilator support is reduced following ECMO initiation. Transfusion is usually required to attain the target hemoglobin. Mixed venous oxygen saturation values are not attainable, so, metabolic monitoring with

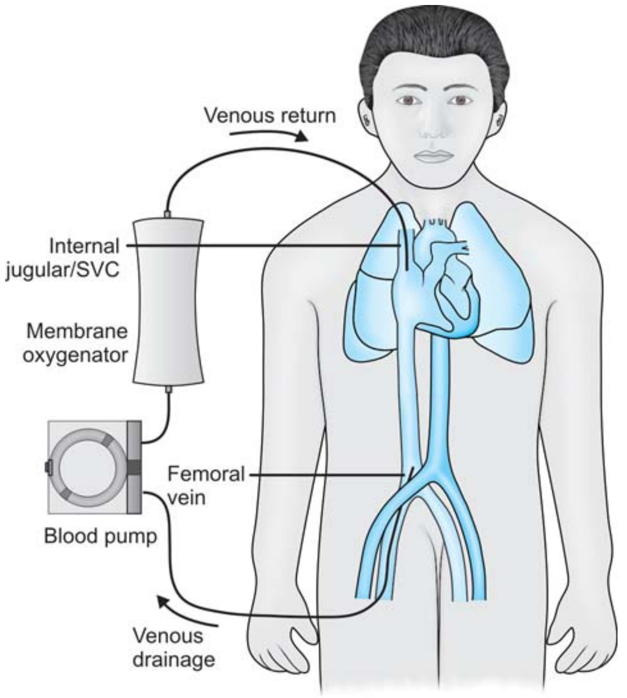

Fig. 152.2: Typical circuit configuration for VV ECMO, in which blood is withdrawn from the central venous system through the internal jugular vein, pumped through the circuit (simplified for this figure), then returned to the venous system through the femoral vein. Reproduced with permission from Nichols DG, Kochanek PM, Ackerman AD, Singhi SC, Argent AC (Eds). Rogers' Textbook of Pediatric Intensive Care, 4th edition. Lippincott Williams & Wilkins; 2008

lactate helps to identify inadequate oxygen delivery. Blood flows in the range of 75–100 ml/kg/min are typical for VV ECMO.

During VV ECMO, oxygen delivery is highly dependent on blood flow, so, achieving an adequate extracorporeal blood flow is necessary. Carbon dioxide removal, on the other hand, is more dependent on the amount of sweep gas delivered to the artificial lung. Typical sweep gas values during VV ECMO range from about 100–150% of blood flow, and lower as native lung function returns.

Venoarterial ECMO

VA ECMO involves drainage of blood from the central venous system and returning it to the arterial system, bypassing the heart and lungs as is done in cardiopulmonary bypass for cardiac surgical procedures (Fig. 152.3). The ECMO circuit contributes to both gas exchange and cardiac output, thus useful for patients with severe reversible cardiac failure. Oxygen saturation values on VA ECMO are high (95% or higher) since there is no admixture with venous blood. Mixed venous oxygen saturation can be monitored to direct the amount of ECMO flow required, and blood flow is set to target a normal SvO_2. Inotropic and vasopressor agents can usually be weaned to low levels or discontinued.

A potential complication of VA ECMO when native Left Ventricular (LV) function is severely impaired is LV dilatation. The added afterload from blood delivery into the arterial system combined with incomplete drainage of right atrial blood may result in LV distention that can impair myocardial oxygen delivery and ventricular recovery. Another complication that can occur when native LV function is somewhat preserved is inadequate oxygen delivery to the coronary vessels. If ventricular ejection during VA ECMO is sufficient to keep the extracorporeal blood from reaching the coronary ostia, then the blood perfusing the myocardium will be deoxygenated blood from the pulmonary system. If a patient is placed on VA ECMO but recovers sufficient ventricular function, consideration should be given to converting the extracorporeal flow from VA to VV.

Venovenous Carbon Dioxide Removal

Patients with severe hypercapnic respiratory failure or those with severe hypoxemic respiratory failure who develop severe hypercapnia as a result of protective ventilator strategies, but otherwise adequate oxygenation may be considered for $ECCO_2R$. $ECCO_2R$ is essentially identical to VV ECMO but with the placement of smaller cannulas and reducing blood flow to 1–1.5 l/min.[6] This blood flow is adequate for complete CO_2 removal since the artificial lung transfers carbon dioxide 20 times more efficiently that it does oxygen, and the CO_2 dissociation curve is nearly linear (unlike the oxygen dissociation curve).

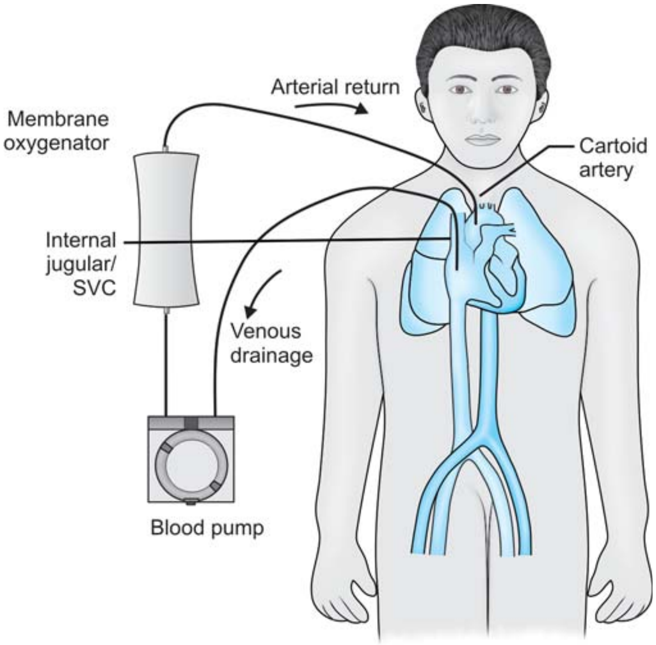

Fig. 152.3: Typical circuit configuration for VA ECMO, in which blood is withdrawn from the central venous system through the internal jugular vein, pumped through the circuit (simplified for this figure), then returned to the aorta through the internal carotid artery. Reproduced with permission from Nichols DG, Kochanek PM, Ackerman AD, Singhi SC, Argent AC (Eds). Rogers' Textbook of Pediatric Intensive Care, 4th edition. Lippincott Williams & Wilkins; 2008

Arteriovenous Carbon Dioxide Removal

Since carbon dioxide removal can be achieved with low blood flows, an alternative to $ECCO_2R$ is pumpless $AVCO_2R$.[3] This simplified circuit uses an artificial lung connected directly to arterial and venous cannulae without a blood pump, relying on the patient's arterial blood pressure to drive blood flow. Using an arterial cannula of 12 Fr and a venous cannula of 16 Fr, blood flows of 600–800 ml/min can be achieved at normal blood pressures, sufficient for total carbon dioxide removal.[17] Cannulation is performed on the femoral vessels, and support for up to several days can be achieved including in pediatric patients.[18]

VASCULAR CANNULATION

Perhaps the most challenging aspect of the application of ECMO is gaining access to the vascular system to support the blood flow required for extracorporeal support.

VV ECMO for respiratory support does not contribute to cardiac output, and the amount of blood flow required depends not on existing cardiac function, but on existing pulmonary function. If native pulmonary gas exchange is absent, the extracorporeal circuit must be able to oxygenate most of the venous return, requiring extracorporeal blood flow approaching that of the native cardiac output. Since an arterial oxygen saturation of 75% or more in the face of preserved cardiac output usually results in adequate systemic oxygen delivery, extracorporeal blood flow can be less than cardiac output.

In VA ECMO, extracorporeal flow depends on the existing native cardiac output. Since extracorporeal blood flow in VA ECMO contributes directly to the cardiac output, it can be as high as the needed cardiac output if native cardiac function is minimal. When native cardiac output is not depressed, blood flow in VA ECMO will be correspondingly less than the required cardiac output.

Cannulas for Venovenous Support

The availability of dual lumen, dual drainage port catheters permit the use of a single cannula to provide full venovenous support. This cannula is placed into the right internal jugular vein, extending across the right atrium and into the inferior vena cava. Its design includes a drainage lumen with two drainage ports that withdraw blood from the superior and inferior vena cava, respectively, and a return lumen with a discharge port that lies in the right atrium directed at the tricuspid valve. The cannula is available in sizes appropriate for neonatal use (12 and 13 Fr) up to adult use (27 and 31 Fr), with a range of sizes in between. The adult cannulas provide typical blood flow of 4–5 liters per minute, adequate for full support of essentially any adult.

An alternative to use of a dual lumen cannula is the placement of two or three single lumen cannulas, as has been the practice prior to availability of dual lumen cannulas. Although the dual lumen cannula has largely replaced the use of multiple single lumen cannulas, the latter technique is capable of providing higher blood flows in those few patients that may require it. With two cannulas, drainage is achieved through a right internal jugular cannula inserted to the superior cavoatrial junction, and return is achieved through a femoral venous cannula inserted to the depth of the iliac vein.

The two-cannula approach is associated with a variable degree of recirculation. Recirculation occurs when oxygenated blood returned to the patient in the inferior vena cava is aspirated by the drainage cannula rather than flowing into the right ventricle (RV), reducing effective oxygen transport only to that fraction not undergoing recirculation. Recirculation is inevitable in this approach since the blood flow in the ECMO circuit is typically greater than the blood returned via the superior vena cava. Paradoxically, attempts to raise overall blood flow can increase the recirculation fraction, worsening oxygenation.

The use of three cannulas can decrease recirculation by mimicking the blood flow pattern of the single lumen cannula.[19] Two short drainage cannulas are placed in the superior vena cava and iliac veins through the right internal jugular and a femoral vein, and a long return cannula is placed in the contralateral femoral vein to the level of the hepatic veins. Since each drainage cannula flows approximately half of the extracorporeal blood flow, each cannula is less likely to exceed the flow in its respective vein, reducing recirculation.

Cannulas for Venoarterial Support

Venoarterial support requires the placement of two single lumen cannulas. The venous drainage cannula is usually placed in the right internal jugular (23–24 Fr) and the arterial cannula is placed in the right common carotid (16–19 Fr) by surgical cutdown. This allows a single incision for both cannulas, and provides arterial return to the ascending aorta to provide blood to the myocardium and cerebral vessels.

Partial venoarterial support by the femoral route can be performed by percutaneous insertion with a 23–24 Fr femoral venous cannula and a 16 Fr femoral arterial cannula. Since this does not provide oxygenated blood to the upper body, it should be used when pulmonary function is adequate to oxygenate blood, or as a component of hybrid venovenoarterial (VVA) support.

Cannulation Technique

Venovenous cannulas for respiratory support can be placed percutaneously with the Seldinger technique as are smaller vascular catheters for monitoring purposes. The selected vein is accessed with a needle and guidewire, a skin incision is made, and the tract dilated in 4 Fr increments to the approximate size of the cannula. The cannula is then placed over a loading dilator and inserted over the guidewire into the vein. When the internal jugular site is accessed, the patient should have neuromuscular blockade to prevent air embolism, since even small respiratory efforts can result in a large volume of air entry. The use of ultrasound prior to cannulation enables the selection of a vein of adequate size to hold the cannula, and its use during cannulation helps ensure appropriate intraluminal placement. Fluoroscopy or transesophageal echocardiography is recommended during placement of dual lumen cannulas, as the distal end of the catheter can enter the RV instead of the inferior vena cava, increasing the risk for complications.

Cannulation for full venoarterial support for cardiac failure is typically performed by surgical cutdown in the neck with open cannulation of the right internal jugular vein and common carotid artery. In this approach, the cannula size can be chosen at the time of insertion, and the vein and artery are ligated following cannula placement. When partial venoarterial support is required and pulmonary gas transfer is adequate, percutaneous femoral vessel cannulation can be considered. The cannula size is smaller to avoid complete luminal obstruction leading to limb ischemia. During partial support using the femoral vessels, oxygenated blood from the ECMO circuit does not reach the brain and myocardium, thus native lung function must be adequate to oxygenate the pulmonary blood. If pulmonary function is not adequate, an alternative is to use hybrid VVA support that combines partial venoarterial femoral bypass with traditional venovenous support for oxygenation failure.

MANAGEMENT DURING SUPPORT

Following institution of extracorporeal support, patient management focuses on application of lung rest, limitation of sedation, optimization of cardiovascular function and organ perfusion, correction of fluid overload, modulation of pulmonary and systemic inflammation, anticoagulation and introduction of nutritional support. ECMO provides support of gas exchange but does not treat the underlying disorder. The benefits of ECMO appear to come from reduced mechanical stress applied to the lungs, improvement in myocardial oxygenation and function, and improved organ perfusion with reduced dependence on cardiovascular pharmacologic support.

Mechanical Ventilation

Reduction in the level of support provided during mechanical ventilation is associated with reduced mechanical stress, reduced pulmonary inflammation and improvement in outcome.[20,21] Lung rest during ECMO consists of the application of a modest level of PEEP, e.g. 10 cm H_2O, limitation of tidal volume to maintain plateau pressures at or less than about 20 cm H_2O, and reduction in respiratory rate to less than 10/minute. There is no evidence that maintaining an “open lung” approach during ECMO is necessary for lung recovery. Since gas exchange no longer has to be provided by the lungs, very minimal ventilator settings can be achieved and are well tolerated.

Spontaneous supported ventilation has numerous advantages over controlled ventilation, including improved ventilator synchrony, improved hemodynamics, avoidance of neuromuscular blockade, reduction in sedation requirements and enhanced patient interaction. Since the patient on supported ventilation has control over the respiratory pattern, she can adapt to altered lung mechanics that minimizes the risk of pulmonary injury. In addition, patients on supported ventilation and lowered sedation levels can provide an effective cough to help maintain clearance of bronchial secretions. When using spontaneous ventilation, intrathoracic pressures are further lowered as compared with controlled ventilation even when inflation pressures provided by the ventilator are comparable. This strategy has resulted in higher survival in one small series of patients.[22]

VV ECMO provides improved oxygenation to the prepulmonary circulation, reducing effective right-to-left shunt and improving myocardial oxygen delivery. Simultaneously, RV afterload is reduced as a result of reduced intrathoracic pressures, thus improving myocardial oxygen delivery and reducing oxygen requirements of the ventricle. The resulting improved myocardial function allows reduction in pharmacologic inotropic support of ventricular function. Vasopressors can be discontinued or their dose reduced in the majority of patients. Organ perfusion is usually improved, and urine output often increases.

Anticoagulation

The extracorporeal circuit is a large surface capable of contact activation of blood coagulation, so anticoagulation is required in all patients except for brief periods of time. The greatest experience is with unfractionated intravenous heparin. Because of the low cost and the ability for point-of-care testing, heparin remains the drug of choice in the vast majority of ECMO centers. Monitoring is performed with the bedside Activated Coagulation Time (ACT) or the Activated Partial Thromboplastin Time (aPTT). The ACT is a whole blood test, which is influenced by factors in addition to heparin such as fibrin degradation products. Although a crude measurement, its utility is great since it looks at overall coagulation including platelet function, and can be obtained on a frequent basis if needed. The normal ACT is on the order of 120 seconds, and the usual therapeutic range is 180–200 seconds. This range can be reduced to 160–180 seconds (or lower) to help manage bleeding complications for extended periods of time, although with an increased risk of clot development in the circuit. The aPTT is a test of plasma clotting factors and correlates better with heparin levels than the ACT, but may not give any indication of nonheparin factors contributing to anticoagulation. Therapeutic levels are on the order of 60–80 seconds. Some centers monitor both, with ACT levels monitored more frequently and aPTT monitored at less frequent intervals. Another test that may prove useful when trying to evaluate bleeding problems on ECMO is the Thromboelastogram (TEG), a whole blood test that provides more insight into the various components of clotting function.

Fluid Management

Patients with severe pulmonary dysfunction may require ECMO prior to optimization of clinical status (such as elimination of fluid overload) as a result of life-threatening hypoxemia. Fluid overload may thus be present and will require diuresis or ultrafiltration. Since continuous renal replacement therapy equipment (or even a simple hemofilter) is easily placed into the ECMO circuit, this modality is commonly used for the correction of fluid overload on ECMO even in the absence of acute kidney injury. Anticoagulation levels required for management of the ECMO circuit are sufficient to maintain hemofilter patency.

Other Management

Many ECMO centers administer corticosteroids throughout the ECMO course in the setting of ARDS (e.g. methylprednisolone 1–2 mg/kg/day), which have been demonstrated to improve outcomes.[23] Patients on spontaneous supported ventilation will usually clear secretions adequately, but patients requiring full sedation and controlled ventilation may benefit from bronchoscopy to assist with secretion management. Prophylaxis against infection is achieved by frequent (every 24–48 hours) skin preparation of the cannulation sites using 4% chlorhexidine. Selective decontamination of the gastrointestinal tract is employed to help reduce risk of nosocomial infections and multiple organ dysfunction.[24,25] Nutritional support is provided via the enteral route,[26] with parenteral nutrition avoided unless absolutely necessary.

TRANSITIONING FROM ECMO

Following initiation, extracorporeal support is continued until pulmonary recovery is adequate to support gas exchange with minimal ventilator settings (e.g. pressure support ventilation with FiO_2 of 0.4 or less). Time to recovery varies considerably, averaging 1–2 weeks, but can be much longer, with pulmonary recovery and survival reported after 3–4 months of support. Pulmonary fibrosis on biopsy, once considered irreversible and a reason to discontinue ECMO, has the potential to improve. As a result, most centers will provide prolonged support in anticipation of recovery.

Recovery of pulmonary function is heralded by improvement in oxygenation independent of changes in ECMO support, improvement in lung compliance manifested by increasing tidal volume to normal with modest pressure support, and clearing of radiographic densities. It is tempting to reduce the level of ECMO support once recovery begins, but loading of the pulmonary system is not recommended until pulmonary recovery is well established. With VV ECMO, a discontinuation of sweep gas alone is sufficient to eliminate support and can be performed intermittently to assess the patient's ability to maintain gas exchange on mechanical ventilation alone. With VA ECMO, elimination of sweep gas alone should not be performed since it amounts to a large right-to-left shunt. A reduction in blood flow to minimal levels and shunting blood flow through an external bridge in the circuit are the two ways to assess the response to discontinuation of support.

Once the patient can sustain gas exchange and hemodynamics with minimal to absent extracorporeal support, the cannulas are removed. Percutaneously placed venous cannulas are removed and a suture is placed in the subcutaneous tract to prevent bleeding. Percutaneously placed arterial cannulas are removed and managed with prolonged pressure, an occlusion device, or surgical repair depending on the size and location of the cannula. Surgically placed arterial and venous cannulas are removed by surgical means.

A major reason for nonrecovery and death or discontinuation of support is the development of progressive pulmonary hypertension and RV failure. Pulmonary artery pressures approach systemic levels and RV dilatation is noted on echocardiography. This usually represents an irreversible condition. Development of this during VV ECMO has been a reason to switch to VA ECMO, but survival is uncommon.

SUMMARY

Technological improvements such as percutaneous cannulation technique, dual lumen cannulas, high efficiency long duration artificial lungs and efficient blood pumps have made the application of extracorporeal support much safer with a lower risk of mechanical complications. With data from a recent clinical trial supporting the addition of ECMO to the management of severe acute respiratory failure, ECMO is moving into the mainstream of support of these patients.

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Hyperbaric Oxygen Therapy*

PS Tampi, SK Jindal

INTRODUCTION

Hyperbaric Oxygen Therapy (HBO_2T) is the administration of oxygen at a pressure greater than that at sea level, which is one atmosphere. Hyperbaric medicine owes its origin to the problems encountered by deep-sea divers, exposed to high pressure diving sports, commercial or military expeditions at depths of 10 m or more. In clinical medicine, this is simulated by exposing a patient to hyperbaric atmosphere in a closed monoplace or multiplace chamber. In either case, the partial pressure of oxygen (PaO_2) will approach 1500 mm Hg at a pressure equivalent to 33 feet of seawater. A century of research in oxygen administration has established that the effects are dose related, and the hyperbaric environment merely provides the opportunity to give higher doses than can be achieved at sea level.

HISTORY OF HYPERBARIC MEDICINE

Development of Hyperbaric Air Therapy

The British physician Henshaw used compressed air for medical purposes in 1662 in an airtight room called a "domicilium" in which variable climatic and pressure conditions could be produced, with pressure provided by a large pair of bellows. According to Henshaw, "In times of good health, this domicilium is proposed as a good expedient to help digestion, to promote insensible respiration, to facilitate breathing and expectoration, and consequently, of excellent use for the prevention of most afflictions of the lungs." There is however, no account of any application of Henshaw's proposed treatment, and there were no further developments in the field of hyperbaric therapy for nearly two centuries.

In the nineteenth century, there was a rebirth of interest in hyperbaric therapy, in France. In 1834, Junod built a hyperbaric chamber to treat pulmonary afflictions using pressures of two to four Absolute Atmospheres (ATA). In 1837, Pravaz built the largest hyperbaric chamber of that time, and treated patients with a variety of ailments. Fontaine, in 1877, developed the first mobile hyperbaric operating theater, and by this time hyperbaric chambers were available in all major European cities. Interestingly, there was no general rationale for hyperbaric treatments, and prescriptions therefore, varied from one physician to another. During the second half of the nineteenth century, hyperbaric centers were advertised as being comparable to health spas. Junod referred to his treatment as "Le Bain d'air comprimd" (the compressed-air bath). In 1855, Bertin wrote a book on this topic and constructed his own hyperbaric chamber.

The first hyperbaric chamber on the North American continent was constructed in 1860 in Oshawa, Ontario, Canada, and east of Toronto. It was later shifted to New York, to treat nervous disorders. The chamber that was built by Cunningham received the most publicity, and was the most actively used in Kansas City in the 1920s. Cunningham claimed to have achieved remarkable improvement in patients who were cyanotic and comatose. Cunningham reasoned that a barometric factor was therefore involved. However, one night a mechanical failure resulted in a complete loss of compression and all his patients died. This tragedy was a sobering lesson but ultimately did not deter Dr Cunningham. His enthusiasm for hyperbaric air continued, and he started to treat diseases such as syphilis, hypertension, diabetes mellitus and cancer. Its reasoning was based on the assumption that anaerobic infections played a role in the etiology of all such diseases. In 1928, Cunningham constructed the largest chamber ever built (five stories high and 64 feet in diameter), in Cleveland. Each floor had one bedroom with all the amenities of a good hotel. At that time, it was the only functioning hyperbaric chamber in the world. The Cunningham chamber was dismantled for scrap in 1937, which brought to a temporary end of the era of hyperbaric air therapy for medical disorders.

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Development of Hyperbaric Oxygen Therapy

Oxygen was not "discovered" until 1775, when the english scientist Joseph Priestley isolated what he called "dephlogisticated air" (Chapter 1). Although, hyperbaric air had been used as early as 1662, oxygen was not specifically added to early hyperbaric chambers. The toxic effects of concentrated oxygen reported by Lavoisier and Segiom in 1789 were reasons enough for hesitation to use it under pressure. Paul Bert, the father of pressure physiology, discovered the scientific basis of oxygen toxicity in 1878. The potential benefits of using oxygen under pressure for the treatment of decompression sickness were first realized by Drager, who in 1917 devised a system for treating diving accidents. It was not until 1937: The very year that Cunningham's "air chamber" hotel was demolished, that Behnke and Shaw actually used hyperbaric oxygen (HBO_2) signifying the arrival of the era of HBO_2 therapy.

Rationale of Hyperbaric Oxygen

An increased atmospheric pressure increases the partial pressure of O_2 in the alveolar air and arterial blood, provided the fractional concentrations of oxygen remains the same. This is easily derived from the alveolar air equation. Since the oxygen dissolved in the plasma depends upon PaO_2, the dissolved O_2 content of blood is also increased. This is independent of Hb levels of the blood. Therefore, under hyperbaric conditions the total oxygen carrying capacity of the blood is significantly more (Table 153.1). At 1 atmosphere (sea level), with a person breathing 100% O_2, the PaO_2 is about 670 mm Hg and the total oxygen content of 18.7 ml/dl. Increasing the pressure to 3 atmospheres, the PaO_2 increases to about 1700 to 1800 mm Hg and the total O_2 content to 22 ml/dl. Of this, about 25% (i.e. 5.5 ml/dl) is dissolved in plasma. This in fact is equivalent to the total oxygen content of blood under normal conditions, at much lower Hb level of 4 gm%. Therefore, under hyperbaric conditions, it is possible to maintain adequate oxygen content of blood as well as delivery to the tissues with a very low or no hemoglobin at all. However, it should be remembered that the whole of the tissue oxygen requirements can be met by dissolved oxygen, only if PaO_2 is around 2025 mm Hg.

TABLE 153.1: Shows the different components of oxygen content of the blood at different atmospheric pressures at constant plasma hemoglobin of 14 gms/dl, when breathing 100% O_2

Pressure	*PaO_2 (mm Hg)*	*Dissolved O_2 (%)*	*Total O_2 content (atmospheres) (ml/dl)*
1	670	11	18.7
2	1200-1300	18	20
3	1700-1800	25	22

Other Physiological Effects of Hyperbaric Oxygenation

Effect on $PaCO_2$: An increased hemoglobin saturation of venous blood reduces its ability to carry CO_2, and results in carbon dioxide accumulation (Haldane effect).
Vasoconstriction: Occurs due to increase in PaO_2, and has a therapeutic value.
Angiogenesis: The mechanism by which this occurs is not known but occurs only when oxygen is administered at more than 1 ATA, and does not occur with 100% oxygen at 1 ATA.

Beneficial Effects of HBO

Hyperbaric oxygen administration achieves two principal objectives:

1. It increases PaO_2 and tissue PO_2 to levels higher than those obtained at 1 atmosphere. This has several potential therapeutic benefits. The oxygen delivery to the tissues is increased, which may promote healing; the phagocytosis and antibiotic action on the microorganisms are augmented. Hyperoxia induces vasoconstriction, which reduces tissue edema. Finally, the oxygen dissolved in the plasma is available to the tissues, without any increase required in the hemoglobin level. This is not associated with any increase by blood transfusions. Problems of increased blood viscosity are therefore, avoided.
2. There is an increase in the ambient pressure which increases interstitial tissue pressures as well. This is

used to treat decompression sickness, which may occur in divers. Similarly, presence of air or gas in the blood either injected accidentally during some procedure or due to embolization can be absorbed with HBO_2 therapy.

Mechanism of Action of HBO_2

i. HBO_2 increases dissolved oxygen in the plasma, which readily diffuses into the hypoxic tissues.
ii. Increased oxygenation results in vasoconstriction at the site, resulting in induced transudation, reduction in capillary pressure, and thereby reducing the tissue edema.
iii. The reduction in tissue edema reduces compression of the cells, thereby enhancing the reabsorption of fluid.
iv. With edema being less, barriers of diffusion are reduced and oxygen diffusion to the tissues improves, resulting of improvement in tissue functions.
v. Improved vascularization due to neovascularization results in speedy recovery of tissues and gives way to tissue regeneration.
vi. Oxide, hydro-peroxide and superoxide radicals of oxygen are toxic, and interfere with cell metabolism of bacteria, and thereby destroy the bacteria.
vii. HBO_2 modulates the immune system and helps in the faster elimination of viruses.
viii. Bacterial killing effect of leukocytes is impaired in the hypoxic state. Increased oxygenation will enhance the killing power of leukocytes.

INDICATIONS

Enthusiasm with the use of HBO_2 now is almost similar to what was seen with use of normobaric oxygen in the 19th century, when its therapeutic applications were first discovered. But this enthusiasm has helped to discover its beneficial role as an adjunct in the treatment of diverse clinical conditions. Indications may vary in different countries in different settings. Some of the more definite indications are the decompression sickness, air embolism, gas gangrene, and carbon monoxide poisoning. The indications apprised by the Undersea and Hyperbaric Medical Society are rather limited and rely on the proof of efficacy of controlled studies.

Decompression Sickness

Decompression sickness occurs, when the ambient air pressure is allowed to lower rapidly after a prolonged exposure to a higher pressure. This is commonly seen in the deep sea divers, after emerging from a diving juggernaut, and occasionally in the aviators or astronauts on reaching the outer atmosphere or space. Due to a sudden lowering of pressure, the inert gases dissolved in body fluids bubble out in both intravascular and extravascular compartments resulting in multiple symptoms. The common clinical manifestations include musculo-skeletal pains, neurological symptoms such as paresthesias and sensori motor deficits, nausea, vomiting, nystagmus, tinnitus, sub-sternal pain, cough, dyspnea, hoarseness of voice, and occasionally shock and death.

Hyperbaric oxygen and recompression to about 60 feet constitute the mainstay of therapy. Both steps help in the reduction and resolution of the bubbles and maintenance of tissue oxygenation. Increased occurrence of oxygen toxicity under higher pressure conditions limits the duration of use of hyperbaric oxygen. Relapse may occur after discontinuation, of therapy. Short-term observation, especially in patients with neurological symptoms for at least six hours is generally recommended. Some people advocate the provision of observation units for about 24 hours after hyperbaric therapy.

Air Embolism

Air bubbles may form in the venous circulation, due to sudden decompression (e.g. decompression sickness) or more commonly get introduced during central venous instrumentation, invasive medical and surgical procedures, hemodialysis, chest trauma or positive pressure ventilation, employing high levels of Positive End Expiratory Pressures (PEEP). These air bubbles finally end up in the lungs, causing obstruction of pulmonary circulation, and presenting a picture of pulmonary air embolism. It may occasionally be fatal if a large pulmonary vessel gets blocked. Bubbles may also form in the arterial circulation, but are rare because of the higher hydrostatic pressure in the larger vessels. Cerebral air embolism is uncommon but more serious in nature.

Treatment of air embolism employs resuscitative and restorative measures for pulmonary circulation through removal and/or absorption of air from the pulmonary vessels. Attempts to remove the air bubbles include the direct needle aspiration, Trendelenburg position or removal through a central venous catheter. Administration of 100% oxygen helps reabsorption of air. Hyperbaric oxygen administration rapidly reduces the bubble size. Generally 50% O_2 at a pressure of 165 feet is administered initially for a few minutes followed by intermittent periods of 100% oxygen at a lower pressure of 65 feet. A recent report on the use of U.S. Navy Treatment suggests this use of oxygen filled monoplace hyperbaric chamber as better tolerated, and safer from oxygen toxicity point of view than a multiplace chamber, for the treatment of both decompression sickness and air embolism.

Gas Gangrene and Other Necrotizing Infections

There is an increased evidence to suggest a major role of HBO_2 on inflammatory cytokines and mediators. It is shown to cause cytokine down-regulation and growth factor up-regulation. HBO_2, therefore is likely to promote wound healing by suppressing inflammation and facilitating repair. It also augments the antibacterial action of leukocytes, which gets otherwise inhibited under hypoxic conditions and thereby improves the efficacy of antibiotics. These effects have been shown in a few clinical trials and clinical experience, when used as an adjunct treatment for gas gangrene, non-healing wounds (e.g. diabetic foot), osteomyelitis and necrotizing fasciitis. It is also shown to shorten the treatment with antibiotics for soft tissue infections.

Hyperoxygenation in particular is valuable in gas gangrene, since it inhibits the growth of the causative anerobic microorganisms, i.e. clostridia and prevents formation of toxins responsible for necrotizing myositis and myonecrosis. Reports on the useful role of HBO_2 are available for treatment of all kinds of clostrial infections including necrotizing fasciitis of upper extremities, orbital gas gangrene, recurrent crepitant cellulitis with extensive subcutaneous emphysema. It has been also used in patients with refractory mycoses, leprosy, and other intractable infections.

Carbon Monoxide Poisoning

Carbon monoxide (CO), a byproduct of incomplete combustion of coal, is a poisonous gas. It is a common cause of death in miners and other personnel working with coal furnaces in foundaries and factories. CO poisoning in India, occurs in people burning indoor coal for heating and cooking during winter months in ill ventilated houses. Deaths in this scenario are commonly reported in individuals sleeping in closed rooms. Malfunctioning air conditioning systems in cabins have been occasionally blamed for CO poisoning.

CO poisoning is generally insidious. Neurological complications are most frequent. Some of the common symptoms include headache, confusion, dizziness, nausea, and vomiting. In more serious forms, syncope, seizures and coma may precede death. Cardiac arrhythmias and pulmonary edema may also occur.

CO has an affinity for hemoglobin, almost 300 times that of oxygen. Exposure to CO therefore quickly results in displacement of oxygen and formation of carboxy hemoglobin (HbCO).

Treatment of CO poisoning needs to be prompt and aggressive. A great degree of evidence supports that hypoxia occurs late in CO poisoning. But the treatment of both, the actually poisoned persons as well as the environmental exposures, are based on a hypoxic theory of toxicity. Oxygen therapy is the mainstay of therapy besides other supportive care. Oxygen accelerates the dissociation of CO from hemoglobin and other heme proteins. Oxygen with an FiO2 of 100% is administered with a high flow and the response is quick, provided the treatment is started in time before any organ damage has occurred.

Hyperbaric oxygen has been used in a few trials. It rapidly decreases blood HbCO. It may also delay the occurrence of delayed brain injury. But there is no conclusive evidence to support its use. Firm guidelines regarding the use of hyperbaric oxygen cannot be established from the available literature.

Adjunct to Treatment of Cancers

HBO_2 may improve the treatment of malignant tumors by increasing the tumor sensitization to radiotherapy. A significant improvement is reported with HBO_2 followed by radiotherapy for local tumor control, mortality for cancers of the head and neck, and local tumor recurrences in cancers of head, neck and uterine cavity. It also improves the response to photodynamic and chemotherapy, possibly by raising intra-tumoral oxygen tension. It was also shown to improve survival in locally advanced breast cancer undergoing neoadjuvant chemotherapy. It may also promote new vessel growth into areas with reduced oxygen tension, thereby promoting healing of radiation induced tissue injury.

Miscellaneous Conditions

- *Plastic and reconstructive surgery:* For non-healing wounds, including radiation wounds and venous leg ulcers, as an aid to the survival of skin flaps with marginal circulation, as an aid to re-implantation surgery, as an adjunct to the treatment of burns
- *Trauma:* Crush injury, compartment syndrome, soft tissue sports injuries

- *Orthopedics:* Non-union of fractures, bone grafts, osteoradionecrosis
- *Peripheral vascular diseases:* Shock, myocardial ischemia, aid to cardiac surgery
- *Neurological:* Stroke, multiple sclerosis, migraine, cerebral edema, multi-infarct dementia, spinal cord injury and vascular diseases of the spinal cord, brain abscess, peripheral neuropathy, radiation myelitis, vegetative coma
- Chronic pain from fibromyalgia syndrome, myofascial pain syndrome, migraine and cluster headache
- *Hematology:* Sickle cell crises, severe blood loss anemia
- *Ophthalmology:* Occlusion of central artery of retina
- *Gastrointestinal:* Gastric ulcer, necrotizing enterocolitis, and paralytic ileus, pneumatoides, cystoides intestinalis, hepatitis
- *Otorhinolaryngology:* Sudden deafness, acute acoustic trauma, labyrinthitis, Meniere's disease, malignant otitis externa (chronic infection)
- *Lung diseases:* Lung abscess, pulmonary embolism (adjunct to surgery)
- *Endocrines:* Diabetes
- *Obstetrics:* Complicated pregnancy, diabetes, eclampsia, heart disease, placental hypoxia, fetal hypoxia, congenital heart disease of the neonate
- *Asphyxiation:* Drowning, near hanging, smoke inhalation
- *Aid to rehabilitation:* Spastic hemiplegia of stroke, paraplegia, chronic myocardial insufficiency, peripheral vascular disease.

CONTRAINDICATIONS

Contraindications for HBO_2 therapy can be divided into the absolute contraindication, which include untreated tension pneumothorax; and relative contraindication, which includes upper respiratory infections, emphysema with CO_2 retention, symptomatic pulmonary lesions seen on chest X-ray, history of thoracic or ear surgery, uncontrolled high fever, pregnancy, claustrophobia, seizure disorders, and malignant diseases.

COMPLICATIONS

The complications in the use of HBO_2 are related to pressure changes and the toxic effects of oxygen. They include baro-trauma to ear, sinuses, or lungs. Trauma to ears or sinuses may be averted with slow compression, the use of decongestants, patient education and rarely myringotomy. Pulmonary baro-trauma is very rare, perhaps occurring 1 in 50,000 treatments. It can be prevented by careful pre-treatment screening for pulmonary blebs, air trapping caused by bronchospasm or secretions, pre-existing pneumothorax, central lines and ventilatory support. Oxygen toxicity with occurrence of grand-mal seizures are noticed beyond a depth of 3 ATA (66 feet or 20 m of seawater). Damage of lung tissue, manifested by decrement in vital capacity and irritation to large airways may occur due to oxygen toxicity following HBO_2. Increased pressure causes increased gas density and airway resistance. This produces an altered voice called the "Donald Duck voice", and an increased awareness of breathing. Hypoventilation may result especially in a patient with the underlying obstructive lung disease. Increased partial pressure of nitrogen causes symptoms of mild euphoria at pressure of 2.5 atmospheres, progressing to frank intoxication, and decreased performance at over 4 atmospheres. Accumulation of O_2 may occur in the event of an exposure for several days. Hyperpnea and occasionally respiratory acidosis may result. Other toxic substances or pollutants, which may continue to accumulate in a closed chamber and reach toxic pressures, include alcohol (from disinfectant solution), sulphur dioxide, hydrocarbons, carbon monoxide, volatile substances and mercury vapors. A regular monitoring is required for their concentrations. The nursing and medical personnel looking after the patient in a hyperbaric chamber may suffer from decompression sickness due to tissue bubble formation. The risk is rather low because the chamber is kept warm; exposure is short and decompression rate slow. Risk of an accidental fire is greater in hyperbaric conditions. All inflammable material should therefore be kept away. Refractive changes and cataract in the lens of the eye may occur as a complication of prolonged HBO_2T. Claustrophobia may be a problem in up to 10% of patients, especially in the monoplace chamber.

HYPERBARIC CHAMBERS

The main facility required for hyperbaric medicine is of course the hyperbaric chamber itself. This is essentially a chamber constructed to withstand pressurization, so that oxygen can be administrated inside at a pressure greater than at sea level. The size, shape and pressure capabilities of the design chambers vary considerably. The technical details of each model, now available, are provided by the manufacturers and a classification of various types of chambers is shown here:

Types of Hyperbaric Chambers

a. Monoplace chamber (Fig. 153.1)
b. Multiplace or "Walk-in" chambers (Fig. 153.2)
c. Mobile or portable.
   Monoplace: Transportable by air, sea or land.
   Multiplace: A chamber can be driven from place-to-place.
d. Chambers for testing and training divers.
e. Small hyperbaric chambers.
f. For neonates.
g. For animal experiments.

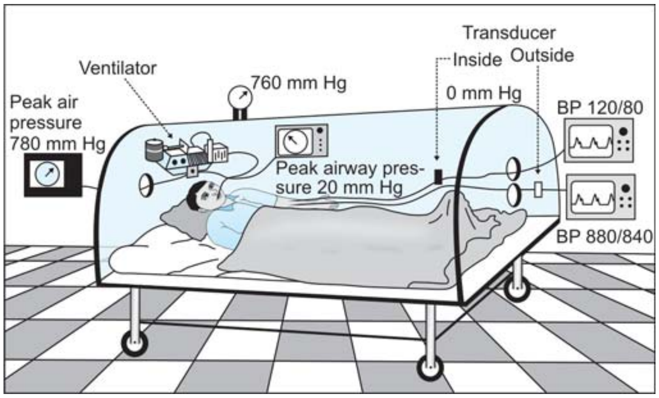

Fig. 153.1: A monoplace hyperbaric chamber

TECHNIQUES OF HYPERBARIC OXYGENATION

The hyperbaric technician follows the prescribed instructions for the hyperbaric physician about pressure, duration, and frequency of treatment. Most of the treatments are given at pressures between 1.5 and 2.5 ATA, and the usual duration of a hyperbaric session is 60 minutes. Of this, 10 minutes are required for compression, and 5 minutes for decompression if a pressure of 1.5 ATA is used. Thus, the maximal oxygen saturation is maintained for about 50 min. In the case of infections, the treatment duration is doubled. The treatment sessions for most chronic conditions are given daily, including on weekends.

World distribution of hyperbaric chambers: Some idea of the quantity of hyperbaric medical facilities in the world can be obtained by a review of the statistics regarding the distribution of hyperbaric chambers in various countries. Accurate information on this subject is difficult to obtain. The largest number of chambers is located in Russia (over 1200). South Korea has the largest number per million inhabitants (4.9 compared with 3.6 in Russia). Within Europe, excluding Russia, Italy has the largest number of installations (34.1% of the European total) and also the largest number per million inhabitants (1.75). The number of hyperbaric chambers per million inhabitants has risen progressively since 1968 in all countries except Germany, where the number has actually declined. The fastest rise has been in China and Japan. The number of chambers does not necessarily correlate with the number of treatments given. There is no separation of multiplace and monoplace chambers in the statistics.

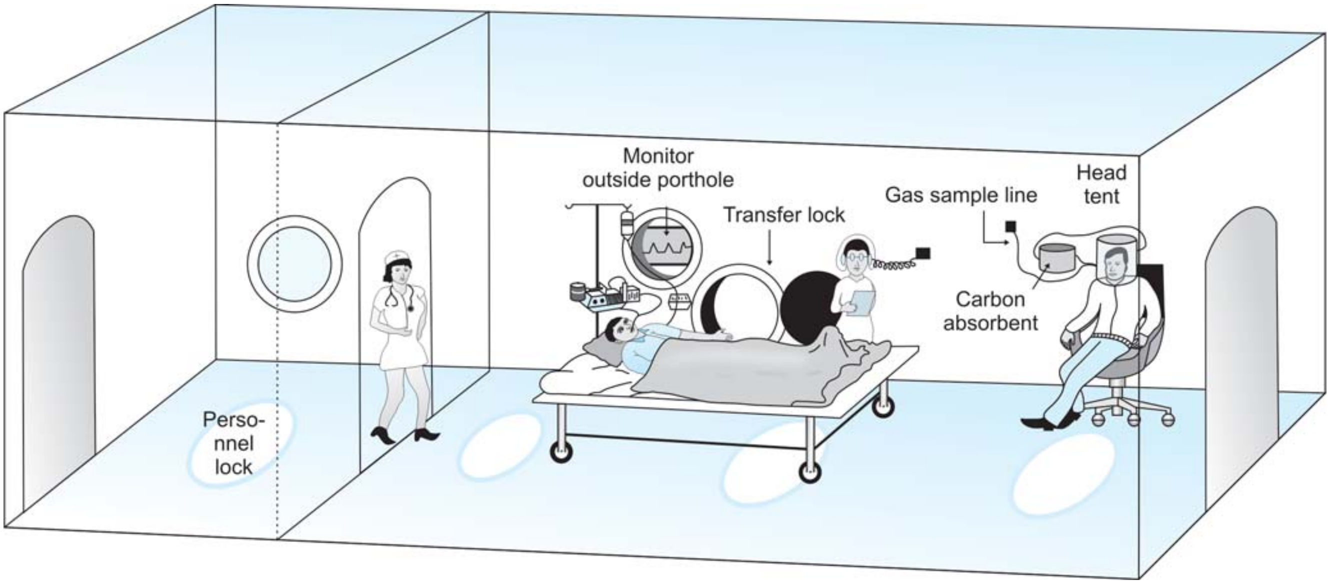

Fig. 153.2: A multiplace hyperbaric chamber

Hyperbaric Chambers in India: As the medical professionals in India are not all aware of the benefits of hyperbaric treatment, the availability of such facilities is also considerably less in number in India. Of 16 hyperbaric chambers in India, nine chambers are available with defence services, and seven chambers are with civil hospitals in metropolitan cities. Of course, the hyperbaric chambers available with the defence services are also being utilized by the civil population. But considering the magnitude of hyperbaric chamber requirements in India, for a billion population, the availability of chambers is grossly inadequate.

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Section

20

PLEURAL DISORDERS

George D'Souza

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Pathophysiology of Pleural Effusion

Srinivas Rajagopala

INTRODUCTION: ANATOMY OF THE PLEURA

The thoracic cavity is constructed like a vertical bellow, with the diaphragm as its base. Within this limited protected cavity lie the two lungs, the heart, and the other mediastinal structures. To decrease the friction generated between the lung and the thoracic wall, during respiratory movements, the inner surface of the thoracic cage and the outer surface of the lungs and the mediastinum are covered by a serous, elastic membrane with a smooth and lubricating surface: the pleura. The pleural cavity is like a sealed, wet, and stretchable elastic bag inserted between the lung and the thoracic wall. The pleura is therefore, crucial for the efficient functioning of the lung.

The pleura is a serous membrane covering the lung, mediastinum, diaphragm, and rib cage. It can be divided into the visceral pleura and the parietal pleura; the former covers the lung parenchyma including the interlobar fissures and the latter lines the inside of the thoracic cavities. The parietal pleura is also arbitrarily classified into the costal, mediastinal, and diaphragmatic pleura according to the structure it invests. The visceral and the parietal pleura meet at the lung root. The surface area of the visceral pleura of one lung is similar to that of the parietal pleura of one hemithorax, approximately 1000 cm^2. The pleural pressure in humans is approximately –5 cm H_2O at mid-chest level at FRC and –30 cm H_2O at TLC. Pleural pressure varies by approximately 0.5 cm per cm height. The *Hydrostatic equilibrium model* and *Viscous flow model* have been proposed to explain why the vertical gradient is less than unity. A thin layer of fluid is normally present between the pleural surfaces to devoid of contact; the pleural space is thus, a "real" and not a potential space and this favors the viscous flow model.[1] This model states that the vertical pressure gradient is a consequence of the viscous flow generating a continuous column of fluid throughout the pleural space. This fluid acts as a lubricant, facilitates lung movement, and enables coupling of the lung with the chest wall.

Histology

The histology of the parietal pleura is fairly constant across species whereas, that of the visceral pleura varies significantly. The parietal pleura has five layers with a mean thickness of 20 to 25 µm, and is composed of loose, irregular connective tissue with blood vessels (capillaries and lymphatic lacunas), covered by a single layer of mesothelial cells.[2] Mesothelial cells may have a variety of functions important to pleural biology. Mesothelial cells can secrete and organize the extracellular matrix components. They also secrete neutrophil and monocyte chemotactic factors. Mesothelial cells also produce several cytokines like TGF-β, EGF and PDGF which are important in pleural inflammation and fibrosis. Microvilli are present on the surface of mesothelial cells and serve to increase the surface area for metabolic activity. Mesothelial cells produce hyaluronin but not mucin, express keratin microfilaments, stain negatively with epithelial-specific antibodies (Ber-EP4, B72.3, Leu.M1 and CEA) and stain positively for calretinin and mesothelin.[3]

Lymphatic lacunae are specialized lymphatics shaped like flat cisterns. Lymphoid cells form aggregates underneath mesothelial cells, forming raised structures called *Kampmeier's foci* which may have an immune function. Lymphatic plexus of the costal pleura drain along the intercostal nodes; those in the mediastinal pleura drain to the tracheo-bronchial and mediastinal nodes. The diaphragmatic pleura drains into the para-sternal, middle phrenic and posterior mediastinal nodes.

The visceral pleura may be thick (humans, sheep, cows, pigs and horses) or thin (dogs, cats and monkeys). This distinction is important physiologically because the blood supply is dependent on the thickness of the pleura. A thick visceral pleura is supplied by the bronchial (systemic) circulation, while a thin visceral pleura depends on the lung parenchyma for nutrition.[4] Only the parietal pleura contains sensory nerve fibers, supplied by the intercostal and phrenic nerves.

Pleural Fluid: Normal Volume and Cellular Contents

The small amount of pleural fluid that is physiologically present, is maintained by fluid exchange across the pleural membranes by the interplay of Starling's forces and lymphatic drainage:

$$\text{Fluid Movement} = L \times S\,[(P\text{cap}-P\text{pl})-\Sigma\,(\Pi\text{cap} - \Pi\text{pl})]$$

where P and C are the hydrostatic and osmotic pressures, respectively, within the capillaries (cap) and pleural space (pl), L is the hydraulic conductivity of the membrane, S is the surface area, and Ï is the osmotic coefficient for proteins.

Normal pleural fluid is a microvascular filtrate formed from the parietal pleural capillaries. It is drained predominantly via the parietal pleural lymphatic stoma.[5] The absorptive gradient in the visceral pleural capillaries and the active transport across mesothelial cells play only a small role.[4] Study of the normal volume and composition of pleural fluid in humans is limited by the difficulty of retrieval, without traumatically entering the pleural space. The disparity of data from animals reflects the difference in retrieval techniques (aspiration or lavage), fixation, staining, identification of cells and genuine interspecies differences. In summary, the amount of pleural fluid in animals varies from 0.04 to 0.60 ml/Kg, has the solute characteristics of interstitial fluid (protein 1 to 2 g/100 ml and total leukocyte cell counts of 1000 to 2500/µl). Most of the protein is composed of albumin (50%), globulins (35%) and fibrinogen.[6]

Limited human data is available on pleural fluid composition (Table 154.1).[7] This small amount of fluid is distributed uniformly along the pleural surface with an average thickness of 20 µm (thicker in dependant portions). The low pleural fluid protein (protein ratio 0.15 to 0.2) indicates a high degree of sieving of protein at the pleural microvasculature.[8]

TABLE 154.1: Composition of pleural fluid from human studies

Parameter	*Yamada et al*	*Noppen et al*
Technique	Puncture of pleural space in healthy soldiers	Thoracoscopic lavage of pleural space during sympthatectomy
Maneuver	Exercise to yield fluid (70%)	Urea used as endogenous marker for dilution
Amount retrieved	Few drops-20 ml	8.4±4.3 ml (0.26 ml/kg)
Total leukocyte count/µl	4500 (1700-6200)	1716
Monocyte %	53.7	75
Lymphocyte %	10.2	23
Mesothelial cells%	3	
Granulocytes %	3.6	
Not classified%	29.5	

Physiology and Pathophysiology of Pleural Fluid Turnover

Pleural fluid is formed by the parietal pleural capillaries. The constant pleural liquid production across species with differing visceral pleural thickness, the closer distance of parietal pleural microvessels (10 to 15 µm vs 20 to 25 µm in visceral pleura), and the higher venous pressure on the parietal pleural side all favor a systemic (parietal pleural) origin of the pleural fluid.[9] The pleural fluid protein decreases as the systemic blood pressure increases, also decreases with age (blood pressure increases and pulmonary resistance decreases with age). Fluid thus filtered, facilitated by the leaky nature of the mesothelial surface, and the strongly negative pleural pressures enter the pleural space. Minimally invasive studies in animals suggest that there is a gradual flow from top to bottom with a slow turnover (0.01 ml/kg × height with a half-time of 6 to 8 hours or about 15 ml in an adult male).

Pleural fluid is absorbed by bulk flow through the lymphatic stoma (2 to 6 µm) in the parietal pleura. Diffusion, active transport and transcytosis also contribute minimally to physiological turnover of pleural fluid.[10] Because of the "bulk flow" as the mode of absorption, the pleural fluid protein remains constant with absorption. This permits the use of concentration of protein in the pleural fluid to differentiate between exudates and transudates.[7] Transudative effusion results as a result of an imbalance between fluid formation at the parietal pleural capillaries, and via visceral pleura in conditions of interstitial fluid excess and removal via parietal lymphatics. Exudative effusion results from an abnormality in the pleural surfaces and an exudation of protein-rich fluid in the pleura. Most of the parietal pleural stoma are distributed dorso-caudally, the visceral pleura is devoid of stoma. Parietal pleural lymphatics have large reserve, can compensate for an increased production of pleural fluid by about 30 times, if absorption via the stoma is normal.

Physiological Changes with Pleural Effusion

When the pleural space is occupied by fluid, the pleural pressure becomes positive. The increase in volume must be compensated by an increase in the size of thoracic cavity [distending pressure = P(atm) – P(pleura)], or a decrease in size of the heart or lungs [distending pressure=P(alv) – P(pleura)].[11]

In experimental settings, the addition of saline in the pleural cavity causes 30% decrease in lung volume at functional residual capacity and 20% at total lung capacity. Therapeutic thoracocentesis has been shown to increase the FEV_1 and FVC by 200 ml for every 1000 ml removed fluid.[11] The increase in maximal inspiratory pressures post thoracocentesis, is greater than the improvement in lung volume; relief of the downward displacement of the diaphragm is probably responsible for this finding. Pleural effusion leads to an ipsilateral intra-pulmonary shunt, which does not significantly change after thoracocentesis. Consequently, PaO_2 does not increase after thoracocentesis, may actually decrease paradoxically. Exercise limitation in pleural effusions results from decline in lung volumes and cardiac function, as reflected by a reduced oxygen pulse. Therapeutic thoracocentesis, however, does not lead to any immediate improvement in exercise capacity as measured by VO_2 (max).[12]

Physiological Changes with Pneumothorax

When pneumothorax occurs, the pleural pressures become uniformly positive unlike in pleural effusion, in which a gradient exists from bottom to top. As a result, the upper lobe is affected more than the lower lobe in pneumothorax, whereas the lower lobes are more affected with pleural effusion. With pneumothorax, the increase in the volume of a hemithorax is four-fold less than the decrease in the volume of the lung. Hypoxemia occurs because of the presence of an intra-pulmonary shunt and due to reduced cardiac output in tension pneumothorax.[11]

Pleural Manometry

Direct measurement of pressures in the normal pleural space is technically challenging because of the close approximation of the two pleural surfaces. Accumulation of fluid leads to a wide range of pleural pressures depending on pleural, chest wall and lung compliances. An abnormally wide pleural space filled with fluid represents a hydrostatic gradient, when viscous flow resistance becomes negligible. Measurement of pleural pressures has several utilities in clinical practice. In general, pressures of less than –5 cm H_2O or pleural elastance (pressure change divided by the amount of fluid removed) of more than 25 cms H_2O/l suggest lung entrapment or atelectasis due to endobronchial occlusion. Pleural elastance can also guide therapeutic thoracocentesis since reperfusion pulmonary edema does not occur until pleural pressures are less than –20 cm H_2O.[13] Also, elastance can predict the success of pleurodesis since pleural opposition is unlikely, if lung entrapment exists.[14]

Pleural manometry can be performed with a vertical-column water manometer with an interposed resistive element or with a hemodynamic transducer connected to a standard physiologic system.[15] Pleural manometry can be easily performed in the absence of complex equipment using CVP manometers connected to a thoracocentesis catheter, inserted in the most dependent portion of the pleural effusion. The manometer is carefully zeroed and purged of air. Pleural pressure is reported as the mean pressure of the oscillating air column. Measurements are performed initially, and after each 250 ml of fluid that is withdrawn and elastance calculated. Coughing invalidates this measurement. The main advantage of water manometers is their conceptual simplicity. The disadvantages are primarily related to the difficulty in reading accurate values from the oscillating water column, and the unfavorable physical characteristics of water manometers. Electronic systems used in critical care units for hemodynamic measurements can also be used by zeroing at the level in which the thoracentesis catheter is introduced into the patient.

In summary, the pleura is a serosal membrane which functions to reduce the friction during lung movement. Normal pleural fluid is a microvascular filtrate formed from the parietal pleural capillaries, predominantly drained via the lymphatic stoma. Pleural manometry is increasingly used to diagnose trapped lung, predict success of pleurodesis and guide therapeutic thoracocentesis.

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Approach to Pleural Effusion

George D'Souza

INTRODUCTION

Pleural effusion, the accumulation of fluid in the pleural cavity, is a common clinical problem encountered in general practice. Normally, the pleural space is a potential cavity encased between the visceral and the parietal pleura. The inner lining of the cavity is covered with a thin film of pleural fluid secreted by the microvilli of mesothelial cells.[1] This thin layer of fluid is essential for the smooth movement of lungs during respiration.[2] Based on chemical characteristics, normal pleural fluid is more representative of the interstitial fluid from the lungs than from the systemic circulation.[3] The fluid, protein and cells exit porous mesothelial cells of parietal and visceral pleurae flow, towards the dependent diaphragmatic pleura, where it passes through the stomata to exit the pleural cavity into the lacunae.[4, 5] Once in the lacuna, the fluid and the cells are drained into the lymphatic channels, which finally join the thoracic duct (Fig. 155.1).

MECHANISMS OF PLEURAL EFFUSION FORMATION

Based on the physiology of normal pleural fluid dynamics in animals, it has been postulated that excessive fluid accumulates in pleural space, due to excessive formation, inadequate drainage, or a combination of excessive formation and inadequate drainage.[6-8] Using a dual isotope method, it has been demonstrated that the mechanism for pleural fluid accumulation in metastatic lung cancer and pancreatitis is due to excessive formation of fluid from the leaky microvasculature, while there is decreased pleural drainage in mesothelioma. In heart failure, there is evidence for both excessive formation and decreased drainage, leading to fluid accumulation in the pleural space.[7] Different pathogenic mechanism have been proposed in the formation of pleural effusion in various clinical conditions (Table 155.1).

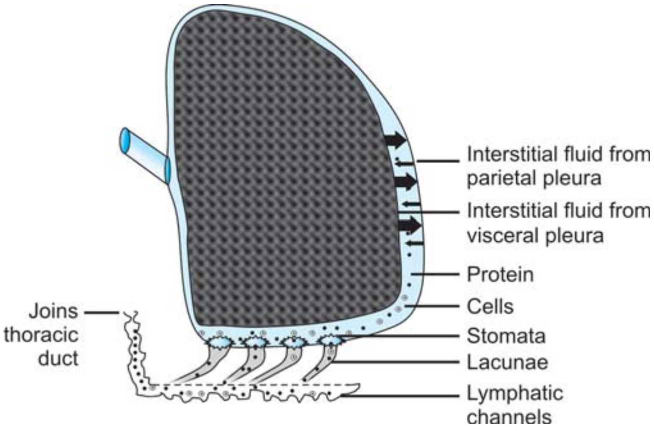
Interstitial fluid from parietal pleura
Interstitial fluid from visceral pleura
Protein
Cells
Stomata
Lacunae
Lymphatic channels
Joins thoracic duct

Fig. 155.1: Anatomy of pleural space

Clinical Approach

A good clinical history can facilitate the work-up of undiagnosed pleural effusion (Table 155.2). Although majority of patients report pleuritic chest pain, dyspnea or cough, a small proportion may have asymptomatic pleural effusion (Table 155.3). While persistent pleuritic chest pain may be a sign of mesothelioma or bone metastasis with pleural involvement, recurrent

TABLE 155.1: Pathogenic mechanisms of pleural effusion formation

Pathogenesis	*Example*
Increased hydrostatic pressure causing increased formation	Cardiac failure, fluid overload
Decreased Oncotic Pressure causing decreased re-absorption	Hypoalbuminemia
Decreased pleural oncotic pressure causing increased formation	Atlectasis, trapped lung
Increased vascular permeability	Pancreatitis, vasculitis, malignancy
Decreased lymphatic drainage	Malignancy, yellow nail syndrome
Movement from peritoneum	Hepatic hydrothorax
Thoracic duct rupture	Chylothorax

TABLE 155.2: Points to elicit in a patient with an undiagnosed pleural effusion

History	*Clinical Association*
Exposure to asbestos	Benign asbestos effusion (BAPE)
Polyarthritis	Rheumatoid arthritis and SLE
Contact with sick animals	Brucella Melitensis Anthrax, Brucellosis
Exposure to TB	Tuberculous pleurisy
Detailed drug history	Amiodarone, Nitrofurantoin, Carbazipine , Dantrolene, Mesalazine, Dasatinib
History of travel	Endemic areas for Paragonimiasis and Filariasis, Amebiasis
Recent coronary bypass surgery	CABG associated and post myocardial injury syndrome
Association with menses	Thoracic endometriosis
History of recent pancreatitis	Pancreatic effusion
History of recent duropleural shunt	Duropleural fistula

TABLE 155.3: Causes for asymptomatic pleural effusion

- Atlectasis
- Benign asbestos pleural effusion
- Hypoalbuminemia
- Nephrotic syndrome
- Peritoneal dialysis
- Rheumatoid effusion
- Trapped lung
- Urinothorax
- Yellow Nail syndrome

hemoptysis should alert the possibility of malignancy, tuberculosis or thoracic endometriosis in women. Also, clinical examination should be focused to elicit the following findings: Yellow nails in yellow-nail syndrome, clubbing in lung cancer, polyarthritis in rheumatoid arthritis and systemic lupus.

Physical examination findings vary with the amount of effusion and state of the underlying lung. The sensitivity and specificity of physical examination are comparable to those of chest radiography.[9] The usual clinical findings include: Diminished chest movement, stony dull percussion, with absent vocal fremitus and absent breath sounds. In the presence of hydro-pneumothorax, shifting dullness and succussion splash may be demonstrable. It is usual to hear egophony at the upper level of a large pleural effusion. Considerable amount of fluid can accumulate before a patient becomes symptomatic, especially if the contralateral lung is normal. Pleural fluid can accumulate following migration of fluid from the peritoneal cavity, as observed in hepatic hydrothorax, from pancreatic bed following pseudocyst formation and from extra-peritoneal extravasation around ureter, as in urinothorax.[10-12] Therefore, clinical examination of abdomen to look for ascites, pancreatic pseudo cyst and hydronephrosis are important in evaluating undiagnosed pleural effusion.

Imaging Studies for Pleural Effusion

Chest Radiography

A posterior–anterior (PA) view of the chest radiograph can show obliteration of costophrenic angle with more than 50 mL of fluid and a meniscus, when more than 200 mL of pleural fluid is present.[13] If pleural effusion is detected on PA view of a chest radiograph, the clinician should proceed with bilateral lateral decubitus views to demonstrate that the effusion is free flowing, as evidenced by layering of the effusion in lateral decubitus view.[14] If the height of the effusion on a lateral decubitus view is more than 1 cm, the effusion can be safely sampled. A large to massive pleural effusion usually causes a shift of the mediastinum to the opposite side. Absence of contra-lateral mediastinal shift with a large pleural effusion may indicate a fixed mediastinum due to an under lying malignancy.[2] The presence of pleural effusion with a shift of the mediastinum to the same side indicates concomitant atelectasis, due to lung fibrosis or the presence of intra-bronchial obstruction.

Presence of interstitial infiltrate and pleural effusion should alert the possibility of rheumatoid pleurisy, Systemic Lupus Erythematus (SLE), sarcoidosis, heart failure, lymphagioleiomyomatosis or lymphangitis carcinamatosis. Presence of hilar or mediastinal lymphadenopathy and effusion should raise the suspicion for tuberculosis, lung cancer, lymphoma and sarcoidosis, while bilateral effusion without mediastinal or hilar lymphadenopathy indicates a trasudative process, such as heart failure, nephrotic syndrome, hypoalbuminemia or constrictive pericarditis.

Ultrasound and Computed Tomography of Pleura

Ultrasound is a non-invasive tool commonly used to confirm the presence of pleural effusion and to aid thoracentesis, especially in the presence of loculated effusion.[15, 16] Computed Tomography (CT) of chest with contrast enhancement is essential for the evaluation of undiagnosed pleural effusion and for management of complicated parapneumonic effusion and empyema. A diagnosis of benign asbestos related pleural effusion can be made in a patient with appropriate history and demonstration of pleural plaques on CT chest.[17]

Thoracocentesis

Who needs a diagnostic thoracentesis? Any patient with undiagnosed pleural effusion should undergo a thoracentesis for laboratory investigations of the fluid (Table 155.4), provided the amount of pleural fluid is sufficient for drainage and there are no contraindications to thoracentesis. Nevertheless, if a patient has typical features of heart failure and pleural effusion, one may choose to observe effusion with follow-up chest X-ray to document resolution. Clinical features which should alert the clinician to proceed with thoracentesis in a patient with heart failure are: Presence of fever, pleuritic chest pain and X-ray evidence of large to massive effusion.[2] Physical appearance of the pleura can help in arriving at clinical diagnosis (Table 155.5). A putrid odor may indicate anaerobic empyema, while ammonia smell may point to urinothorax.

Diagnostic Classification of Pleural Fluid

Pleural fluid is classified as transudative or exudative, based on the biochemical and cellular features. In a trasudative effusion, the underlying pleural structure is normal and the fluid is formed because of an abnormal increase in pulmonary hydrostatic pressure, a decrease in plasma oncotic pressure or a combination of the two processes. However, in an exudative effusion, the integrity of pleura is abnormal due to an infection, infarction or infiltration, the principle process driving the effusion formation is not an elevated hydrostatic pressure, but an increase in vascular permeability. The diagnostic separation of pleural effusion into transudates and exudates was previously done using pleural fluid to serum total protein ratio, pleural fluid Lactate Dehydrogenase (LDH) to serum LDH ratio, and the absolute value of LDH.[18] These old criteria set in 1972, were critically assessed on the basis of results of a large cohort of patients with pleural effusion and were modified to the new criteria; pleural fluid absolute LDH value over 80% of the normal serum level or a Total Protein Ratio (TPR) over 0.5 for the diagnosis of an exudative pleural effusion.[19] Using pleural fluid to serum LDH ratio for the diagnostic separation can be confusing.[19-21] Finally, serum to fluid albumin gradient has no role in the routine diagnosis of transudates and exudates.[22]

The clinical utility of classifying pleural effusions into transudates and exudates relies on the convenience, that transudates are caused by a limited number of benign clinical conditions (Table 155.6), which require no further

TABLE 155.4: Tests useful in the evaluation of pleural effusion

1. Pleural fluid Chemistry
   pH
   Fluid total protein and corresponding Serum protein
   Fluid LDH level
   Fluid glucose and corresponding serum glucose
2. Special chemistry
   Fluid Amylase
   Triglycerides
   Cholesterol
3. Total and differential cell count
4. Cytological examination
   Special stains for malignancy, fungal infections
5. Immunological studies
   Fluid ANA, Rheumatoid factor, Adenosine deaminae
6. Special Immuno-Cytology
   Flow Cytometry for diagnosis of lymphoma
   Tumor markers for diagnosis of malignant pleural effusion

TABLE 155.5: Pleural fluid appearance in unique effusions

Appearance	*Underlying Disease*
Pale yellow	Most transudates
Turbid	Inflammatory exudates
Pus	Empyema
Hemothorax	Trauma, malignancy, Pulmonary embolism, Thoracic endometriosis
Milky fluid	Chylothorax
Brown	Amebic liver abscess
Black	Fungal infection (aspergillus niger)
Yellow to green	Rheumatoid pleurisy

TABLE 155.6: Causes of trasudative pleural effusion

Common Causes of Trasudative Pleural Effusion

- Heart Failure (left and bi-ventricular failure)
- Cirrhosis of liver
- Nephrotic syndrome
- Hypoalbuminemia

Uncommon Causes of Trasudative Pleural Effusion

- Pulmonary embolism 10–20%
- Malignancy 5%
- Constrictive perocarditis
- Peritoneal dialysis
- Duropleural fistula
- Urinothorax
- Subclavian vein thrombosis

TABLE 155.7: Common causes of exudative pleural effusion

Infection	*Infiltration*
Parapneumonic effusion	Primary lung cancer
Tuberculous pleuritis	Metastatic lung cancer
MTB and Atypical mycobacterium	
Fungal infections	Mesothelioma
Coccidioidomycosis	
PCP	Primary Effusion Lymphoma
Parasitic infections	
Paragonimiasis	Kaposis's Sarcoma
Amebiasis	
Inflammation	*Infarction*
Collagen vascular disease	Pulmonary Embolism
Rheumatoid arthritis	Vasculitis Syndromes
SLE	
Pancreatitis	
Sarcoidosis	
Benign asbestos pleural effusion (BAPE)	
Post CABAG	
Induced by Drugs	*Other Causes*
Nitrofurantoin	Esophageal rupture
Amiodarone	Lymphatic rupture or obstruction (chylothorax)
Carbamazipine	
Dantrolene	Yellow nail syndrome
Mesalazine	Meig's syndrome
Dasatinib	Thoracic Endometriosis

invasive diagnostic procedures such as the pleural biopsy, or thoracoscopy.[2] Usually, transudates resolve with treatment of the underlying condition. An exudative pleural effusion (Table 155.7) requires further diagnostic testing if the physician cannot find a definite cause.

TABLE 155.8: Common causes of low pH pleural effusion

Diagnosis	*Estimated %*
Empyema	100
Complicated parapneumonic effusion	100
Esophageal rupture	100
Urinothorax	100
Rheumatoid effusion	90
Malignant effusion	40
Lupus pleurisy	20
Tuberculous pleurisy	10

Additionally, an exudative pleural effusion secondary to primary lung cancer has grave prognostic significance, therefore the need to confirm the diagnosis before embarking on curative chemotherapy.

Pleural Fluid pH

Pleural fluid pH can be measured with a blood gas analyzer, normally it is alkaline at 7.64.[2] Pleural fluid pH should be routinely done on all thoracocentesis samples, as it helps to narrow down the differential diagnosis, to prognosticate the need for chest tube drainage in complicated parapneumonic effusion and to prognosticate the outcome of malignant pleural effusion. Urinothorax is the only transudative effusion with an acidic pH.[12] A low pleural fluid pH (Table 155.8) has been identified as the single most reliable predictor, necessitating chest tube drainage in a complicated parapneumonic effusion.[20,23-25] In a malignant pleural effusion, a lower pleural fluid pH is correlated with a higher tumor burden, and therefore with poor survival.[26] Finally, a lower pleural fluid pH has been associated with lower rates for successful pleurodesis in malignant pleural effusion.[27]

Pleural Fluid Glucose

Glucose is a small molecule that can easily diffuse across pleural membranes from plasma. Therefore, pleural fluid glucose mirrors the plasma glucose concentration. Interpretation of pleural fluid glucose should always be done with reference to plasma glucose. A low pleural fluid glucose is most often observed in empyema, complicated parapneumonic effusion, malignancy, rheumatoid pleurisy, systemic lupus and esophageal rupture.[2] A high glucose effusion designated as "Sweet hydrothorax" may indicate esophageal perforation in a patient receiving tube feeding, and in patients developing effusion, while on peritoneal dialysis.[28,29]

Total and Differential Cell Count

The total pleural fluid white cell count is seldom utilized in the evaluation, but a differential cell count is useful in narrowing the differential diagnosis of exudative effusion.[2] Neutrophil predominant pleural fluid observed in acute pleural inflammatory processes is mediated by interleukin-8 (IL-8), whereas monocyte chemotactic peptide 1 (MCP-1) mediates the monocyte predominance observed in malignant pleural effusion.[1] Following an acute pleural inflammation, polymorphonuclear cells tend to predominate within 24 hours to 48 hours of pleural fluid formation, thereafter the percentage of neutrophils begins to decline acutely, leading to the predominance of lymphocytes.[30] Therefore, the interpretation of pleural fluid differential cell count should be done with reference to the time of onset of pleural inflammatory processes leading to effusion formation.

Pleural effusions are classified arbitrarily as lymphocyte rich if the percentage of lymphocytes is more than 80%, neutrophil-predominant if the PMN's are more than 80% and eosinophilic if the percentage of eosinophils is more than 10%. The presence of even 1% of eosinophils in pleural effusion was diagnostic of coccidioidomycosis related pleural effusion.[31] One can clinically approach pleural effusion in a systematic fashion (Figs 155.2 to 155.4).

Hemorrhagic Pleural Effusion

In a case of hemorrhagic pleural effusion, the odds of malignancy are higher in the absence of trauma.[32] The diagnostic approach should include the exclusion of common benign causes, such as post coronary artery, bypass surgery, and pulmonary embolism (Fig. 155.5). Thoracic endometriosis should be considered in women during their reproductive period, especially if it occurs on the right side.[33]

TABLE 155.9: Causes of amylase rich pleural effusion

Pancreatic Type Amylase	*Salivary Type Amylase*
Acute pancreatitis	Adenocarcinoma of lung
	Squamous cell lung cancer
Chronic pancreatitis	Undifferentiated lung cancer
	Ovarian Cancer
Pancreatic pleural fistula	Multiple myeloma
	Lymphoma
	Lymphatic leukemia
	Pneumonia
	Tuberculosis

Pleural Fluid Amylase

An effusion is classified as "amylase rich", if the pleural fluid amylase value is more than the corresponding serum value or if the fluid to serum amylase ratio is over 1.[34,35] Occasionally, raised fluid amylase with normal serum amylase has been reported in pancreatitis related pleural effusion.[36] Amylase rich effusion has been observed in a variety of clinical conditions (Table 155.9) and therefore, determination of the pleural fluid amylase isoenzymes into pancreatic or salivary type will help to narrow the differential diagnosis.[34,37] The presence of

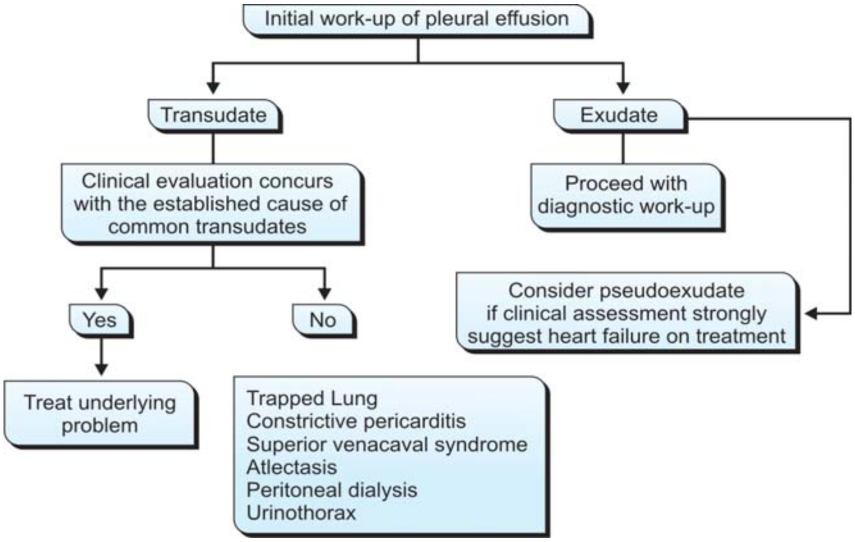
Initial work-up of pleural effusion
Transudate
Exudate
Clinical evaluation concurs with the established cause of common transudates
Proceed with diagnostic work-up
Consider pseudoexudate if clinical assessment strongly suggest heart failure on treatment
Yes
No
Treat underlying problem
Trapped Lung
Constrictive pericarditis
Superior venacaval syndrome
Atlectasis
Peritoneal dialysis
Urinothorax

Fig. 155.2: Initial workup of pleural effusion

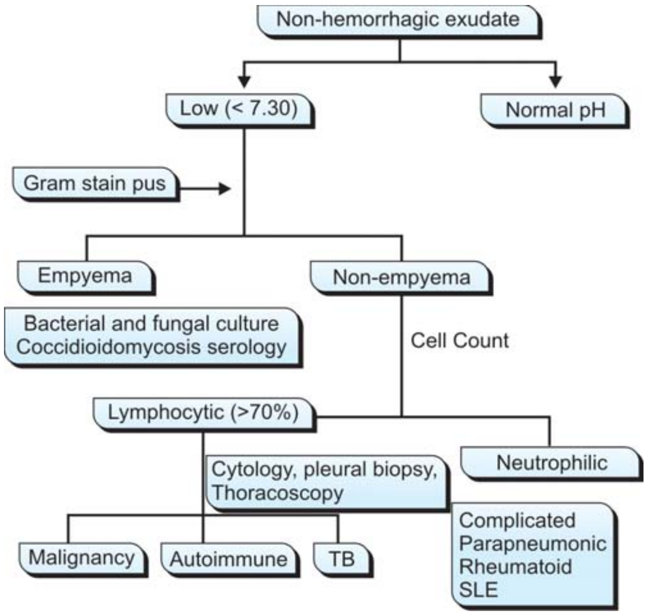
Non-hemorrhagic exudate
Low (< 7.30)
Normal pH
Gram stain pus
Empyema
Non-empyema
Bacterial and fungal culture
Coccidioidomycosis serology
Cell Count
Lymphocytic (>70%)
Neutrophilic
Cytology, pleural biopsy, Thoracoscopy
Complicated
Parapneumonic
Rheumatoid
SLE
Malignancy
Autoimmune
TB

Fig. 155.3: Approach to non-hemorrhagic low pH exudates

salivary amylase in pleural fluid suggests the diagnosis of malignancy in the absence of esophageal rupture,[34] the pancreatic type of amylase confirms a pancreatitis related pleural effusion.

Triglycerides and Cholesterol

Thoracentesis yielding milky fluid should alert the clinician concerning the possibility of chylothorax and pseudochylothorax (Table 155.10). Occasionally, chylothorax can be bloody, especially when it occurs following trauma; yellow to turbid appearing chylothorax has been also reported.[2,38,39] A diagnosis of chylothorax is highly likely, if the pleural fluid triglyceride concentration is more than 110 mg/dl.[40] A chylothorax can be ruled out if the pleural fluid triglyceride level is less than 50mg/dl. Pleural fluid electrophoresis is recommended for confirmation of chylothorax when the pleural fluid triglyceride level is between 50 mg and 100 mg/dL.[38,41] Presence of chronic inflammation as in rheumatoid pleurisy and tuberculosis can lead to accumulation of cholesterol crystals, causing a milky appearance of the pleural effusion called chyliform or pseudochylothorax.[2,42]

TABLE 155.10: Causes of chylothorax

Traumatic	*Non-traumatic*
Mediastinal, lung and cardiac surgery Neck surgery especially on left side Central line placement especially on left side	*Benign* Lyphangioleiomayomatosis Tuberous sclerosis Filariasis Amylodosis Benign mediastinal tumors
Endoscopic sclerotherapy Penetrating surgery to neck and thorax Post delivery	*Malignant* Lymphoma Mediastinal metastasis Primary lung cancer Kaposi's Sarcoma

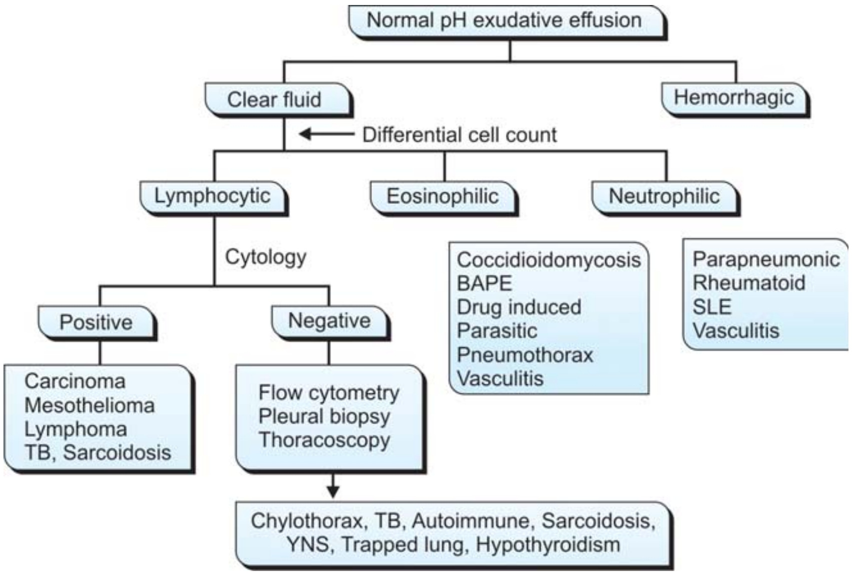
Normal pH exudative effusion
Clear fluid
Hemorrhagic
Differential cell count
Lymphocytic
Eosinophilic
Neutrophilic
Cytology
Coccidioidomycosis
BAPE
Drug induced
Parasitic
Pneumothorax
Vasculitis
Parapneumonic
Rheumatoid
SLE
Vasculitis
Positive
Negative
Carcinoma
Mesothelioma
Lymphoma
TB, Sarcoidosis
Flow cytometry
Pleural biopsy
Thoracoscopy
Chylothorax, TB, Autoimmune, Sarcoidosis,
YNS, Trapped lung, Hypothyroidism

Fig. 155.4: Non-hemorhagic normal pH exudates

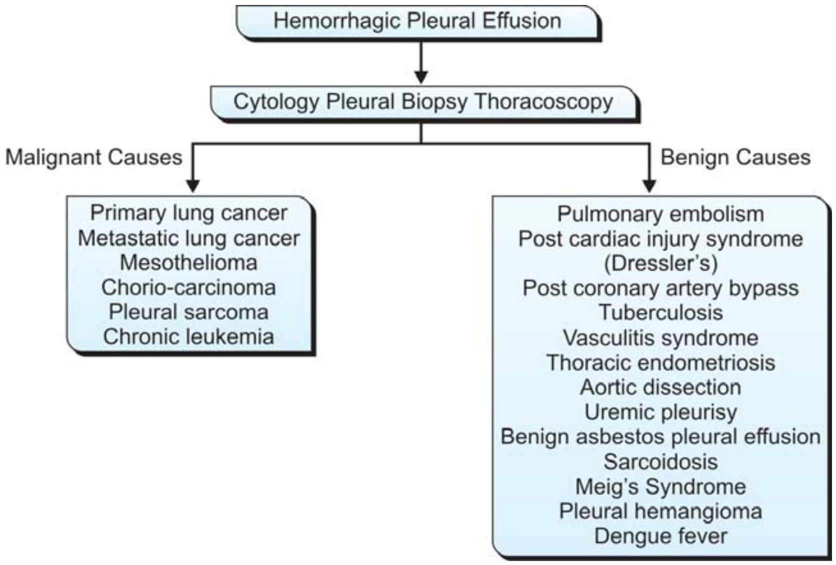
Hemorrhagic Pleural Effusion
Cytology Pleural Biopsy Thoracoscopy
Malignant Causes
Benign Causes
Primary lung cancer
Metastatic lung cancer
Mesothelioma
Chorio-carcinoma
Pleural sarcoma
Chronic leukemia
Pulmonary embolism
Post cardiac injury syndrome (Dressler's)
Post coronary artery bypass
Tuberculosis
Vasculitis syndrome
Thoracic endometriosis
Aortic dissection
Uremic pleurisy
Benign asbestos pleural effusion
Sarcoidosis
Meig's Syndrome
Pleural hemangioma
Dengue fever

Fig. 155.5: Hemmoragic effusion

Pleural Fluid Immunology

Measurement of pleural fluid Anti Nuclear Antibodies (ANA) titer can be helpful in diagnosing systemic lupus related effusion. A pleural fluid ANA titer that exceeds 1:160 is diagnostic of lupus pleurisy.[43] However, a speckled pattern with low titers indicates an alternate diagnosis. Accordingly, it has been suggested that the pleural fluid ANA testing does not provide additional information in a patient with a clinical diagnosis of lupus.[44] Similarly, a pleural fluid rheumatoid titer exceeding 1:320 has been reported as diagnostic of rheumatoid pleurisy.[2] The role of newer tests such as measurement of anti-cyclic citrullinated peptide level in pleural fluid (anti CCP) has not been evaluated in the diagnostic work-up of rheumatoid pleurisy.

Measurement of pleural fluid Adenosine Deaminase (ADA) concentration is promising in the diagnosis of tuberculous pleurisy.[45-47] The increased pleural fluid ADA level results from an increased production of ADA by monocytes and macrophages sensitized to tuberculous antigens. Although the sensitivity of pleural fluid ADA has been shown to be over 90%, the specificity is low due to false positive results observed in effusions due to carcinoma, lymphoma, empyema, rheumatoid pleurisy, mesothelioma, and *Legionnella* pneumonia.[48] Measurement of pleural fluid ADA-2 isoenzyme concentration improves the diagnostic accuracy for tuberculous pleurisy.[49] Pleural fluid ADA measurement is recommended as a diagnostic test in countries with a high prevalence of tuberculosis.[50] However, its value in countries with low incidence of tuberculosis remains controversial.[51]

Pleural Fluid Cytology

Pleural fluid cytology is an integral part of work-up for exudative effusion. Cytology is helpful in arriving at a diagnosis of malignant effusion in over 60 to 80% of cases.[52,53] A cell block preparation fixed with formalin made from a centrifuged pleural fluid specimen increases the diagnostic yield for malignancy.[54] The use of multiple tumor markers in addition to cytology improves the yield.[55,56] Examination of pleural fluid for DNA methylation abnormalities has been shown to improve the sensitivity in diagnosing malignant effusions.[57] Cytological and immuno-histological examination of pleural fluid should be an essential tool in evaluating patients with Aqcuired Immunodeficiency Syndrome (AIDS), especially if fungal infection or primary pleural lymphoma is suspected.[58-60]

Pleural Fluid Culture

Pleural fluid cultures are positive for bacteria in 40 to 58% of patients with parapneumonic effusion (Table 155.11).[61,62] Part of the reason for poor yield is the prior antibiotic therapy. Interestingly, pleural fluid culture for

TABLE 155.11: Causes of bacterial parapneumonic effusion

Staphylococcus aureus, MRSA, *S. epidermidis*
Streptococcus intermedius, *St pneumoniae*, *St pyogenes*, *Streptococcus milleria*
Anaerobes: *Fusobacterium*, *Bacteriods*, *Peptosteptococcus*, *Prevotella* spp., *Clostridium spp.*
Klebsiella pneumoniae
Pseudomonas aeruginosa
Escherichia coli
Enterobacter spp.
Mycobaterium tuberculosis
Actinomyces spp.

anaerobic bacteria is positive in only about 20% of cases.[62] Pleural fluid nucleic acid amplification with bacterial probes improves the diagnostic yield of S. *Pneumoniae* related parapneumonic infection.[62] Pleural fluid pneumococcal antigen assay has been found to be useful in diagnosing *S. Pneumoniae* related parapneumonic effusion.[63]

Tuberculosis is the most common cause of exudative pleural effusion worldwide; one should process the fluid for smear and TB culture studies in all suspected cases of tuberculous pleurisy. Although the yield from the smear is low, the low cost and rapidity with which the diagnosis is made, makes this a useful test in the developing world. The reported yield from smear is about 5-20% in non-HIV patients and higher in HIV patients.[64] Positive pleural fluid culture is confirmatory for tuberculous pleurisy. Cultures for fungi should be processed in all suspected cases, especially in patients with AIDS, and parapneumonic effusion.[59]

Invasive Diagnostic Testing

Bronchoscopy

In the absence of hemoptysis, bronchoscopy has limited role in the investigation of pleural effusion.[65] Bronchoscopy is however required to investigate the airway and the lung parenchymal lesion suspected in the aetiology of effusion.

Pleural Biopsy

Closed pleural biopsy has been reported as a safe procedure in the diagnosis of exudative effusion.[66] The sensitivity can be improved to 80% by the modified Abram's technique, whereby suction is applied with the syringe during each biopsy and the needle is not removed from the thoracic cavity, until all biopsies are done.[67] The yield from biopsy with an Abram's biopsy needle was significantly better than biopsy with a true cut needle, when used with ultrasound guidance.[68] Based on a small series of patients with negative pleural fluid cytology, CT guided biopsy was reported to be better than the blind pleural biopsy.[69] Complications are rare, but serious intrathoracic hemorrhage can occasionally occur following closed pleural biopsy.[70]

Thoracoscopy

Thoracoscopy is now increasingly used for the evaluation of undiagnosed pleural effusion.[71] The advantages include the direct visualization of parietal and visceral pleurae, guided biopsies of lesions and for the lysis of adhesions. The mortality in experienced hands is about 0.24%.[72] The reported sensitivity for malignant and benign pleural disease was about 93% with 100% specificity.[72,73]

Pleural Manometry

Pleural manometry is useful in confirming trapped lung related pleural effusion. An increase in negative pressure of more than 15 cm per liter of removed fluid is diagnostic of trapped lung related pleural effusion.[74]

Approach to Pleural Disease in Acquired Immune Deficiency

Pleural effusions are common in acquired immunodeficiency syndrome (AIDS), the reported prevalence in hospitalized patients with AIDS varies from 7 to 27% .[75,76] Infections account for the majority of pleural effusions, about 30% of cases occur from non-infectious causes (Table 155.12).[59,75] The general approach is the same as described for non-AIDS patients. Nevertheless, the emphasis is laid on special staining techniques to identify fungal infections. In debilitated patients with hypoalbuminemia, it is prudent to use pleural fluid LDH rather than the total protein ratio for diagnostic separation of transudates and exudates.[77]

TABLE 155.12: Causes of pleural effusion in AIDS

Infectious Causes	*Non-Infectious Causes*
Parapneumonic effusion	Congestive heart failure
Septic embolism with empyema	Hypoalbuminemia
Bordetella bronchiseptica	Uremic pleurisy
Mycobacterium tuberculosis	Kaposis's sarcoma
Mycobacterium avium intracellulare	Lymphoma
Nocardiosis	Primary effusion lymphoma
Pneumocystis jirovecci pneumonia	ARDS
Cryptococcal infection	Atlectasis
Coccidioidomycosis	

Pneumocystis Jiroveci Pneumonia

Pneumocystis Jiroveci Pneumonia (PJP) related pleural effusion varies from 6 to 11% in hospitalized patients with HIV.[75,76] Pleural effusions are usually small to moderate in size, can occasionally be bloody. Pleural fluid LDH concentration is elevated and the differential cell count is predominantly mono-nuclear. A definite diagnosis of PJP effusion requires the demonstration of trophozoite or cyst forms of Pneumocystis in pleural fluid.[78] Grocott silver staining can improve the sensitivity by demonstrating the cyst forms of PJP.[78] The presence of trophozoite forms is best detected with an air-dried and Diff-Quik stained cytospin preparation.[79] The demonstration of granular eosinophilic aggregates, numerous vacuolated macrophages, and scattered benign mesothelial cell clusters in the pleural fluid are surrogate markers of PJP effusion. A clinical diagnosis of PJP effusion can be made, if the cyst form is identified in Bronchoalveolar Lavage (BAL) fluid and the effusion resolves with the specific treatment for PJP.

Tuberculosis

About 8-13% of pleural effusions in patients in India are caused by tuberculosis.[75,76,80,81] *Mycobacterium tuberculosis* is the most commonly identified agent, but Mycobacterium avium complex can occasionally cause pleural effusions.[75, 82] Acid-fast staining of pleural biopsy is likely to be positive in patients with AIDS.[83]

Cryptococcal Pleural Effusions

Pleural effusion usually occurs in association with radiographic parenchymal abnormalities in the non-AIDS population, isolated findings on chest radiograph can occur in AIDS.[75,84,85] *Cryptococcus laurentii*, a new strain, has been reported to cause pleural effusion in patients with AIDS.[86] The pleural fluid is a serous exudate with a low nucleated cell count, the culture is positive in 42% of cases. Identification of cryptococcal antigen in the fluid of non-AIDS patients has proved a rapid and specific test.[87] Pleural biopsy has been helpful in making a definite diagnosis.[88]

Histoplasma capsulatum

Histoplasma capsulatum can cause pleural effusion in the AIDS and the non-AIDS populations.[89,90] The effusion is serous or serosanguinous with a low number of nucleated cells. A cytocentrifuged pleural fluid specimen stained with Wright-Giemsa stain will demonstrate intracellular yeast typical of *Histoplasma capsulatum*.

Toxoplasma gondii

Toxoplasma gondii is a rare cause of pleural effusion, occurs in the late stages of AIDS.[91] A cytocentrifuged Giemsa-stained specimen of pleural fluid can demonstrate *T. gondii* tachyzoites within neutrophils.

Hypoalbuminemia

Hypoalbuminemia has been reported as a cause for pleural effusion in 7 to 15% of hospitalized patients with AIDS.[75] The effusion is a transudate, small to moderate in size, and bilateral. The nucleated cell count is low with mononuclear cell predominance.

Lymphoma

Lymphoma has been reported to cause pleural effusion in about 16% of patients with AIDS.[58, 82, 92] However, autopsy series have documented pleural effusion in over 65% patients. Isolated pleural effusion can occur as the sole manifestation of AIDS-related lymphoma without pulmonary parenchymal abnormality and lymphadenopathy.[93] The effusion tends to be large. Fluid chemistry is exudative with normal glucose and high LDH concentration.[94] Pleural fluid cytology clinches the diagnosis in about 60% of cases.[95] Flow cytometric examination of pleural fluid is useful in establishing the diagnosis in patients with a high index of suspicion for lymphoma.

Kaposi's Sarcoma

Pleural effusion occurs in 36 to 60% of patients with Kaposi's sarcoma.[96,97] Majority of patients will show pulmonary parenchymal infiltrates or lymphadenopathy. The pleural effusion is serosanguineous, free flowing and large. Chylous effusion has been reported in Kaposi's sarcoma secondary to lymphatic obstruction.[96,98] Pleural fluid cytology is seldom positive. Closed pleural biopsy is of no use, since the parietal pleural is not involved. The finding of characteristic cherry-red endobronchial lesions on bronchoscopy is helpful in making a clinical diagnosis.

Primary Effusion Lymphoma (PEL)

Primary effusion lymphoma has been reported as a unique entity in AIDS.[99] The majority of PEL exhibits indeterminate immuno-phenotypes, i.e. express CD45, CD138 and activation-associated antigens (CD30, CD38 and HLA-DR), lack surface expression of B cell markers (CD19, CD20, CD79a and immunoglobulin), but exhibit clonal rearrangements and somatic hypermutation of the immunoglobulin genes, suggesting that they take origin from post-germinal center B cells.[100] Although Kaposi's sarcoma-associated herpes virus has been suggested as the causative agent in PEL, concomitant presence of Epstein-Barr virus in most PEL suggests the role of Epstein-Barr virus as a co-factor in the development of PEL.[101]

PEL occurs predominantly in HIV-seropositive homosexual men between the age of 30 and 50 years.[102] Pre-existing Kaposi's sarcoma has been reported in about 33% of patients with PEL. Pleural effusion with parietal pleural thickening occurs in the absence of lung parenchymal lesions or mediastinal lymphadenopathy. Pericardial effusion and ascites are other common radiological findings. Peripheral lymphadenopathy and bone marrow involvement are unusual findings in PEL.[103] The most valuable marker for PEL is the demonstration of Kaposi's sarcoma-associated herpes virus-associated LANA-1 in the nuclei of most cells.[60]

Congestive Heart Failure

Transudative pleural effusion secondary to cardiac failure has been reported in hospitalized patients of AIDS.[59] Dilated cardiomyopathy, secondary to HIV, has been implicated as the cause of cardiac failure.[104]

In conclusion, pleural effusion is a common clinical problem of multiple etiologies that requires a systematic approach for a definitive diagnosis. Even after extensive investigations, about 10% cases remain undiagnosed. The first step is to classify the effusion into a transudate or an exudate, using the results of pleural fluid biochemistry. Total and differential cell count will help to narrow down the differential diagnosis. An elevated pleural fluid ADA is a useful test in the diagnosis of tuberculous pleurisy, in areas with high prevalence of tuberculosis. The diagnostic possibilities for pleural effusion in patients of AIDS are complex and require special staining techniques to rule out opportunistic infection and rare malignancies.

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156

Tubercular Pleural Effusion

Pranab Baruwa, Kripesh Ranjan Sarmah

Pleural involvement in tuberculosis has been reported in approximately 5% of all Tuberculosis (TB) patients.[1] Apart from lymph node tuberculosis, pleural effusion is the second most common form of extra pulmonary tuberculosis.[2] Frequency of pleural involvement in TB is variably reported from 4% in US to 23% in Spain.[3,4] Incidence of TB pleural effusion in Acquired Immunodeficiency Syndrome/ Human Immunodeficiency Virus (AIDS/HIV) is also variably reported from 15 to 90%.[5, 6] Without treatment, TB pleuritis may resolve spontaneously but most of them develop active TB at a later date. Spontaneous resolution occurs in 4 to 16 weeks without treatment.[7,8] Of 141 cases of TB pleural effusion and positive tuberculin test followed from 1940 to 1944, 92 (i.e. 65%) developed some form of active tuberculosis.[8]

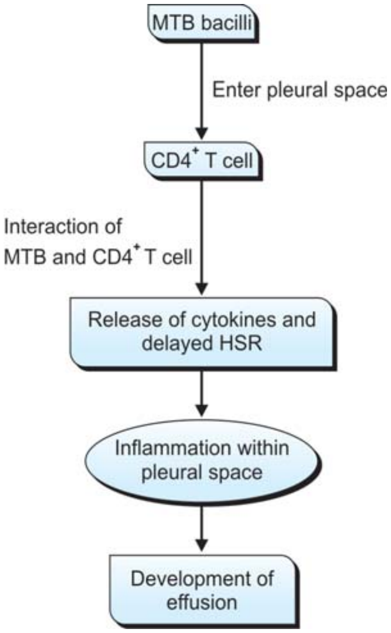
MTB bacilli
Enter pleural space
CD4$^+$ T cell
Interaction of MTB and CD4$^+$ T cell
Release of cytokines and delayed HSR
Inflammation within pleural space
Development of effusion

Fig. 156.1: Pathogenesis of tubercular pleural effusion

PATHOLOGY AND PATHOGENESIS

Pleural TB can be a manifestation of primary or post-primary disease.[1] In primary disease, rupture of sub-pleural foci occurs as the initial event.[9] Postprimary form is frequently associated with parenchymal disease like consolidation or cavity formation.[1] When TB pleural effusion occurs in the absence of radiologically apparent TB, it may be the sequel to a primary infection.[10,11] Delayed hypersensitivity plays a major role in the pathogenesis of TB pleural effusion. Hypersensitive reaction is initiated when tubercular protein gain access to pleural space in case of an infected individual. Tubercle bacilli in pleural space interact predominantly with CD4$^+$ T cells, resulting in delayed hypersensitive reaction (Fig. 156.1).[12] This leads to accumulation of fluid in the pleural space which is mostly exudative, but sometimes serosanguineous and contain few bacilli.[11,13] Fluid accumulates due to increased capillary permeability and impaired lymphatic clearance because of the occlusion of pleural stomata.[14] Pleural fluid predominantly contains neutrophils for the first 24 hours.[15] The neutrophils in the pleural space appear to secrete a monocyte chemotaxin that recruits monocytes to the pleural space, thereby contribute to the formation of granulomas.[15] In Bacillus Calmette-Guérin (BCG) model of experimental TB pleuritis, macrophages predominate in the pleural space from day 2 to day 5 after the initial neutrophil predominance.[15] After this period, lymphocytes are the predominant cells.[16] The late phase is denoted by marked CD4$^+$/CD8$^+$ cell response with release of interferon γ and granuloma formation.[17]

CLINICAL FEATURES

Unlike pulmonary TB, most pleural TB effusion manifest as acute illness. One-third of patients are symptomatic for less than 1 week and two-third for less than 1 month.[18] The average duration of symptoms before presentation is about 14 days for primary TB and 60 days in reactivation disease.[19] Asymptomatic effusion is a rare presentation.[20] Pleural TB has been considered a disease of young age, increased incidence is seen among middle aged people, 19% cases due to reactivation.[21] In general, patients with TB pleuritis are younger than patients with parenchymal disease. Patients with pleural effusion secondary to reactivation tend to be older than those with primary pleural effusion.[10]

The most common symptoms in pleural tuberculosis are cough (71 to 94%), fever (71 to 100%), chest pain (78 to 82%) and dyspnea.[22,23] The pleuritic pain usually precedes the cough. Usually, patients are febrile, but some may have normal temperature. TB pleural effusion is typically unilateral, small to moderate in size and usually occupy less than 2/3 of hemithorax.[24] Patients of tubercular pleural effusion with HIV positivity tend to be older, more likely to have fluid smear and culture positive for MTB[25] Moreover, HIV-positive patients tend to have positive pleural biopsy and show high incidence of disseminated disease than the non HIV cases.[25,26] Fever, dyspnea, night sweat, fatigue, diarrhea, marked tachypnea, hepatosplenomegaly, lymphadenopathy are other symptoms, more common in HIV-positive patients.

Physical examination of chest in a case of TB effusion is similar to that in any other types of pleural effusion. The percussion note over an effusion is usually dull. Auscultation characteristically reveals decreased or absent breath sounds. Near the superior border of the fluid, however, breath sounds may be accentuated and take a bronchial characteristic. This phenomenon has been attributed to the increased conductance of breath sounds through the partially atelectatic lung, compressed by the fluid. In case of a loculated effusion, the typical findings of pleural effusion may not be present.

Diagnosis

Pleural Fluid Analysis

TB pleural fluid is usually clear and straw colored, it can be turbid or serosanguinous, but rarely bloody. Effusion is usually exudative with pleural fluid protein of more than 3.5 gm/dl.[27] Pleural fluid LDH is usually high, in most cases more than 200 U/dl, the pH ranges from 7.3 to 7.4 (rarely over 7.4), although it can be less than 7.3 in approximately 20% cases.[28] The fluid glucose concentration is more than 60 mg/dl in 80 to 85% cases and less than 30 mg/dl in about 15% of cases.[21,24] The total cell counts are usually in the range of 100 to 5000 per dl with more than 90% lymphocyte in two-thirds of cases.[11] Although in the initial stages of illness (up to 1–2 weeks) there is neutrophil predominance, serial thoracentesis show shift to the lymphocyte predominance.[16,18,29] Presence of more than 5% mesothelial cell in the pleural fluid is rarely compatible with TB pleural effusion, most likely due to chronic pleural inflammation that prevents exfoliation of mesothelial cells into the pleural cavity.[30] HIV infected patients may have numerous mesothelial cells.[31] Similar reports are also seen in immune-competent patients.[32] Pleural fluid eosinophilia (more than 10%) reduces the possibility of TB, provided the patient does not have a concomitant pneumothorax or had a previous traumatic thoracentesis that had resulted in hemorrhage within pleural space.

Adenosine Deaminase Enzyme Activity

Adenosine Deaminase (ADA) is an enzyme in purine salvage pathway that catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine with release of ammonia. Although wide in distribution, it plays an important role in the differentiation of lymphoid cells and is more abundant in activated T lymphocytes.[33] High levels of ADA are reported in patients with TB pleural effusion.[34] ADA level of more than 70 IU/L is highly suggestive of TB while a level of less than 40 IU/L virtually excludes the diagnosis.[35] A meta-analysis of 40 studies from 1966 to 1999 showed ADA sensitivity of 47.1 to 100% and specificity of 0 to 100%.[36] Several Indian studies have also reported similarly variable results.[37-39] These discrepancies in results from different studies are attributable to different methods of ADA analysis. Specificity increases when the lymphocyte to neutrophil ratio in the pleural fluid (more than 0.75) is considered in conjunction with an ADA concentration of more than 50 IU/L.[40] When prevalence of disease is low (i.e. less than 1%), the positive predictive value may also be as low as 15%, however negative predictive value increases.[41]

In areas with high prevalence of tuberculosis, ADA measurement is inexpensive, minimally invasive, rapid and readily accessible test that has sensitivity and specificity of 95% and 90%, respectively.[11,42] Elevated ADA in lymphocyte rich pleural fluid has been reported in other diseases, such as rheumatoid arthritis, bronchoalveolar carcinoma, mesothelioma, *Mycoplasma* and *Chlamydia pneumonia,* psittacosis, paragonimiasis, infectious mononucleosis, brucellosis, Mediterranian fever, histoplasmosis, coccoidiodomycosis and in most patient with empyema.[33,41,42] Of the two isoenzymes, ADA1 is found in all cells with highest activity observed in lymphocytes and monocytes. On other hand, ADA2 isoenzyme is predominantly found in monocytes/macrophages. ADA2 isoenzyme is primarily responsible for increased ADA activity in TB pleural effusion with median contribution of 88%.[43] Therefore, pleural effusion with high ADA level and ADA1/total ADA ratio less than 0.45, makes the diagnosis of TB highly likely.[44] The levels of ADA in patients of TB effusion with or without AIDS are comparable.[45]

Radiological Investigations

Radiological evaluation for pleural effusion is done with the help of chest X-rays, Computed Tomography (CT) scans and ultrasonography. Radiological findings are usually similar in pleural effusion of different etiologies. They can be suggestive but not specific to tuberculosis. Chest X-rays reveal usually unilateral small to moderate effusion (Figs 156.2 and 156.3). The classical X-ray picture in posteroanterior projection is the obliteration of the lateral Costophrenic (CP) angle with high density laterally with a gentle, medial, downward curve and a smooth, meniscus shaped upper border which terminates at the mediastinum (Fig. 156.4). In supine posture, there are signs of increased homogeneous density superimposed over the lung, loss of hemidiaphragm silhouette, apical capping, elevation of hemidiaphragm, blunting of CP angle, decreased visibility of lower lobe vasculature and accentuation of minor fissure.[46,47] An amount of 175–525 ml of fluid produces noticeable increase in density over lower lung zone on supine radiograph.[47] The lateral decubitus view shows homogeneous density with a straight horizontal superior border between the dependent chest wall and the lower border of the lung, provided the accumulated fluid is not loculated (Fig. 156.5). Minimum of 75 ml fluid is required to obliterate the posterior CP angle (Fig. 156.3). Sometime, pleural effusion may present as subpulmonic or loculated effusion. Rarely, pleural TB may present as pleural nodules and thickening.[48]

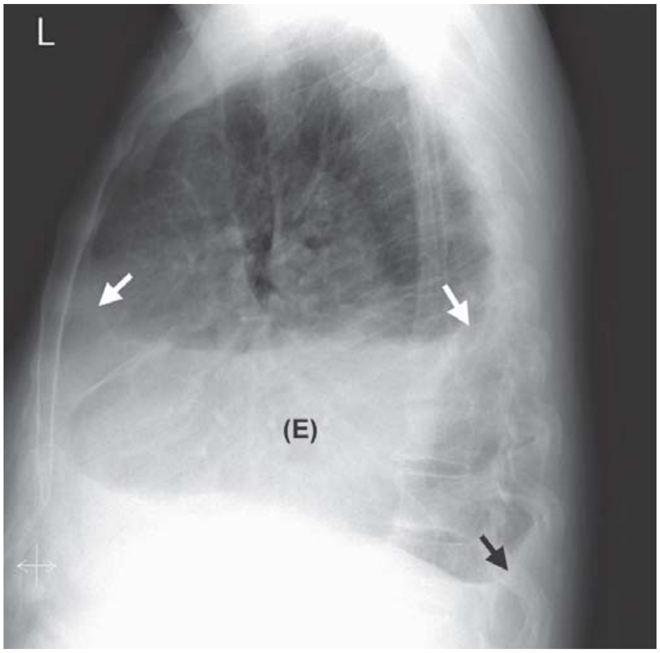

Fig. 156.2: Lateral view showing effusion in posterior CP angle

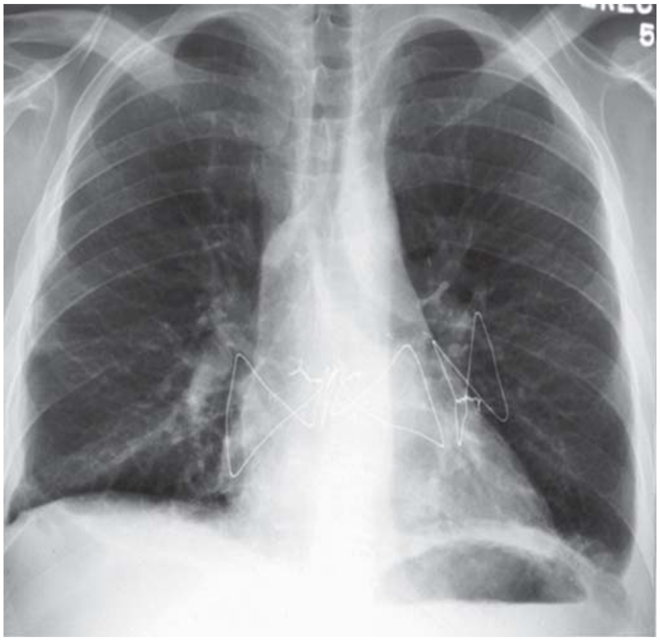

Fig. 156.3: PA view showing minimal left sided pleural effusion

On CT scan, the typical finding of free flowing pleural fluid is seen as a sickle shaped opacity in the most dependent part of the thorax, posteriorly (Fig. 156.6).[49] CT scan is also helpful to demonstrate pleural loculation

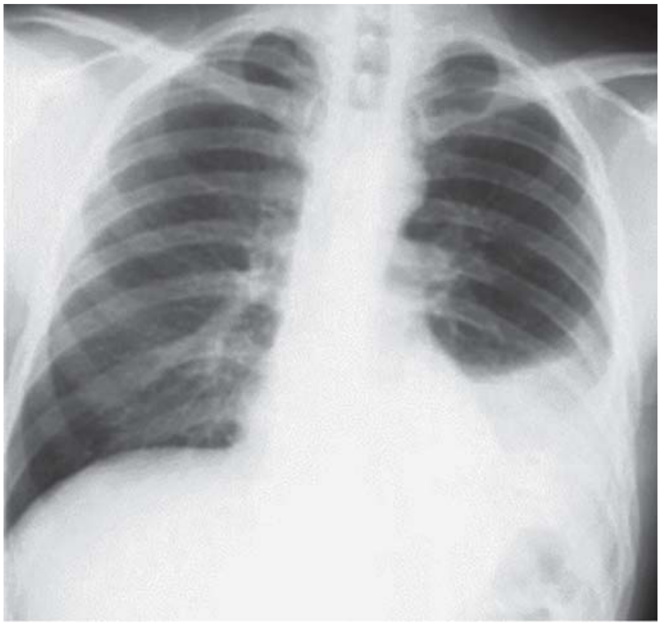

Fig. 156.4: PA view showing left sided moderate pleural effusion

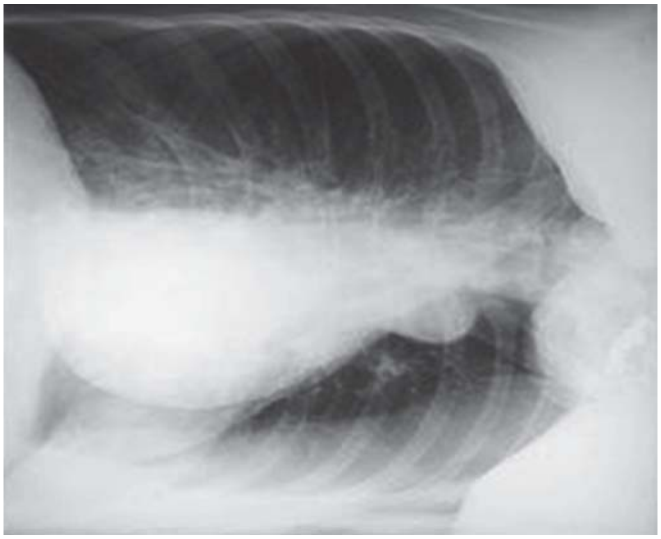

Fig. 156.5: Lateral decubitus view showing horizontal fluid level

(Fig. 156.7), as well as to see the associated parenchymal and pleural pathology (Fig. 156.8). Associated parenchymal lesions are seen in 20–50%, or even to 67% patients.[50-52] Lung parenchymal lesions have been observed in 86% of patient with TB pleural effusion using CT scans, 37% show features of radiologically active pulmonary TB.[52] Computed tomography can also help to detect other complications associated with TB pleural effusion, such as the pleural thickening, calcification,

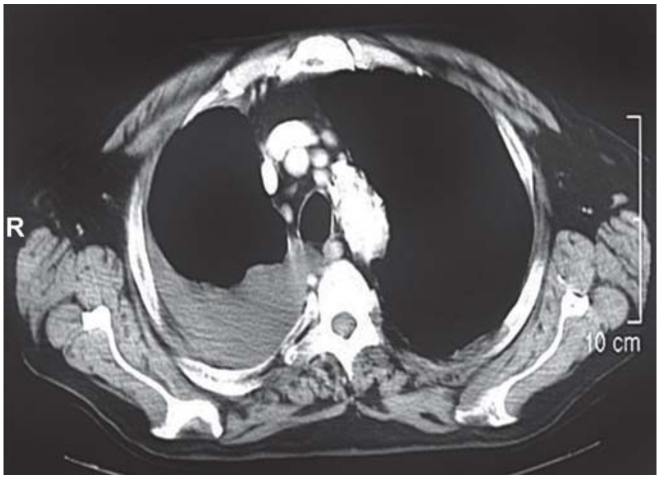

Fig. 156.6: CT showing right sided pleural effusion

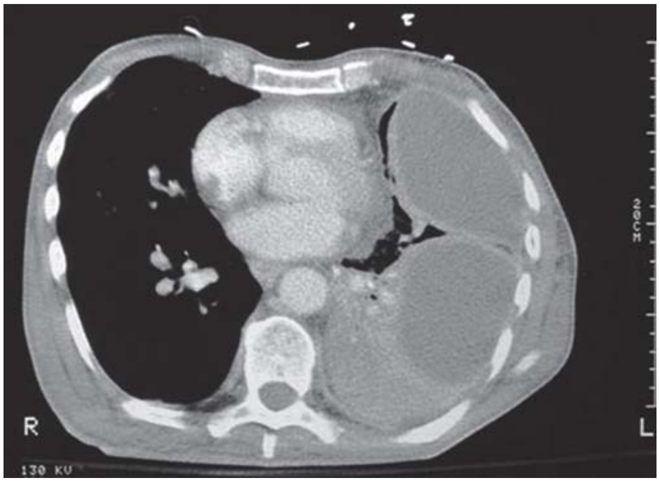

Fig. 156.7: CT showing loculated pleural effusion

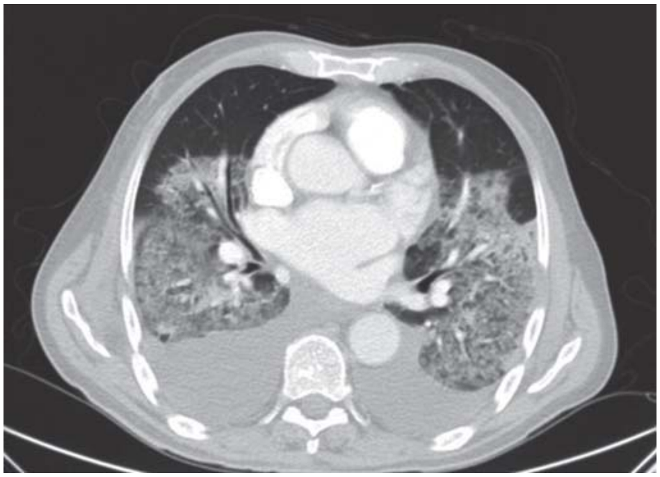

Fig. 156.8: CT showing bilateral pleural effusion with underlying parenchymal lesions

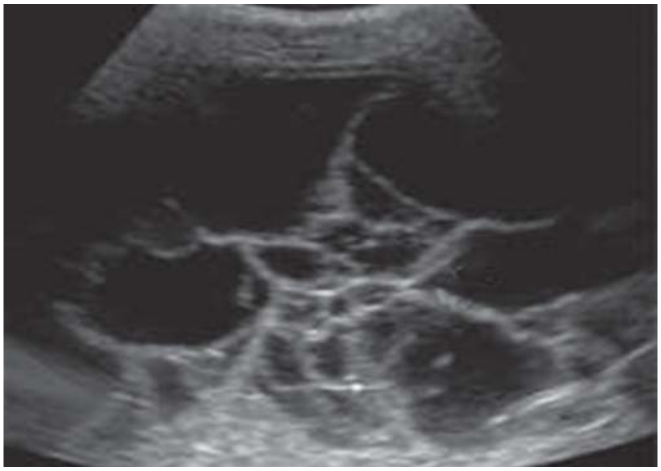

Fig. 156.9: USG showing multiple loculated pleural effusion

loculated effusion, empyema, empyema necessitans and bronchopleural fistula.[53]

Ultrasonography (USG) is a useful modality in the evaluation of pleural diseases.[54-56] It helps to differentiate pleural fluid from pleural thickening, helps in guided thoracentesis, identification of loculations (Fig. 156.9) and for differentiation of pyopneumothorax from lung abscess. USG is also useful to demonstrate fibrin bands of varying length, mobile delicate septation, encysted pleural effusion, pleural thickening and pleural nodules.[57]

Sputum Examination

Sputum examination, both smears and culture are generally not rewarding. Smears of sputum are rarely positive in primary cases, cultures are positive in only 25 to 33% of patients, especially if there is an associated underlying lung disease. In its absence, sputum examination may be positive in only 4 to 10% cases.[50,58,59] Induced sputum culture is positive in 52% and smear in 12% of cases.[60] Even in patients with normal lung parenchyma on chest X-ray, the yield of induced sputum examination in tubercular pleural effusion approaches 55%.[60]

Tuberculin Test

Positive tuberculin test constitutes a supportive evidence for tuberculosis. Negative tuberculin test in tubercular pleural effusion is attributed to anergy secondary to immunosuppression or malnourishment, recent infection, circulating mononuclear cells suppressing the specifically sensitized circulating T-cells in the peripheral blood or sequestration of tuberculin reactive T lymphocytes in the pleural space.[61,62]

Pleural Fluid Culture and Smear

Pleural fluid of tubercular origin contains fewer bacilli, detects AFB in less than 10% of cases.[21,22,24,35] In patient with HIV co-infection, the yield is over 20%.[25] Culture which requires a minimum of 10 live bacilli to 100 live bacilli, is positive in 12–70%.[22] Culture sensitivity can be increased by bed side inoculation of fluid, by using liquid media.[63]

Pleural Biopsy

Pleural biopsy reveals granulomas in 50–97% of patients with TB pleural effusion. When both biopsy and culture methods are used together, the diagnostic yield is high, from 60 to 95%.[20, 21, 24, 35, 50] Other causes of granulomatous pleuritis, such as the fungal disease, sarcoidosis, rheumatoid arthritis, and nocardial infection need to be excluded.

Thoracoscopy

Thoracoscopy is useful for direct pleural visualization. TB pleuritis may be seen as yellow white tubercles on the parietal pleura, reddening and adhesions. Thoracoscopy has been reported to be the most accurate, yet an invasive and expensive tool for establishing the diagnosis with a diagnostic accuracy of 100% on histology and 76% positive on culture.[64]

Miscellaneous Indirect Investigations

Interferon Gamma Assay: Interferon Gamma (IFN-γ) is produced by CD4 lymphocytes in patients with TB pleuritis. A cut off level of 3.7 IU/ml has shown both sensitivity and specificity of 98%.[65-71] Other diseases that can cause elevated levels of IFN- γ in pleural fluid include hematogenous malignancy and empyema.[66-68] Immunosuppressed patients have similar level of IFN-γ as the immune-competent.[66] Both ADA and IFN-γ has shown accuracy in detecting TB pleural effusion, the joint sensitivity and specificity of 93% for ADA and 96% for IFN-γ.[72] Although, a few studies have shown IFN-γ level to be more sensitive and specific than ADA, it is more expensive and less readily available than ADA estimation.[72-74] Pleural fluid IFN-γ estimation does not seem a cost-effective investigation for differentiating TB from non-TB effusion, compared to ADA in resource limited countries.[75]

Other cytokines: The serum to pleural fluid IL-6 level is significantly higher in TB effusion rendering it a novel marker in the differential diagnosis of exudative pleural effusion.[76] IL-1α and TNFα produced predominantly by mononuclear phagocytes have been shown to be present in tubercular, malignant and parapneumonic effusions with considerable cut-off levels for these diseases.[76,77] Levels of soluble IL-2 receptors, IL-18, immunosuppressive acidic protein and IL-12p40 are all significantly elevated in TB pleural effusion in a decreasing order of sensitivity, with soluble IL-2 receptor being a more sensitive marker than ADA.[78] These markers need further evaluation for routine clinical use.

Polymerase Chain Reaction (PCR)

PCR can detect as few as 10 bacilli.[79] For diagnosis of pleural TB, the test shows a sensitivity ranging from 20 to 90% and specificity 78 to 100%.[80-89] PCR finding are positive in 100% culture positive pleural TB and in only 30 to 60% of culture negative fluid.[35,83] False positive results are seen due to DNA contamination or presence of non-viable organisms. PCR of pleural biopsy tissue has 90% sensitivity and 100% specificity, the overall accuracy is similar to that of biopsy.[84]

Immunodiagnosis

Several immunological markers of tuberculosis such as IgA against MPT 64 and MT-10.3, anti IgM and IgG antibodies against anti-A60 and others have been evaluated for diagnosis.[85-87] Serum antibody levels against TB antigens have poor sensitivity and specificity, the performance of serological tests for diagnosis of TB pleuritis has been disappointing, regardless of HIV co-infection.[88]

Neopterin

Neopterin is a marker of Th1 immune-activation, it is secreted by activated macrophages.[89] Neopterin level in pleural fluid have been found to be higher in patients with TB than in patients with malignancy or other conditions.[90-92] Very high levels have been observed in uremic pleural effusions, raising doubts about its specificity for TB.[93] When histological evidence of caseating granulomas was used as the reference standard for TB, sensitivity and specificity of neopterin were found to be 44% and 85%, respectively.[91]

Leptin

Leptin is a 16kDa product of obese (ob) gene and may be involved in cross regulation between nutritional status and the immune response in TB.[89] Serum leptin level has been shown to be reduced in patients with active pulmonary TB and cancer.[94,95]

Lysozyme

Lysozyme is present in the epithelial cells of granulomas, macrophages and activated granulocytes. A value of 1.2:1 for ratio of pleural fluid to serum lysozyme has been proposed as a good test for diagnosing TB pleural effusion.[96]

Complement Activation

Complement plays an important role in the pathogenesis of tubercular pleural effusion. Complement activation in the pleural fluid of 83 patients measured by using commercial ELISA tests had a sensitivity of over 80%.[97]

Cell Subsets

TB pleural effusions are usually rich in mononuclear cells.[98] Although the pleural ADA activity correlated with the number of $CD4^+$ T cells in the pleural space, the number of pleural $CD4^+$ T cell was not an accurate diagnostic test for TB.[99]

Scoring Systems

There are limitations of individual tests used for the diagnosis of TB pleural effusion. Therefore, several scoring systems have been developed based on multiple tests.[100] In one of the model, the parameters of ADA, age, temperature and pleural fluid RBCs were used to predict tubercular etiology.[100] In the second model, all of the parameters of first model except ADA were used with addition of "no history of malignancy", pleural protein and pleural to serum LDH ratio.[100] Summated score of at least 5 in model one and at least 6 in model two had sensitivity of 95% and 97% and specificity of 94% and 91%, respectively. In another study, sensitivities for ADA activity, IFN-c levels and PCR of 88%, 91% and 74%, respectively and the specificities of 86%, 97% and 90%, respectively were used; when all the three variables were combined, the sensitivity and specificity increased.[101] There are several other models employing combination of ADA and neutrophil to lymphocyte ratio; duration of symptoms, pleural protein level, leukocyte count, percentage of lymphocytes and ADA, which have shown promising results in the preliminary studies.[102,103]

Future Diagnostic Modalities

Several new TB diagnostic modalities have been developed in the recent time - the loop-mediated isothermal amplification, detection of LAM (a TB antigen) using ELISA, phage-based assays and rapid culture systems.[104,105] However, these tests are not evaluated adequately for TB pleuritis.

HIV Infection and Pleural TB

Pleural tuberculosis in HIV positive patients occurs in the younger age group.[106] Patients with HIV/AIDS tend to have a longer duration of illness and lower incidence of chest pain.[107] Systemic signs and symptoms, such as night sweats, fatigue, diarrhea, hepatomegaly, splenomegaly and lymphadenopathy are significantly more common in HIV infected patients.[108] They are also more likely to have concomitant parenchymal lesion.[109] Their pleural fluid is more likely to be smear and culture positive for AFB.[107,110] If CD4 count is less than 100, approximately 50% will have positive smear for AFB in their pleural fluid and these patients have significantly lower lymphocyte count.[110]

Patients with HIV/AIDS and TB pleural effusions are treated with the same drugs for the same duration, as those with HIV negative status.[111] HIV positive persons with tuberculosis and all TB patients living in the HIV-prevalent settings should receive daily TB treatment, at least during the intensive phase as per the WHO guidelines, 2009.[111] One should be aware of drug interactions between the antiretroviral therapy (ART) and the anti tubercular drugs, adverse drugs reactions and the immune reconstitution syndrome. The later is manifested by the worsening of symptoms, an increase in the volume of existing pleural fluid or development of pleural effusion during treatment. Co-trimoxazole preventive therapy should be initiated in all HIV-positive TB patients, as soon as possible and given throughout the period of anti-TB treatment.[111] Continuation after completion of TB treatment can be considered in accordance with national guidelines. Antiretroviral therapy improves survival in patients with TB and HIV coinfection.

MDR-TB and Pleural Effusion

Drug resistance in pleural tuberculosis follows similar pattern to that of parenchymal TB.[112] Therefore, drug susceptibility testing is sought in areas where there is high incidence of resistance. Multidrug-resistance occurs in only 1% of patients with pleural TB, any 1st line drug resistance occurs in less than 10%.[112] The drug resistant patients are treated according to the culture and sensitivity pattern of the bacilli.

MANAGEMENT

The major objectives of treatment lie in the resolution of effusion, healing of active lesion and prevention of subsequent reactivation of tuberculosis. The other objectives of management are to prevent development of pleural fibrosis and to treat complications that may develop due to pleural effusion. The treatment can be broadly divided into medical and surgical management. A large majority of patients require only the medical treatment.

Medical Management

Tubercular pleural effusion is a type of extrapulmonary paucibacillary, disease. With adequate antitubercular treatment, most cases resolve completely with fewer chances of recurrence. According to the Revised National Tuberculosis Control Program (RNTCP) guidelines in India, the severely ill patients with extensive or bilateral pleural effusion are given treatment under category I which includes a thrice weekly regimen containing isoniazid, rifampicin, pyrazinamide and ethambutol, for initial two months followed by isoniazid and rifampicin for four month $[2(HRZE)_3/4(HR)_3]$ under direct supervision.[113] Unilateral or minimal TB effusions are given treatment under category III with thrice weekly isoniazid, rifampicin and pyrazinamide for the initial two months, followed by isoniazid and rifampicin for four months $[2(HRZ)_3/4(HR)_3]$ under direct supervision. Other guidelines have also recommended similar regimen, daily or thrice weekly.[114-116]

The WHO tuberculosis treatment guidelines 2009 recommend that both pulmonary and extrapulmonary tuberculosis need to be treated alike.[111] Patients should be categorized as new and previously treated. Thus, all new patients, irrespective of pulmonary or extrapulmonary TB, should receive a regimen containing 6 months of rifampicin and isoniazid. New patients may receive a daily intensive phase followed by three times weekly continuation phase $[2HRZE/4(HR)_3]$, if each dose is directly observed. Three times weekly dosing directly observed throughout therapy $[2(HRZE)_3/4(HR)_3]$ is another alternative, provided the patient is not living with HIV or in an HIV-prevalent setting. If there is high degree of isoniazid resistance, new TB patients should receive HRE in the continuation phase as an acceptable alternative to HR.[111]

The penetration of isoniazid in the pleural fluid is excellent, as of pyrazinamide is very poor, whereas the penetration of rifampicin is intermittent.[117] An average patient with TB pleural effusion becomes afebrile within 2 weeks of starting chemotherapy, but temperature elevations may persist for as long as 2 months.[118] Patients do not require any bed rest and need isolation only when there is associated parenchyma disease with positive sputum.[119] The incidence of pleural thickening at 6–12 months after beginning of therapy is approximately 50%. Residual pleural thickening is not related to the initial pleural fluid findings, patients with low glucose, high LDH and high cytokine level are only slightly more likely to have residual thickening.[120,121] However, in patients with loculated pleural effusion, there can be delayed resorption, even after completion of 6 month of treatment.[122]

Role of Corticosteroid

Prednisolone in a dose of 0.5 to 1 mg/kg per day has been used for a period ranging from 4 to 12 weeks, for an early resolution of clinical symptoms and signs (fever, chest pain and dyspnea).[123] Use of steroid has demonstrated a trend towards less residual pleural fluid at the end of treatment but there has been no difference in the development of residual pleural thickening or adhesion. There is insufficient data to determine whether steroids are effective in the treatment of TB pleural effusion.[124] The use of steroids in HIV/AIDS associated TB pleural effusion is not currently recommended because of the lack of survival benefit and an increased risk of Kaposi sarcoma.[125]

Role of Surgery

The emergence of drug resistance has redefined the role of surgery. Surgical intervention is required in a few cases of failure of medical therapy, complication of scarring and to establish a proper diagnosis.[126] Pleural effusion remain undiagnosed in 25% cases after routine investigations, this can be reduced to 4% by thoracoscopic biopsies.[126] Diagnostic, as well as therapeutic thoracentesis is the most common surgical procedure. Decortication is required when pleural thickening persists and causes significant clinical symptoms. Surgical interventions are also required for complications of empyema, bronchopleural fistula and others.

COMPLICATION OF TB PLEURAL EFFUSION

Pleural Thickening and Fibrothorax

Tubercular pleural effusion can lead to residual changes ranging from minimal pleural thickening to fibrothorax.[127] Fibrothorax may be associated with extensive volume loss of the underlying lung and ventilatory impairment.[128] Dull ache, heaviness and chest pain are other common complaints.

Empyema (Chronic Persistent Pleural Effusion)

Chronic TB empyema represents chronic, active infection of pleural space. Such complication can occur due to progress of primary TB effusion that is usually moderate to large in size. Empyema can also form due to direct extension of infection from thoracic lymph nodes or subdiaphragmatic foci, through hematogenous spread and following pneumonectomy. Chronic TB empyema may present as an abnormality on routine chest X-ray with bronchopleural fistula or as empyema necessitans.[129] Besides antituberculosis chemotherapy, intercostal tube drainage is necessary. Decortication, extrapleural pneumonectomy or thoracoplasty may also be required.

Empyema Necessitans

Empyema necessitans is formed by the break of empyema through the parietal pleura for spontaneous discharge of its content. It is usually formed in the subcutaneous tissues of the chest wall, but may sometimes occur at other sites, such as the esophagus, breast, retroperitonium, flanks, groins, pericardium and vertebra.[130] Surgical drainage is required, along with routine antitubercular treatment. Certain rare complications of tuberculosis include pseudochylothorax and chylothorax formation.[131-133]

Bronchopleural Fistula (BPF)

It is the direct communication between the pleural cavity and the bronchial tree or the lung parenchyma. Due to the effective modern antitubercular chemotherapy, BPF is an uncommon complication in current era. Fistulas are seen with old healed TB and after therapeutic pneumothorax, not followed by proper treatment.[134-136] Patients present with variable amounts of sputum production and fluctuating air fluid levels on serial X-rays. Confirmation of diagnosis can be made by injecting the methylene blue dye in the pleural space and demonstrating its presence in sputum or in the trachea-bronchial tree. Treatment requires adequate ATT, followed by surgical management.

In conclusion, TB pleural effusion is the second most common extrapulmonary form of tuberculosis. Patients usually present with acute illness, in most cases it is self-limiting. With adequate treatment, the outcome is usually good and the complications are few.

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157

Parapneumonic Effusion and Empyema

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INTRODUCTION

Pleural effusion frequently accompanies bacterial pneumonia occurring in up to 40% of hospitalized patients.[1] Bacterial pneumonias continue to be a cause of morbidity and mortality despite the availability of effective antibiotics and their widespread use. In the US, the annual incidence of bacterial pneumonia is around 4 million and a quarter of them require hospitalization.[2] Thus, the annual incidence of Parapneumonic Effusion (PPE) would amount to be substantial. Hospitalized patients with pleural effusion, accompanying bacterial pneumonias are 2.7 times more likely to have treatment failures than those without accompanying effusion.[3] Although PPE normally responds to antibiotic therapy, non-responsive effusions may progress to become purulent. Some of the increased morbidity and mortality in PPE occurs due to the mismanagement of pleural effusion.[4]

Historically, the first description of pleural infection has been ascribed to the Egyptian physician Imhotep around 3000 BC. It was Hippocrates in 500 BC, who recommended open drainage for the management of empyema.[5] This practice was replaced by the present day treatment of closed tube drainage only in the latter part of the 19th century.[6] Hippocrates also appeared to have understood that open drainage would be dangerous if the fluid had not become purulent. Enzymatic adhesiolysis for the management of loculated PPE was first described in 1950.[7] In the past two decades, people have used Video Assisted Thoracic Surgery (VATS) for the management of loculated PPE.[8]

DEFINITIONS

Empyema

Empyema is defined as pus within the pleural space. In its development, pleural fluid passes through stages of increasing host-defense activity and bacterial invasion. Not all infected pleural effusions progress to empyema.

Parapneumonic Effusion

Any pleural effusion associated with bacterial pneumonia, lung abscess or bronchiectasis is a PPE.

Complicated Parapneumonic Effusion

Complicated PPEs are conditions that do not resolve without therapeutic thoracentesis or tube throracostomy. Some of these are purulent (empyemas), while others have non-purulent pleural fluid.

PATHOGENESIS

The formation of an infected pleural space is a complicated interaction of the host defense mechanisms and the organisms. There are three distinct pathophysiological stages in PPE, reflecting the changing physiology within the pleural space. The distinctions between the stages are not sharply demarcated. There are different characteristics of pleural fluid seen during the different stages of PPE (Table 157.1).

TABLE 157.1: Characteristics of parapneumonic pleural effusions

Stages	*Macroscopic appearance*	*Pleural fluid characteristics*
• Simple parapneumonic	Clear fluid	pH >7.2 LDH <1000 IU/l Glucose >2.2 mmol/l No organisms on culture or Gram stain
• Complicated parapneumonic	Clear fluid or cloudy/turbid	pH <7.2 LDH >1000 IU/l Glucose >2.2 mmol/l May be positive Gram stain/culture
• Empyema	Frank pus	May be positive Gram stain/culture

LDH = lactate dehydrogenase

Adapted with permission from CWH Davies, FV Gleeson, RJO Davies, BTS guidelines for the management of pleural infection. Thorax 2003;58 (Suppl II):ii18–28[35]

Exudative Stage

This stage is characterized by accumulation of sterile fluid within the pleural space. This is in response to inflammation induced by bacterial infection within the lung parenchyma and the pleural membranes. Proinflammatory cytokines, such as interleukin-8 (IL-8) and Tumor Necrosis Factor-alpha (TNF-α), are released locally.[9] These probably act on the mesothelial cells and the capillaries within the visceral and the parietal pleura, leading to increased tissue and capillary permeability. The pleural fluid at this stage is a combination of interstitial tissue fluid and the microvascular exudate, characterized by low Lactate Dehydrogenase (LDH), normal glucose levels, and is not infected. If appropriate antibiotic therapy is instituted, the effusion is likely to resolve and intercostal drainage is not required.

Fibrinopurulent Stage

The fibrinopurulent stage occurs in response to bacterial invasion, usually as a consequence of inadequate or inappropriate therapy. Early on, there is increase in pleural fluid which contains polymorphs, bacteria and cellular debris. Later, there is formation of fibrin clots and fibrinous septae due to clotting factors from the serum entering the pleural space. This results in a heavily loculated pleural space that may be resistant to drainage with a single intercostal tube. As infection progresses, the pleural fluid pH and glucose levels reduce and LDH level goes up. Pus is formed by the lysis of bacteria and inflammatory cells.

Organizational Stage

The last stage is characterized by fibroblast proliferation and deposition of fibrous tissue on both the visceral and the parietal pleural membranes—the inelastic "pleural peel". This results in restriction of lung expansion and impairment of gas exchange. If untreated, there is potential for chronic infection resulting in penetration of fluid into the chest wall (empyema necessitans) or into the lung, resulting in a bronchopleural fistula.[10] The further course after organization is variable, some individuals undergo spontaneous healing with resolution of pleural thickening, others are left with "pleural peel".[11]

EPIDEMIOLOGY

Pleural infection is usually a complication of bacterial pneumonia. Independent risk factors for empyema include diabetes mellitus, alcohol abuse, gastroesophageal reflux disease, and intravenous drug abuse.[12] Empyema occurs more commonly during childhood, and in the elderly.[13, 14] Poor dental hygiene and aspiration may predispose to infection with anaerobic organisms.[15] It should also be appreciated that empyema can occur without an underlying bacterial pneumonia.[16-18] These may occur as a complication of surgery and pleural procedures such as thoracentesis or tube thoracostomy; presumably from unsterile technique.

BACTERIOLOGY

Published reports of PPEs have shown substantial variations in the bacteriology of isolated aerobes. It is likely that the introduction of antibiotics may have at least partially contributes to this variation. Over the years, the most commonly isolated organisms have varied between *Strep. pneumoniae, Strep. hemolyticus, Staph. aureus.*[19] In children, bacteriology is slightly different than in adults, *H. influenzae* being the most commonly isolated aerobe, the anaerobes being much less frequent.[20] Anaerobes require stringent transport process to preserve viability; the investigators with interest in culturing anaerobes have had greater success.[21]

Probably the most thorough bacteriological evaluation occurred during the Multicenter Intrapleural Sepsis Trial (MIST I); that evaluated the role of Streptokinase on a large number (454) patients, with complicated parapneumonic effusions.[22] Of the 434 patients who had pleural fluid cultures, 250 (58%) achieved a microbiological diagnosis using conventional methods.[23] In those with community-acquired infections, *Streptococcu*s was the commonest aerobe (52%), followed by *Staphylococcus* (10%), and gram-negative organisms (9%). Anaerobes were grown in 20% of the cases. Of hospital-acquired cases, the commonest aerobe was *Staphylococcus* (35%, nearly three quarter of which was methicillin-resistant) followed by gram-negative organisms (23%) and *Streptococcus* (18%).[23] Bacteriological diagnosis in 16% of the total samples was made by molecular diagnostic methods only.[23] In a quarter of the patients, organism could not be isolated. These results have implications for empiric therapy, and the choice of antibiotics. The important difference between the hospital and the community-acquired infections was that the predominant organism in the former was the *Staphylococcus*, and in the later the *Streptococcus;* a large fraction being *Methicillin-Resistant Staphylococcus aureus* (MRSA). The over all mortality was significantly higher in the hospital-acquired infections than in the community-acquired infections (Table 157.2).

TABLE 157.2: Description of the bacteriology of community and hospital-acquired pleural infection

Organism	*Community ascquired number (%)*	*Hospital acquired number (%)*
Aerobes		
Streptococcus	176 (52%)	11 (18%)
Streptococcus intermedius– anginosus–constellatus (“milleri”) group	80	4
Streptococcus pneumoniae	71	3
Streptococcus pyogens	9	0
Other *Streptococcus* species	16	4
Staphylococcus	35 (10%)	21 (35%)
S. aureus	27	6
Methicillin-resistant *S. aureus*	7	15
S. epidermidis	1	
Enterococcus spp.	4 (1%)	7 (12%)
Gram-negatives	29 (9%)	14 (23%)
Escherichia coli	11	2
Other coliforms	4	6
Proteus	6	2
Enterobacter spp.	5	1
Pseudomonas aeringosa	3	3
Anaerobes	67 (20%)	5 (8%)
Fusobacterium	19	1
Bacteroides	16	1
Peptostreptococcus	9	
Mixed anaerobes, unclassified	8	2
Prevotella spp.	13	1
Clostridium spp.	2	
Mycobacterium tuberculosis	2 (1%)	
Actinomyces spp.	4 (1%)	
Other*	17 (5%)	2 (3%)
Total	336	60

Both infections differ bacteriologically from pneumonia.

* Includes Burkholderia anthina, *Eikenella, Haemophilus influenzae,* Oral bacterium, *Pasteurella multocida, Klebsiella spp.*

Nick A Maskell, Sarah Batt, Emma L Hedley, et al. The Bacteriology of Pleural Infection by Genetic and Standard Methods and Its Mortality Significance. American Journal of Respiratory and Critical Care Medicine. 2006.[22]

CLINICAL FEATURES AND DIAGNOSIS

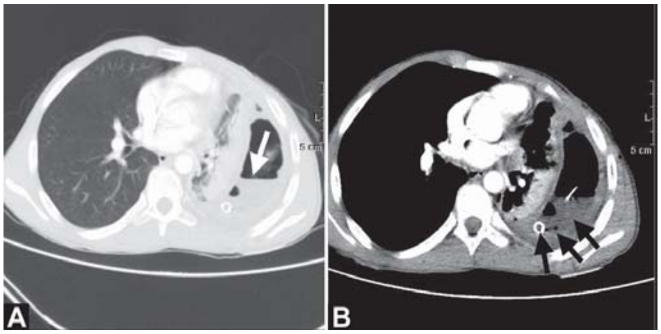
Patients with aerobic pleural infection usually present with features of pneumonia with an acute febrile illness, cough, purulent sputum and dyspnea. Pleuritic chest pain (due to parietal pleural involvement) is present in around 60% of patients. Absence of pain does not exclude the diagnosis of pleural infection.[1] Anaerobic infections present often in an indolent manner with weight loss, anorexia and malaise.[24]

There are no clinical criteria that could distinguish between pneumonia with or without PPE. Therefore, PPE should be considered while evaluating all patients with pneumonia, particularly those who are unresponsive to antimicrobial therapy. Further, not all patients with PPE have an acute illness.

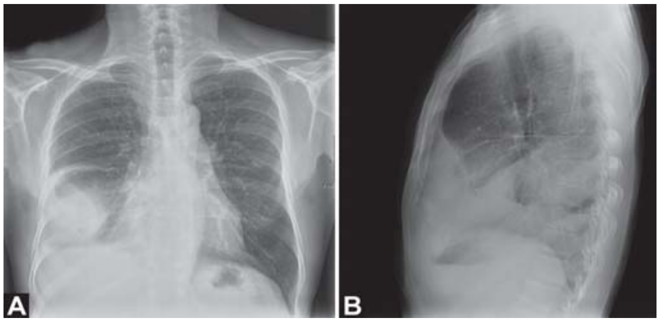
Radiological Investigations

Chest radiograph (PA view) (Figs 157.1A and B) can detect significant effusion and is often the only required imaging for its detection. Effusion may be free or loculated, may show evidence of air-fluid level. Empyema may give the appearance of pleural mass or tumor within the lung, when the collection occurs within a fissure. Computed Tomography (CT) scan of the chest is used to detect and quantitate minimal effusion. In resource limited settings like in India, blunting of the costophrenic angle on a lateral chest radiograph or obscuration of the dome of the diaphragm are considered sufficient to detect the presence of pleural fluid. Decubitus views may complement the information obtained from the erect chest radiographs.

In the lateral decubitus film, the amount of fluid can be roughly quantitated by measuring the distance between the chest wall and the lower part of the adjacent lung. If the length is less than 10 mm, the effusion is deemed to be too small to be clinically significant. Such effusions resolve with antibiotics alone.[1] CT evidence of pleural thickening is present in 80-100% of the empyemas (Figs 157.2A and B), so, its presence would favor this diagnosis, when PPE is being evaluated. “Split pleura sign” on contrast CT enhancement of visceral and parietal pleura differentiates empyema from a peripherally situated lung abscess[25, 26] (Fig. 157.3)



Figs 157.1A and B: CT thorax (left-lung window, right-mediastinal window) showing left sided loculated pleural effusion. Single arrow shows intercostal drainage tube; double arrow shows thickened and enhanced parietal pleura; triple arrow shows collapsed lung



Figs 157.2A and B: Chest radiograph PA and lateral views showing right sided loculated pleural effusion and fluid extending into the fissures

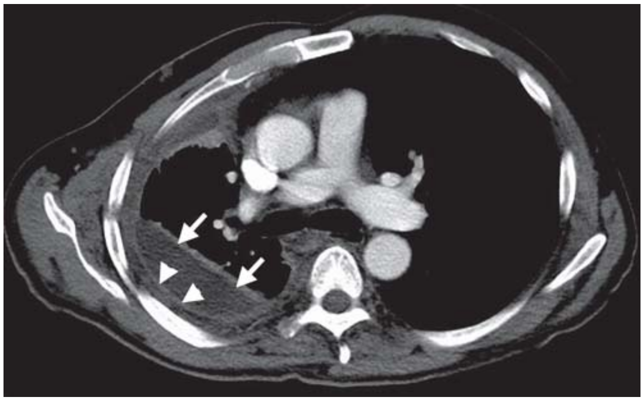


Fig. 157.3: CT thorax (mediastinal window) showing split-pleura sign. Arrow heads show thickened and enhanced parietal pleura and arrows show enhanced visceral pleura

Ultrasonography is an excellent method to assess pleural effusion. It can also help to quantify the amount of effusion by assessing the depth of fluid. It can also be used at the bedside for example in the Intensive Care Units (ICUs). Empyema results in dense echogenicity and loculations which are detectable on ultrasonogram. It is also helpful in ensuring successful pleural fluid aspiration in as high as 97% of the cases[27] (Fig. 157.4).

Thoracocentesis

Clinical features and routine blood tests are poor predictors of the need for drainage; the delay in instituting

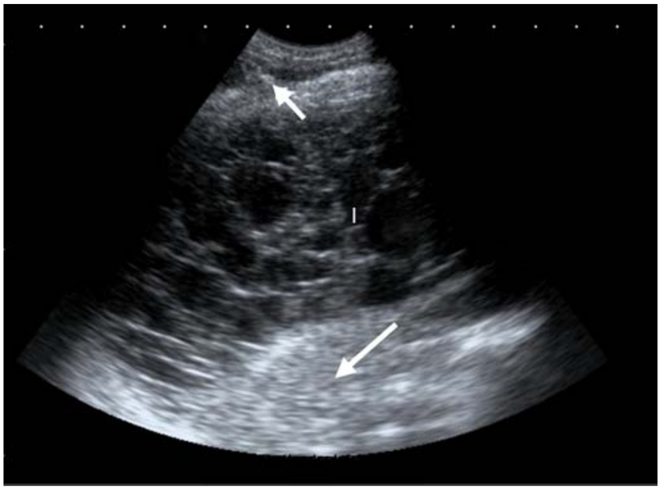


Fig. 157.4: Ultrasonogram chest showing multiple loculations. Short arrow indicates needle performing biopsy of the parietal pleura. Long arrow indicates collapsed lung

adequate drainage increases the morbidity. It is thus recommended that diagnostic pleural aspiration should be performed in all patients with PPE.[28] The exception to this rule is a small pleural effusion (<10 mm on a lateral decubitus chest radiograph), which may resolve with antibiotics alone.[29,30] When the effusion is small and does not completely cover the dome of the diaphragm in a chest radiograph (P-A view), it is safer to perform an ultrasound-guided aspiration. It is more accurate and reduces the patient discomfort.[31] The presence of frank pus on thoracentesis is diagnostic of empyema, no further tests are needed to confirm the diagnosis. If not, the pleural fluid should be sent for microbiological and biochemical studies. Pus from empyema is also sent for microbiological cultures to aid in the choice of antibiotics. Tuberculous etiology should always be kept in mind while evaluating empyma in high TB prevalence settings. It is our practice to perform closed pleural biopsy in all patients with exudative effusions or empyema, unless the effusion is of acute onset and preceded by a documented pneumonia. The biopsy yield in tuberculosis is higher than the pleural fluid smears, when positive it aids in prompt commencement of anti-TB treatment.

PLEURAL FLUID ANALYSIS

In paraneumonic effusion, the fluid may vary between clear or straw colored and odorless to thick, purulent and foul smelling. Only around 11% of effusions exhibit foul smell.[32] Foul odor could indicate an anaerobic or mixed (aerobic and anaerobic) etiology. Absence of foul smell however does not rule out an anaerobic infection.[32, 33] After gross examination, the pleural fluid is tested for proteins, LDH, glucose and pH. Another sample is sent for microbiological studies—Gram stain, aerobic cultures, mycobacterial and fungal cultures, as deemed necessary. If the resources permit, anaerobic cultures too should be done on all exudative effusions of undetermined etiology. In countries, like India, with a high prevalence of tuberculosis, AFB smears and mycobacterial cultures are also important. The pleural fluid from PPEs and empyemas is an exudate; presence of a transudate on the basis of the light's criteria suggests an alternative diagnosis. The presence of a predominance of lymphocytes should raise the possibility of malignancy or tuberculosis. Fluid drainage is imperative in the presence of purulence of fluid. In the absence of purulent fluid and of positive microbiology, biochemical markers are used as surrogates for evidence of active pleural infection.

It is well understood that PPE with an acidic pH (< 7.20) is more likely to run a complicated course with loculated fluid collections and empyema when compared to an effusion with pH greater than 7.20. Intercostal drainage is instituted to avert this complication, antibiotic treatment alone may not suffice.[29,34] Furthermore, there is more likelihood of the need for surgical intervention in those with an acidic pH (< 7.20).

Several investigators have looked at the evidence for the use of biochemical markers.[35] Pleural fluid pH emerged as the best predictor of a complicated course in a meta-analysis that critically assessed the markers to separate effusions that were likely to run a simple course from those that were likely to run a complicated course (i.e. became frankly purulent, nonpurulent fluid requiring drainage and nonpurulent fluid progressing to frank pus later in the clinical course or at autopsy).[36] The pleural fluid glucose and LDH did not improve the diagnostic accuracy, reliance on these values (glucose <35 mg/dL and LDH >1000) is recommended only when accurate pH values not available. More recently, these findings have been confirmed; the pleural fluid pH had the highest accuracy followed by pleural fluid glucose and LDH and pleural fluid volume.[37] Poor prognostic and other factors that distinguished complicated from uncomplicated PPE could be summarized as pH less than or equal to 7.2, pleural fluid glucose less than or equal to 60 mg/dL and pleural fluid LDH greater than or equal to 3 times upper limit for serum. Current guidelines do not recommend institution of tube drainage in effusions with pH of greater than 7.20 (Table 157.3).[30,35] If there is no response to antibiotic treatment, repeat pH

TABLE 157.3: Categorizing risk for poor outcome in patients with PPE

	Pleural space anatomy			*Pleural fluid bacteriology*			*Pleural fluid chemistry**	*Category*	*Risk of poor outcome*	*Drainage*
A_0	Minimal, free-flowing effusion (<10 mm on lateral decubitus)[†]	AND	B_x	Culture and Gram stain results unknown	AND	C_x	pH unknown	1	Very low	No[‡]
A_1	Small-to-moderate free-flowing effusion (>10 mm and <½ hemithorax)	AND	B_0	Negative culture and Gram stain[§]	AND	C_0	pH ≥7.20	2	Low	No[‖]
A_2	Large, free-flowing effusion (>½ hemithorax)[¶] loculated effusion,[#] or effusion with thickened parietal pleura**	OR	B_1	Positive culture or Gram stain	OR	C_1	pH <7.20	3	Moderate	Yes
			B_2	Pus				4	High	Yes

*pH is the preferred pleural fluid chemistry test, and it must be determined using a blood gas analyzer. If a blood gas analyzer is not available, pleural fluid glucose should be used (P_0 glucose $ 60 mg/dL; P_1 glucose, 60 mg/dL). The panel cautions that the clinical utility and decision thresholds for pH and glucose have not been well-established.

[†] Clinical experience indicates that effusions of this size do not require thoracentesis for evaluation, but will resolve.

[‡] If thoracentesis were performed in a patient with A_0 category pleural anatomy and P_1 or B_1 status found, clinical experience suggests that the P_1 or B_1 findings might be a false-positive. Repeat thoracentesis should be considered if effusion enlarges and/or clinical condition deteriorates.

[§] Regardless of prior use of antibiotics.

[‖] If clinical condition deteriorates, repeat thoracentesis and drainage should be considered.

[¶] Larger effusions are more resistant to effective drainage, possibly because of the increased likelihood that large effusions will also be loculated.

#Pleural loculations suggest a worse prognosis.

**Thickened parietal pleura on contrast-enhanced CT suggest presence of empyema.

(Gene L Colice, Anne Curtis, Jean Deslauriers, et al. Medical and surgical treatment of parapneumonic effusions: An evidence-based guideline.[30] Chest. 2000; 118:1158-71 with permission)

measurement is recommended.[28] The presence of bacteria demonstrated by smear or culture of pleural fluid should merit treatment with intercostal drainage regardless of pleural fluid pH.

False positive acidic pH measurement can be seen in malignant effusion, tuberculosis, rheumatoid and lupus pleuritis. Since pleural fluid pH is crucial to decision making, the fluid should be collected in a heparinized syringe, without contamination with lignocaine (which is acidic), and analyzed immediately using a blood gas analyzer.[38] Other methods of measuring pH, such as using litmus paper, have been shown to be unreliable.[39] Measurement of pH should not be performed on obviously purulent pleural fluid; it may damage the blood gas analyzer. Moreover, tube drainage should be instituted regardless of the pH value in case of purulent effusion.

The PPE caused by *Proteus* is known to present paradoxically with alkalotic pleural fluid pH, because the proteus split urea to produce ammonia.[40] Recent studies have evaluated the possible role of markers for complicated PPEs. For example, TNF-α using a cut off of greater than 80 µg/ml and polymorphonuclear elastase (PMN-E) at a cut off of greater than 3,500 µg/ml have shown a good sensitivity and specificity.[41-43]

TREATMENT

Prompt recognition is essential for optimal management of pleural infection. Antibiotic therapy and drainage of

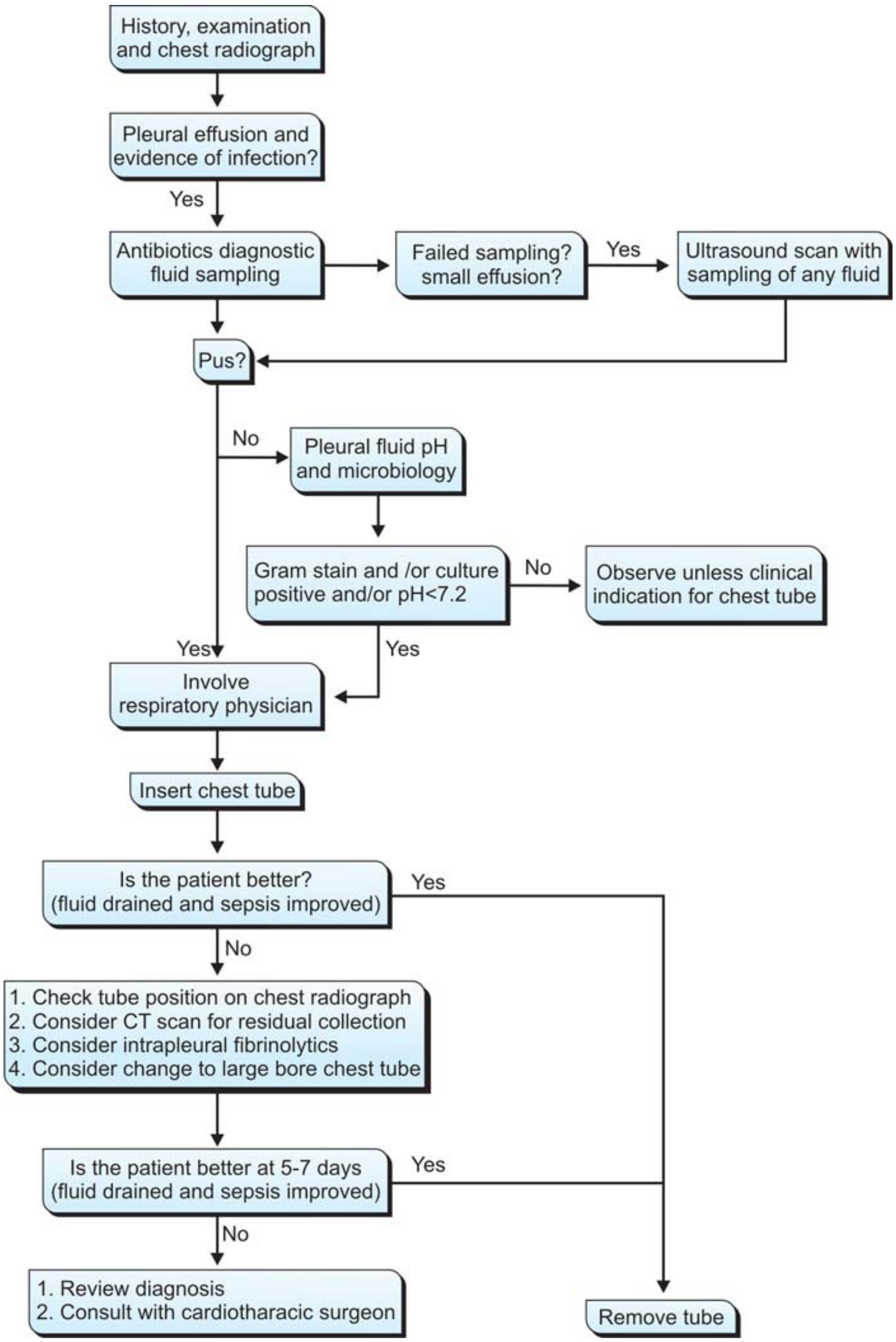

History, examination and chest radiograph
Pleural effusion and evidence of infection?
Yes
Antibiotics diagnostic fluid sampling
Failed sampling? small effusion?
Yes
Ultrasound scan with sampling of any fluid
Pus?
No
Pleural fluid pH and microbiology
Gram stain and /or culture positive and/or pH<7.2
No
Observe unless clinical indication for chest tube
Yes
Yes
Involve respiratory physician
Insert chest tube
Is the patient better? (fluid drained and sepsis improved)
Yes
No
1. Check tube position on chest radiograph
2. Consider CT scan for residual collection
3. Consider intrapleural fibrinolytics
4. Consider change to large bore chest tube
Is the patient better at 5-7 days (fluid drained and sepsis improved)
Yes
No
1. Review diagnosis
2. Consult with cardiotharacic surgeon
Remove tube

Fig. 157.5: Diagnostic algorithm for the management of patients with pleural infection.[35] (Davies CWH, Gleeson FV, Davies RJO. BTS guidelines for the management of pleural infection. Thorax. 2003; 58(Suppl II):ii18-ii28 with permission

fluid collection constitute the cornerstone of management. The British Thoracic Society has drawn an excellent algorithm for the management of patients with pleural infection (Fig. 157.5).

Antibiotic Treatment

All patients suspected of having pleural infection need treatment with antibiotics.[35] While it is ideal to prescribe antibiotics based on the results of pleural and/or blood cultures, this causes a delay in the commencement of treatment. Therefore, appropriate "empiric" antibiotic treatment should commence for all patients. Selection of antibiotics should be based on Gram stain results, presence of hospital acquired versus community acquired infection and on the clinical severity of the illness. Antibiotic penetration into the pleural space is variable in the descending order from metronidazole, penicillin, clindamycin, vancomycin, ceftriaxone to gentamycin and other aminoglycosides.[44] Other studies showed that quinolones and clarithromycin had good penetration into the pleural space.[45, 46]

Cultures do not always grow pathogens, but may remain negative in up to 42% of the cases.[23] In community-acquired infection, the likely organisms include *Streptococcus milleri, Streptococcus pneumoniae,* staphylococci, and *Haemophilus infiuenzae.* Although the *S. milleri* group is highly sensitive, a substantial proportion of the others are resistant to β-lactams.[47] "Atypical" bacteria constitute an exceedingly rare cause of pleural infection, although they can cause a simple PPE, anaerobic infection occurs in approximately 10%.[48] When cultures are negative, antibiotics should cover community acquired or hospital acquired pathogens as the case may be, anaerobes should be covered too. Antibiotic choice should be directed by local policy guided by standard international and national recommendations one such guideline is provided (Table 157.4).

Empirical antibiotic regimen should be rationalized once culture results become available. Given the difficulty in culturing anaerobic organisms, continuation of anti-anaerobic therapy is usually necessary. Direct data do not exist on how long to treat empyema. Most physicians continue antibiotic treatment for at least 3 weeks, with at least 1 week of intravenous antibiotics. Support for this recommendation comes mostly from the experience in treatment of lung parenchymal abscesses.[47]

Closed Intercostal Drainage

Open drainage as a treatment for infected pleural effusions was established since the time of Hippocrates, and this practice continued till the influenza epidemic of 1917-19, when the closed-tube drainage was first introduced.[49] There is consensus of opinion regarding the need of pleural space drainage under the following circumstances:

- Frank pus or turbid/cloudy fluid within the pleural space[30, 35]
- Presence of organisms identified by gram stain or culture from (non-purulent) effusion
- Effusion fluid with a pH less than 7.2
- Large uncomplicated effusions for relief of dyspnea.

Repeated thoracentesis is an alternative, albeit a less popular strategy compared to intercostal drain insertion. It facilitates increased mobility and lower complication, in particular infection rates. This management strategy has support from experimental and clinical trials.[50-52] However, there is no randomized trial that has compared this approach with tube drainage.

Many experienced clinicians believe that a large-bore chest drain (>20 French) is necessary to treat empyema. However, studies with smaller bore catheters (11-14 French) have shown equal success.[31,53-56] CT or ultrasound guided insertion of drain may be more optimal for an appropriate placement of the tube. In loculated effusions, the tube can be placed under guidance into the biggest locula. The role of suctioning and flushing the drainage tube with around 30 ml of

TABLE 157.4: Illustrative antibiotic regimens for the initial treatment of culture negative pleural infection

Origin of infection	*Intravenous antibiotic treatment*	*Oral antibiotic treatment*
Community acquired culture negative pleural infection	Cefuroxime 1.5 g tds IV + Metronidazole 400 mg tds orally or 500 mg tds IV Benzyl penicillin 1.2 g qds IV + Ciprofloxacin 400 mg bd IV Meropenem 1 g tds IV + Metronidazole 400 mg tds orally or 500 mg tds IV	Amoxycillin 1 g tds + Clavulanic acid 125 mg tds Amoxycillin 1 g tds + Metronidazole 400 mg tds Clindamycin 300 mg qds
Hospital acquired culture negative pleural infection	Piperacillin + Tazobactam 4.5 g qds IV Ceftazidime 2 g tds IV Meropenem 1 g tds IV ± Metronidazole 400 mg tds orally or 500 mg tds IV	Not applicable

No particular regimen is the single "ideal" choice. Drug doses should be appropriately adjusted in the presence of renal or hepatic failure. CWH Davies, FV Gleeson, RJO Davies. BTS guidelines for the management of pleural infection. Thorax. 2003; 58 (Suppl II):ii18-ii28[35] with permission sterile saline four times daily can be helpful, particularly when a small bore chest tube is used. The optimal timing of drain removal is unknown, although clinical response is clearly the most important parameter. It is our practice to remove the drainage tube, when the drainage is less than 50 ml; provided the fluid is clear and non-turbid. If on the other hand the fluid is turbid, we remove it only after the drainage reduces to less than 10 ml. If there is inadequate drainage or failure of resolution with a single chest drain, there may be a need to re-position the tube after radiological assessment or placement of additional tubes. Failure of chest tube drainage heralds increased morbidity and mortality.[57]

Intrapleural Fibrinolytics

Loculated pleural collections pose challenge in the treatment, by hampering efforts at drainage which can also lead to failure of "medical treatment". Instillation of intrapleural fibrinolytics has been practiced for more than 50 years.[58] Over the years, streptokinase, streptodornase, urokinase and tPA have been used to break fibrin adhesions and facilitate drainage.

The apparent benefit of fibrinolytics was supported by five randomized studies in adults which showed success rates between 60% and 95%.[59-62] Although fibrinolytics conferred benefits, such as decreased hospital stay, improved radiographic appearance and decreased rate of surgery, the benefits were variable and inconsistent.[63] Thus, doubts began to arise about the unequivocal benefits of fibrinolytics in pleural infection. Subsequently, the MIST 1 study, a large trial across 52 UK hospitals; showed no difference between intrapleural streptokinase and saline.[22] The routine use of fibrinolytic agents at this point is not supported by evidence. Nevertheless, intrapleural fibrinolytics probably aid in thoracic decompression in the case of large infected pleural collections and alleviate respiratory embarrassment in this situation.[22] The dosage schedule for instillation of streptokinase is 250 000 units (once or twice daily for 3 days) and for urokinase, 100 000 units (once daily for 3 days).

Surgical Treatment

Medical therapy fails in up to 30% of patients with empyema.[22,64] No good-quality data exists on the optimum timing of surgery and indications for reference.[35] Patients who do not improve clinically and radiologically after 7 days of standard treatment, can derive benefit from surgical interventions.[35,57] The Video-Assisted Thoracic Surgery (VATS) is the possible next step in the treatment of empyema when tube drainage has failed. The adhesions and septae can be divided to aid drainage, although this may need to be done early.[65] More recent series report higher success rates with VATS.[66,67] There are no randomized trials comparing VATS with thoracotomy, its role in the treatment of early disease as well as in chronic empyema is yet to be defined.[68] The outcome of thoracotomy and decortication is generally good, with success rates of up to 95% in this highly selected group, with significant associated complications.[64,69] Rib resection and open surgical drainage under local anesthesia are possible in patients who are unfit for general anesthesia.

Decortication is likely the only treatment option in cases of chronic empyema with persistent sepsis and pleural fibrosis.[70]

Nutrition

Patients with empyema enter a catabolic state; hence, good nutrition is vital. It has been observed that patients with low serum albumin have a worse outcome from empyema.[71] Although no trial has addressed this issue, an aggressive nutritional support is important for the patients.

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Pneumothorax

Uma Devaraj, George D'Souza

INTRODUCTION

A pneumothorax is air in the pleural space. Pneumothoraces can be classified as "spontaneous", which occur without antecedent trauma or other obvious cause, and "traumatic", which occur from direct or indirect trauma to the chest (Fig. 158.1).

Traumatic pneumothorax is further subcategorized as "iatrogenic", which is a consequence of a diagnostic or therapeutic maneuver. Spontaneous pneumothoraces are subdivided into primary (PSP) and secondary (SSP) spontaneous pneumothoraces. Primary spontaneous pneumothoraces occur in otherwise healthy individuals, though many have occult lung disease as evidenced by subpleural blebs on Computed Tomography (CT) scans. Secondary spontaneous pneumothoraces occur as a complication of underlying lung disease.

Some Definitions

Recurrent pneumothorax: A recurrent pneumothorax is one that occurs on the same side after seven days of the initial resolution. A pneumothorax is considered "persistent" if the air leak lasts for more than five days.

Closed pneumothorax: A closed pneumothorax[1] is one in which the alveolar pleural communication is sealed. The degree to which the lung collapses depends on the volume of air introduced during the air leak.

Tension pneumothorax: The intrapleural pressure rises in proportion to the volume of air in the pleural cavity and when it is above atmospheric pressure, it is called tension pneumothorax.

Open pneumothorax: An open pneumothorax[1] communicates with the atmosphere and results in pendulum breathing (shunting of the physiological dead space between the two lungs) in addition to lung collapse.

Pathophysiology

Normally, the pressure in the pleural space is negative with reference to the atmospheric pressure during the entire respiratory cycle. The negative pressure is due to the inherent tendency of the lungs to collapse and of the chest wall to expand. The resting volume of the lung, the Functional Residual Capacity (FRC), is the volume at which the outward pull of the chest wall is equal, but opposite in direction, to the inward pull of the lung with the respiratory muscles relaxed. Pneumothorax causes alterations of lung volumes and mechanics; for example on FRC as shown in Fig. 158.2.

The negative intrapleural pressure is not uniform throughout the pleural space; a gradient of 0.25 cm of water per centimeter exists from the base to the apex of the lung. This result in greater distension of the alveoli at the apex as the pressure is more negative at the apex. This makes the apex vulnerable due to greater swings in pressure during a respiratory cycle.

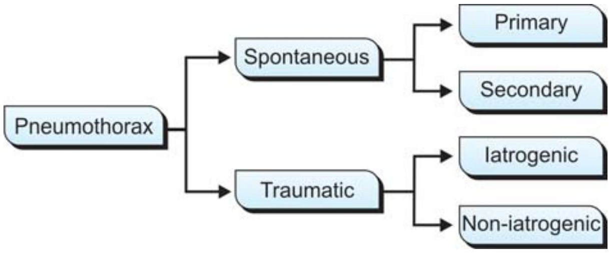


Fig. 158.1: Classification of pneumothorax

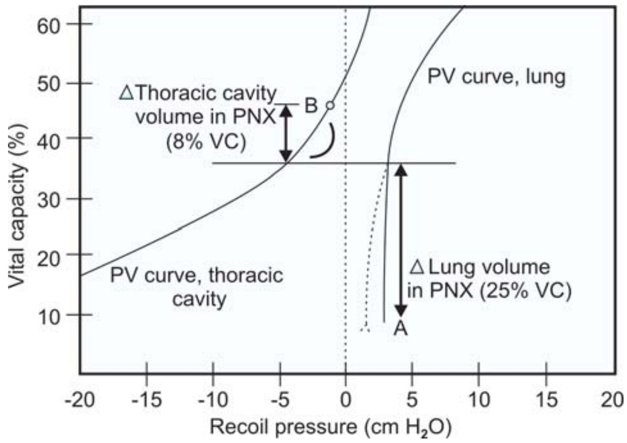


Fig. 158.2: Influence of pneumothorax on the volumes of the lung and hemithorax. In this illustration, the pneumothorax has caused the intrapleural pressure to rise from -5 to -2.5 cm H_2O. The change in lung and thoracic cavity volumes depends on their respective pressure volume curves [(dashed lines) to new volumes for the lung (A) and thoracic cavity (B)]. The volume of the hemithorax becomes larger by 8% for a fall in lung volume by 25% of VC because of the difference in slopes of the two pressure volume (PV) curves.
PNX, Pneumothorax[2]

A bleb is a gas-containing space within the visceral pleura and is usually seen at the apex. A bulla is a space lined partly by thickened fibrotic pleura and partly by fibrous tissue within the lung itself.[3] Air reaches the pleural space either due to rupture of a subpleural bulla or bleb, rupture of overdistended alveoli into the adjacent bronchovascular sheath medially to produce pneumomediastinum, which may be accompanied by subcutaneous emphysema or pneumothorax, or rupture of overdistended alveoli that can dissect air from alveoli to the peripheral portion of the lung.

The pleural pressure is always less than the alveolar pressure and the atmospheric pressure owing to the elastic recoil of the lung. Therefore, if a communication develops between the pleural space and an alveolus or between the pleural space and the atmosphere, air will flow into the pleural space until a pressure gradient no longer exists or until the communication is sealed.

At FRC, the thoracic cavity is below its resting volume and the lung is above its resting volume. Hence with a pneumothorax, the thoracic cavity enlarges and the lung becomes smaller. This results in the main physiologic consequences of decreased vital capacity and arterial PO_2. The reduction in arterial PO_2 appears to be caused by areas with low ventilation-perfusion ratios, anatomic shunts and occasionally, alveolar hypoventilation.[4] The decreased vital capacity is usually well tolerated in patients with PSP whereas it can precipitate respiratory failure in patients with SSP. The total lung capacity, functional residual capacity and diffusing capacity are also reduced, although less than the vital capacity.[3] When perfusion to the collapsed lung is preserved, there is an increase in pulmonary shunt and substantial hypoxemia. If perfusion to the collapsed lung is reduced by hypoxic vasoconstriction, hypoxemia may be minimal. In general, pneumothoraces occupying less than 25% of the hemithorax are not usually associated with significant shunts. Redistribution of pulmonary blood flow results in improvement of hypoxemia within 24 hours, despite the extent of the pneumothorax in most circumstances.

Resolution of Pneumothorax

Normally, there is no air in the pleural space as the sum of all the partial pressures in the capillary blood with a person breathing room air is about 706 mm Hg (PN_2 + PO_2 + PH_2O + PCO_2 =573 + 40 + 47 + 46 = 706) which is less than atmospheric pressure. When there is air, it is reabsorbed from the pleural space by simple diffusion into the venous blood. The rate of gas resorption depends on the following:

1. The pressure gradient for the gases between the pleural space in relation to the venous blood
2. The diffusion properties for the gases present in the pleural space
3. The area of contact between the pleural gas and pleura
4. The permeability of the pleural surface (i.e. fibrotic pleura absorbs less than a normal pleura)

The net gradient for gas absorption, from pleural space into capillary blood, is only 54 mm Hg (760 to 706) on assuming that the pleural pressure is approximately zero when there is a pneumothorax. If the patient is given 100% oxygen, the sum of all the partial pressures in the capillary blood will probably fall below 200 mm Hg (the PN_2 will approach zero, whereas the PO_2 will remain under 100 mm Hg; PN_2 + PO_2 + PH_2O + PCO_2 = 0 + 100 + 47 + 46 = 193). Therefore, the net gradient for gas absorption will exceed 550 mm Hg or be 10 times greater than it was with the patient breathing room air. The solubility and diffusion properties of different gases vary considerably and the speed of reabsorption depends on the type of gas. Oxygen is absorbed 62 times faster than nitrogen, the slowest gas to be reabsorbed. Carbon dioxide is absorbed 23 times faster than oxygen, and carbon dioxide and water vapor equilibrate almost instantaneously. This can be made use of to hasten the absorption of a pneumothorax, by making the patient breathe 100% oxygen.

PRIMARY SPONTANEOUS PNEUMOTHORAX

Primary Spontaneous Pneumothorax (PSP) occurs more commonly in men between ages of 20–40 years of age. Women tend to develop PSP, 2–5 years earlier than men though they have a much lower incidence with a male: female ratio of 2.5:1.[3]

Incidence

The incidence of PSP reported in the Western literature is 7.4–18 cases/1,00,000 population per year in males and 1.2–6 cases/1,00,000 population per year in females (age-adjusted incidence).[5] The reported incidence of PSP among all patients presenting with spontaneous pneumothorax have been widely variable in the few studies available from India and has ranged from 12.5 to 64%.[6] The annual incidence for primary and secondary spontaneous pneumothorax are 20.0 and 80.0 per 1,00,000 hospital admissions, respectively.[6] This figure probably overestimates the true incidence of SP in the general population, since the study is hospital based with the denominator being all hospitalized patients.

Etiology

Though PSP by definition occurs in people without underlying lung disease, most often it is associated with the rupture of subpleural blebs or bullae on the apical portion of the upper lobes. Blebs can be found in more than 75% of patients undergoing thoracoscopy for treatment of PSP. It is however unclear how often these lesions are actually the site of air leakage. Fluorescein-Enhanced Autofluorescence Thoracoscopy (FEAT), a novel method involving an administration of fluorescein aerosol administration, followed by sequential white light and blue light thoracoscopy using a blue light, shows FEAT-positive lesions that are normal when viewed under normal White-light Thoracoscopy (WLT).[7] Several areas of subpleural fluorescein accumulation, undetectable by normal WLT, were observed. This observation supported the concept that air leakage in PSP is not necessarily associated with, or located at blebs or bullae, but can occur at areas that have a completely normal appearance during WLT.

Only in a small number, blebs are ruptured at the time of thoracoscopy or surgery. In the remaining, other lesions are present, called “pleural porosity”; these are areas of disrupted mesothelial cells at the visceral pleura, replaced by an inflammatory elastofibrotic layer with increased porosity, allowing air to leak into the pleural space.

The development of blebs, bullae and areas of pleural porosity may be linked to a variety of factors. These include distal airway inflammation, hereditary predisposition, anatomical abnormalities of the bronchial tree, ectomorphic physiognomy with the more negative intrapleural pressures and the relative apical ischemia, low body mass index and caloric restriction and abnormal connective tissue.

There is a significantly increased risk of spontaneous pneumothorax in smokers. When four separate series of patients with PSP were combined, (461 of 505 patients) 91% with PSP were smokers or ex-smokers. The occurrence of a spontaneous pneumothorax is related to the level of cigarette smoking. In men there appears to be a dose effect with the relative risk of a pneumothorax, seven times higher in light smokers (1–12 cigarettes/day), 21 times higher in moderate smokers (13–22 cigarettes/day) and 102 times higher in heavy smokers (>22 cigarettes/day) than in nonsmokers.[8]

Patients with PSP tend to be taller and thinner than control subjects. A study on military recruits who developed spontaneous pneumothorax found that they were, on average, 2 inches taller and 25 pounds lighter than the typical military recruit.[2] As pleural pressure drops by 0.20 cm of H_2O per cm of vertical height, pleural pressure is more negative at the apex of lung in tall people; therefore the alveoli at their lung apex are subjected to a greater mean distending pressure. In the long run, this could lead to the formation of subpleural blebs in those tall people who are genetically predisposed to bleb formation.

In women, smoking and body shape appear to be less relevant than in men. Catamenial pneumothorax is seen in about 3% of PSP in women.[9] There are few reports (56 so far) of pneumothorax in pregnancy.[10] Another cause exclusive to females is lymphangioleiomyomatosis.

Genetics

Various studies have shown an important genetic contribution in the development of spontaneous pneumothorax. Some cases are due to an autosomal dominant gene[11] with incomplete penetrance, the penetrance being lower in women (21%) than in men (50%). There also appears to be an inheritance due to an X-linked recessive gene.[12]

Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant condition characterized by the presence of facial fibrofolliculomas and pulmonary cysts which may be associated with spontaneous pneumothorax and renal tumors. BHD is caused by loss of functional mutations in the folliculin (FLCN) protein.[13] The molecular function of

FLCN is still largely unknown and debated. There is opposite and conflicting evidence of the role of FLCN in mammalian target of rapamycin signaling/phosphorylated ribosomal protein S6 (p-S6) activation.

Other genetic conditions associated with spontaneous pneumothorax are lymphangioleiomyomatosis,[14] alpha-1 antitrypsin deficiency[15] and cystic fibrosis.[16] Pneumothorax also occurs with increased frequencies with Marfan syndrome,[17] Ehlers-Danlos syndrome[18] and homocystinuria.[19]

Clinical Manifestations

PSP occurs most commonly between 20 and 40 years, and rarely after 40 years. Most often PSP occurs during rest rather than exertion. The main symptoms are chest pain and dyspnea. Chest pain is acute in onset, pleuritic in nature and localized to the side of pneumothorax. Though onset is acute, there is a delay in seeking medical attention as the symptoms subside in the next 24 hours. In one series, 18% of patients waited more than one week after development of symptoms before seeking medical help. Other uncommon manifestations due to a pneumothorax are cough, hemoptysis, orthopnea and Horner's syndrome.[3]

The physical findings depend on the size of the pneumothorax; small pneumothoraces (occupying less than 20%) may have normal physical findings. In PSP, the vital signs are usually normal, except for moderate tachycardia. A tension pneumothorax should be suspected if the pulse rate exceeds 140 beats/minute, or if hypotension, cyanosis or electromechanical dissociation is present.

On examination of the chest, the ipsilateral hemithorax is larger and has reduced respiratory movements than the contralateral side. On the affected side, tactile fremitus is absent, the percussion note is hyperresonant and the breath sounds are absent or reduced. The lower edge of the liver may be shifted inferiorly with a right-sided pneumothorax. With a large pneumothorax, the trachea may be shifted toward the contralateral side. Hamman's sign which is a crunching or clicking noise heard synchronous with the heartbeat, may be auscultated with a pneumothorax (particularly on the left side) or pneumomediastinum and is influenced by respiration and body position.[20]

Lab Investigations and Diagnosis

Diagnosis can be confirmed in the majority of cases with an upright posteroanterior chest radiograph demonstrating a pleural line. Chest radiograph shows collection of lucent gas, with absent pulmonary vascular markings, between the outer margin of visceral pleura (lung) and parietal pleura (chest wall) (Fig. 158.3). Expiratory radiographs add little and are not recommended in diagnosis of pneumothorax any longer.[21] The lateral decubitus radiograph is superior to erect or supine chest radiograph and is as sensitive as CT scanning in pneumothorax detection.

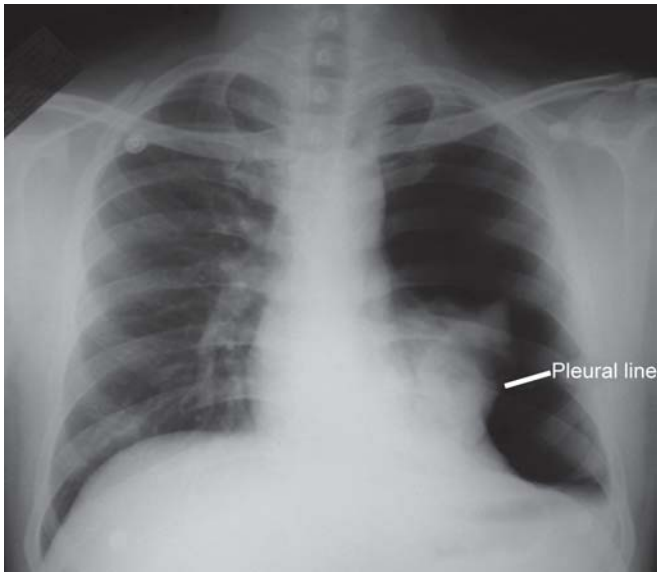


Fig. 158.3: Chest radiograph showing left sided pneumothorax

Quantifying a Pneumothorax

There are many ways to calculate the size of the pneumothorax:

Light Index

The degree of collapse (PNX %) can be measured by taking the average diameters of the lung and the hemithorax (Fig. 158.4), cubing these diameters and using the following equation, PNX% =100 [1-(lung diameter^3/hemithorax diameter^3)]. As lung collapses asymmetrically in a pneumothorax, computed tomography best predicts the light index.[2]

Collins et al. have described an alternate method for estimating the percentage of collapse.[22] With their method, the distance between the apex of the partially collapsed lung and the apex of the thoracic cavity (distance A), and the midpoints of the upper (distance B) and lower (distance C) halves of the collapsed lung and the lateral chest wall are measured in centimeters (Fig. 158.5). The percentage of the pneumothorax can be calculated by the formula: % PNX=4.2+ [4.7-(A+B+C)]

When the volume calculated from a helical CT scan was compared with the volume measured with this

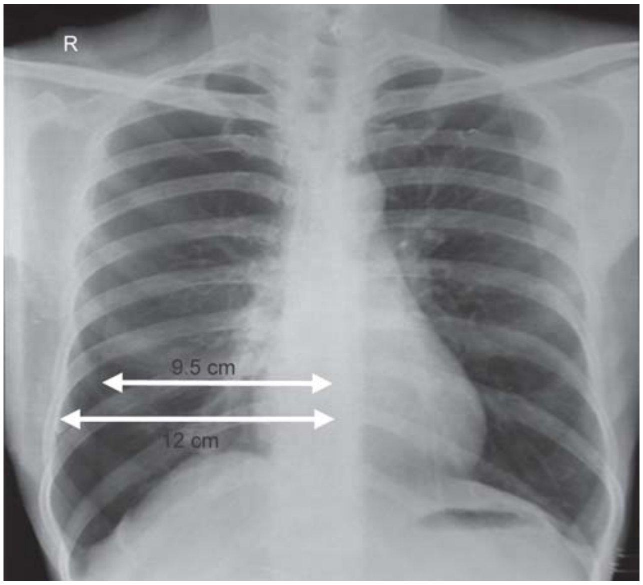


Fig. 158.4: Quantitation of pneumothorax by light index: 100 $(12^3 - 9.5^3/12^3)$

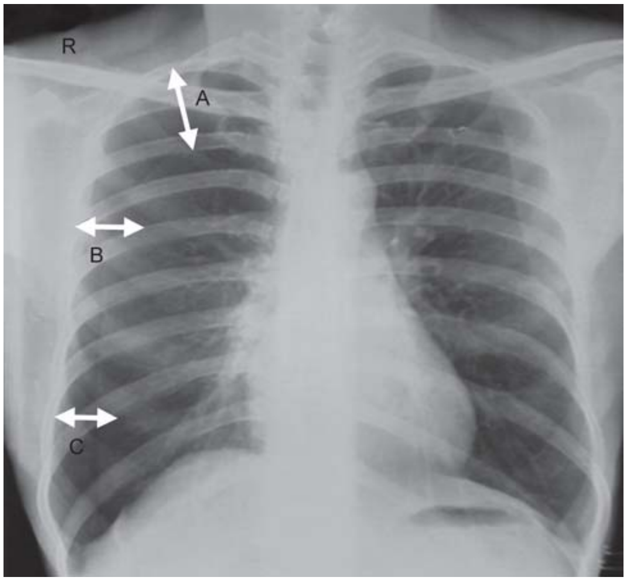


Fig. 158.5: Alternative formula for quantitation of pneumothorax by Collin et al.

formula in 20 patients, the correlation coefficient was 0.98. However the British Thoracic Society prefers to group pneumothoraces into "small" or "large" depending on the presence of a visible rim of <2 cm or ≥2 cm between lung margin and the chest wall.[21] This is a more practical way of calculating the size of a pneumothorax for therapeutic purposes.

Thin walled cysts or avascular bullae can be mistaken for pneumothorax. Skin fold, clothing, tubing, or chest wall artifacts are other artifactuals which can mimic pneumothorax on the chest radiograph. In patients with severe bullous lung disease, computed tomography scan should be done and will help to differentiate emphysematous bullae from pneumothoraces and save the patient unnecessary and potentially dangerous aspiration (Fig. 158.6). Computed Tomography scans are useful in critically ill patients when upright or decubitus films are not possible and in detecting small pneumothoraces not evident on the chest radiograph.

Pleural effusions may accompany a pneumothorax in 20 to 25% of cases. A hemo-pneumothorax occurs in 2 to 3% of spontaneous pneumothoraces. This is due to bleeding from rupture or tearing of vascular adhesions between the visceral and parietal pleura as the lung collapses.

Electrocardiographic changes may be seen due to mechanical effects of a pneumothorax. A left sided pneumothorax may mimic anterolateral myocardial infarction showing rightward shift of the frontal QRS axis, diminution of precordial R voltage, decrease in QRS amplitude, and precordial T-wave inversion.[23] Absence of significant Q wave and ST segment elevation helps differentiate ECG changes due to pneumothorax from that due to myocardial infarction. With a right sided pneumothorax, the changes mimicking a posterior myocardial infarction may be seen like diminution of precordial QRS voltage, right-axis deviation and a prominent R wave in lead V_2 with associated loss of S-wave voltage.

Arterial blood gas analysis is frequently abnormal in patients with pneumothorax with the PO_2 being less than 80 mm Hg in 75% of patients.[21]

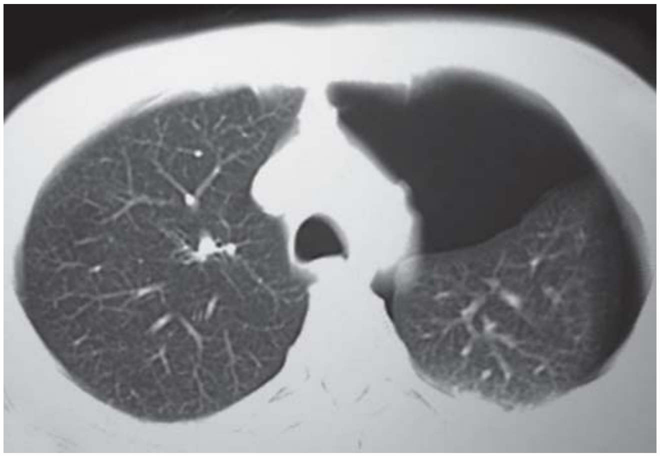


Fig. 158.6: Chest CT scan showing left pneumothorax

Recurrence Rates

There is a risk of recurrence, particularly soon after the initial episode. Sadikot et al. followed 153 patients with PSP for a mean of 54 months and reported a 39% recurrence rate on the ipsilateral side, the majority within the first year.[24] Once a patient has a PSP, there is also an increased risk of having a pneumothorax on the contralateral side. In the same study, Sadikot et al. showed that 15% of the 153 patients developed a pneumothorax on the contralateral side. The rate of recurrence increases with each successive pneumothorax. Thus there is a recurrence in a third of patients after the first PSP, but this may increase to 62% after a first recurrence and to 83% after a third.

Treatment

The main goals of therapy are to clear the air from the pleural space and to prevent recurrence. A multitude of therapeutic options are available for treatment of PSP, varying from observation to surgery (Table 158.1). An algorithmic approach can be employed for management (Fig. 158.7).

Observation

This is generally reserved for asymptomatic patients with a small pneumothorax (less than 20%). This is based on the fact that once the communication between the alveoli and the pleural space is sealed, the pleural space air is gradually reabsorbed. Rate of spontaneous reabsorption is slow. Kircher and Swartzel[23] estimated that 1.25% of the volume of the hemithorax is absorbed every 24 hours. Therefore, if a patient has a 20% pneumothorax, it will take roughly 16 days for pleural air to be absorbed spontaneously.

A patient presenting with a first episode and a small (i.e. only partial, usually apical) pneumothorax should not be treated, but can safely be discharged and followed on an outpatient basis.

TABLE 158.1: Treatment options for PSP

- Observation
- Oxygen treatment
- Simple manual aspiration
- Small catheter drainage
- Chest tube drainage
- Medical thoracoscopic talc poudrage or pleural abrasion
- Video-assisted thoracoscopic surgery (VATS) with blebectomy or bullectomy
- VATS with pleural abrasion or partial pleurectomy
- Axillary thoracotomy

Supplemental Oxygen

The administration of supplemental oxygen accelerates the rate of pleural air absorption. Chernick and Avery[25] demonstrated that the administration of humidified 100% oxygen to rabbits with experimentally induced pneumothoraces increased the rate of absorption six fold. Subsequent studies in patients with a spontaneous pneumothorax have demonstrated that pleural air is absorbed about four times faster when the patients are given high concentrations of supplemental oxygen to breathe.[26] Supplemental oxygen at high concentrations is recommended in hospitalized patients with any type of pneumothorax who are not subjected to aspiration or tube thoracostomy.

Simple Aspiration

There is now sufficient evidence that simple manual aspiration should be the first-line treatment approach in these PSP patients.[27,28] The success rates vary between 50 and 80% of cases, averaging two third of cases. Complications are absent; pain and discomfort are minimized and recurrence rates are similar to those seen after typical chest tube drainage. It can be done in the outpatient with immediate discharge in over half the cases and the length of stay, when necessary, is significantly shortened. Patients residing more than 15 minutes from the hospital should be considered for overnight observation in the hospital. Patients should be followed up in 24–72 with a chest radiograph.

PSP recurrence prevention should only be proposed after a first recurrence because thereafter the rate of recurrence increases with each successive pneumothorax. Exceptions are patients at professional risk (aviation personnel, divers) and when a prolonged air leak (14 days) is present. Anxious patients are a relative indication. Intrapleural insertion of a catheter or tube has only a minimal (if any) effect on prevention of recurrence (34 to 36% observed recurrence rates after chest tube drainage only).[21]

Procedure

A 16- or 18-gauge plastic catheter is introduced, at the second anterior intercostal space in the mid-clavicular line, into the pleural space under local anesthesia using a sterile technique. The catheter is connected to a three-way stopcock and a large-volume syringe. Aspiration is performed until no further air can be withdrawn. Follow-up chest radiograph is performed. As there is a necessity for repeat aspiration or insertion of a catheter in a third of patients, placement of a small catheter attached to a

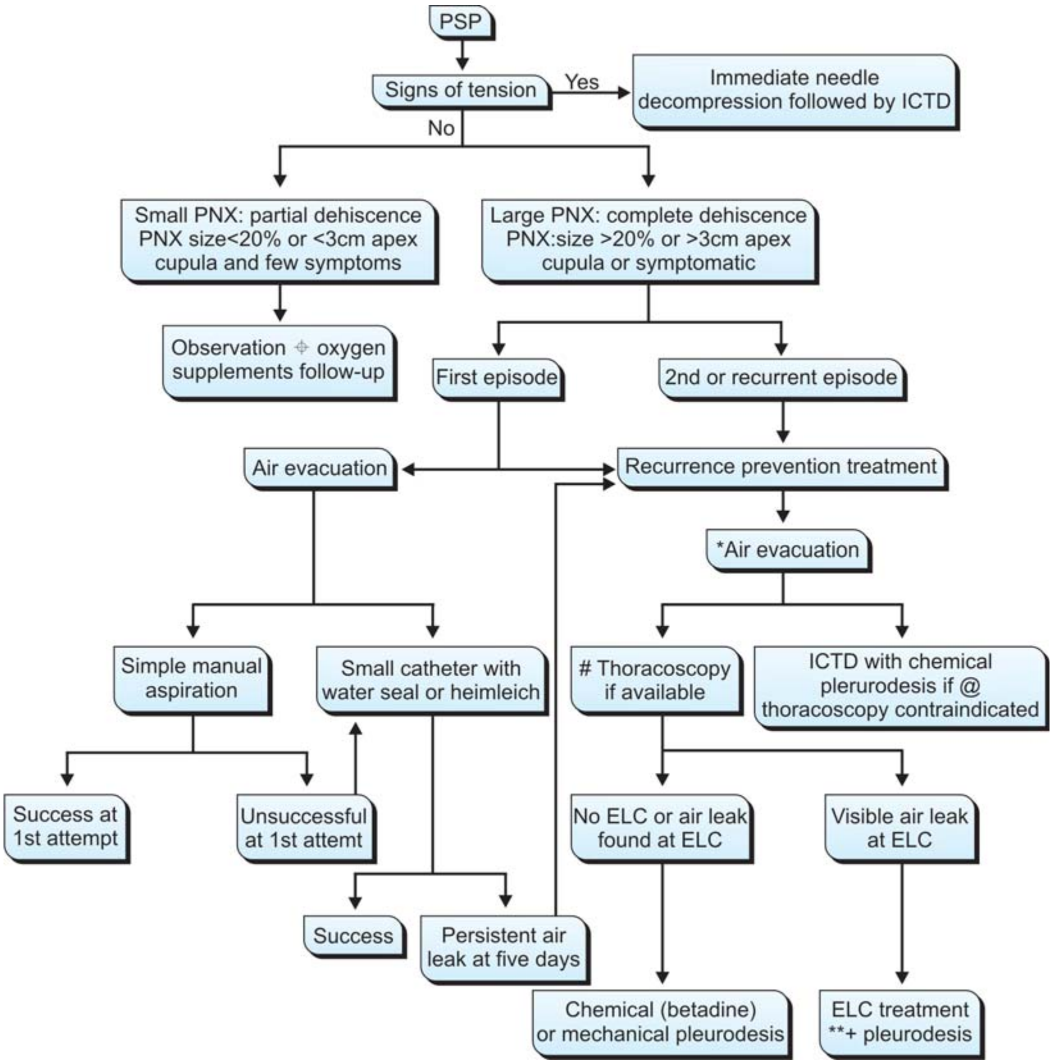

PSP
Signs of tension
Yes
Immediate needle decompression followed by ICTD
No
Small PNX: partial dehiscence PNX size<20% or <3cm apex cupula and few symptoms
Large PNX: complete dehiscence PNX:size >20% or >3cm apex cupula or symptomatic
Observation + oxygen supplements follow-up
First episode
2nd or recurrent episode
Air evacuation
Recurrence prevention treatment
*Air evacuation
Simple manual aspiration
Small catheter with water seal or heimleich
# Thoracoscopy if available
ICTD with chemical plerurodesis if @ thoracoscopy contraindicated
Success at 1st attempt
Unsuccessful at 1st attemt
No ELC or air leak found at ELC
Visible air leak at ELC
Success
Persistent air leak at five days
Chemical (betadine) or mechanical pleurodesis
ELC treatment **+ pleurodesis

Fig. 158.7: An algorithmic approach to the treatment of PSP[5]

* After informed consent or in certain patient groups (aircraft personnel, divers).

#,@ In resource poor settings, pleurodesis without thoracoscopy is successful and cost effective.

** Staple bleb/bullectomy, electrocoagulation, ligation

ICTD: Chest tube drainage; PTX: pneumothorax; ELCs: emphysema-like changes

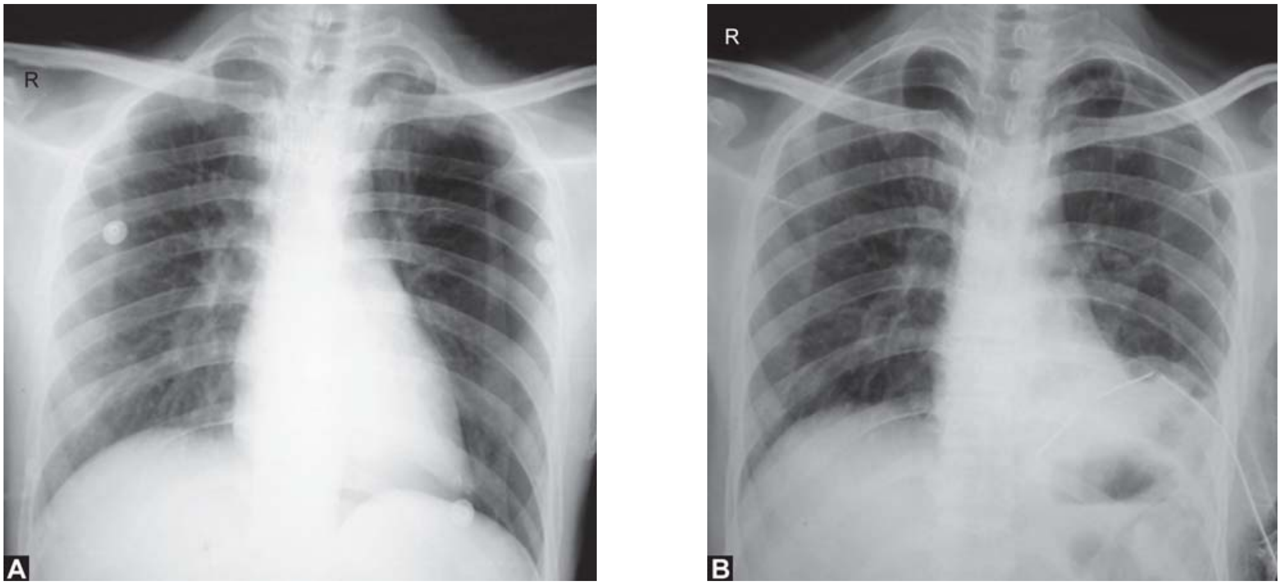
Heimlich valve followed by immediate discharge has been proposed as an alternative management.[21]

Tube Thoracostomy

Tube thoracostomy is recommended if simple aspiration is ineffective and thoracoscopy is not readily available; it rapidly results in the re-expansion of the underlying lung and does not require prolonged hospitalization.[29,30,31] A water seal is used with intercostal tube drainage which allows bubbling of air to be easily recognized. However, use of a flutter valve instead is advantageous in that it allows outpatient management, but care is required to ensure that it is connected correctly.

Smaller intercostal tubes (sizes from 14 to 22 French) minimize the discomfort, but larger size tubes (24–28 French) may be required, if the patient is unstable and has a large pneumothorax, if the patient is suspected to have a large bronchopleural fistula (air leak), hemopneumothorax or is at risk for positive-pressure ventilation (Figs 158.8 and 158.9).

Suction should be avoided for the first 24 hours of tube thoracostomy to reduce the risk of re-expansion pulmonary edema. Randomized studies have shown that



Figs 158.8A and B: Intercostal tube drainage for left sided pneumothorax

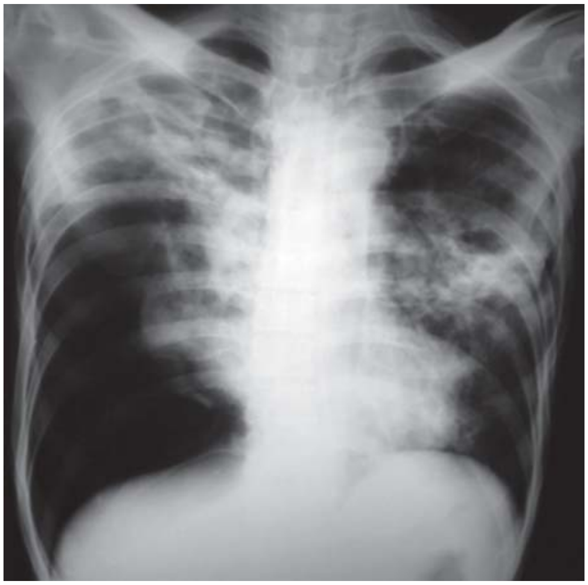


Fig. 158.9: Right spontaneous pneumothorax secondary to tuberculosis

applying suction to chest drains delays tube removal and lengthens hospital stay. Air leaks are present when there is persistent bubbling through the water seal chamber of the drainage system. If there is no bubbling on quiet respiration, the patient should be asked to cough. The absence of bubbling indicates that there is no air leak. Clamping of the intercostal drain is not advised as it confers no advantage if the air leak has stopped, but if it has not a dangerous situation may develop unrecognized. After the lung has re-expanded and the air leak has ceased for 24 hours, the chest tube can be removed.

Persistent Air Leak

In PSP, air leak would have already ceased in two third at the time of presentation and in 88% within the next week. Hence intervention with video assisted thoracoscopy or open thoracotomy, should be considered when the air leak persists beyond five days in PSP.

Pleurodesis

Pleurodesis is done with the help of tube thoracostomy and instillation of a sclerosing agent.

The goal of pleurodesis is to prevent recurrence in both PSP and SSP. Pleurodesis is a procedure that causes the symphysis of the two pleural membranes. Medical intervention consists of chemical pleurodesis using agents such as quinacrine, silver nitrate, talc or tetracycline derivatives. Chemical pleurodesis creates an intense inflammatory reaction which obliterates the pleural space. Talc slurry (100 mg/kg) results in effective pleurodesis but may be associated with Acute Respiratory Distress Syndrome (ARDS), hypoxia and hypotension in a small number of patients. ARDS is probably more common if smaller talc particles (<10 µm) are used.

Parenteral preparation of tetracycline (35 mg/kg) or doxycycline (10 mg/kg), or 20 ml 10% iodopovidone and 80 ml normal saline solution are effective in producing pleurodesis in patients.[32,33] Since severe chest pain is a common side effect with tetracycline pleurodesis, adequate analgesia is indicated prior to the procedure.

Recurrence rates can be reduced from approximately 40 to 25% by pleurodesis and to 5% by stapling of pleural bleb and pleural abrasion through a thoracoscopic procedure. Hence the latter is preferred when available, but in most centers it would not be available and chemical pleurodesis may be an acceptable alternative.

Thoracoscopy

Video-assisted Thoracoscopic Surgery (VATS) is being increasingly used in patients with PSP. The current indication is usually in recurrent PSP.[34,35] The entire lung can be inspected and a search for the cause of air leak carried out. VATS is appropriate for recurrent PSP or SSP. VATS with resection of large bullous lesions is associated with a recurrence rate of 2 to 14%. Pleural blebs responsible for pneumothorax are treated by a method called endo-stapling or suturing followed by pleurodesis by pleural abrasion.

In a meta-analysis of 12 trials that randomized 670 patients, VATS was associated with shorter length of stay (reduction 1.0–4.2 days) and less pain or use of pain medication than thoracotomy in 5 out of 7 trials. In the treatment of pneumothorax, VATS was associated with substantially fewer recurrences than pleural drainage in two trials. In one study of 59 patients, pleuroscopy with the insufflation of talc had a recurrence rate of 5% during a follow-up period of five years.[36]

More recent studies suggest that it may be the procedure of choice. It causes less postoperative discomfort than regular surgery. In addition the length of hospital stay is reduced even in patients with a first attack.[36] The recurrence rates and the days on CTD are also decreased.

Open Thoracotomy

Open thoracotomy with suturing of the blebs and pleural abrasion is a reasonable alternative when VATS is not available. A transaxillary minithoracotomy is preferred, to minimize the trauma and the length of the scar.

Indications for operative management are:

1. First recurrence
2. High-risk professions/lifestyles such as pilots or scuba divers
3. Bilateral or tension pneumothorax[21,23]

Persistent air leak after 72 hours, patients with previous forms of therapy resulting in incomplete re-expansion of the lung and patients from remote areas without ready access to medical care are relative indication for surgical care during the first occurrence, due to the risk to patient should the pneumothorax recur.

SECONDARY SPONTANEOUS PNEUMOTHORAX

Pneumothorax occurring in patients with underlying lung disease is more serious as previously diminished lung function is further compromised with the occurrence of pneumothorax and can be life threatening. Secondary Spontaneous Pneumothorax (SSP) may be associated with a host of underlying lung diseases, with pulmonary tuberculosis being the most common condition reported in India and Chronic Obstructive Pulmonary Disease (COPD) the most common condition in the western world. In Olmsted County, Minnesota, the incidence of SSP was 6.3/1,00,000/year for males and 2.0/1,00,000/year for females.[37] On an average, patients with SSP are 15–20 years older than patients with PSP. The incidence of SSP peak occur a little earlier in Indian population (40–50 years) as compared to the 60–65 years range reported in the Western studies.[6] The recurrence risk of 40 to 80% in SSP is higher than that for PSP.

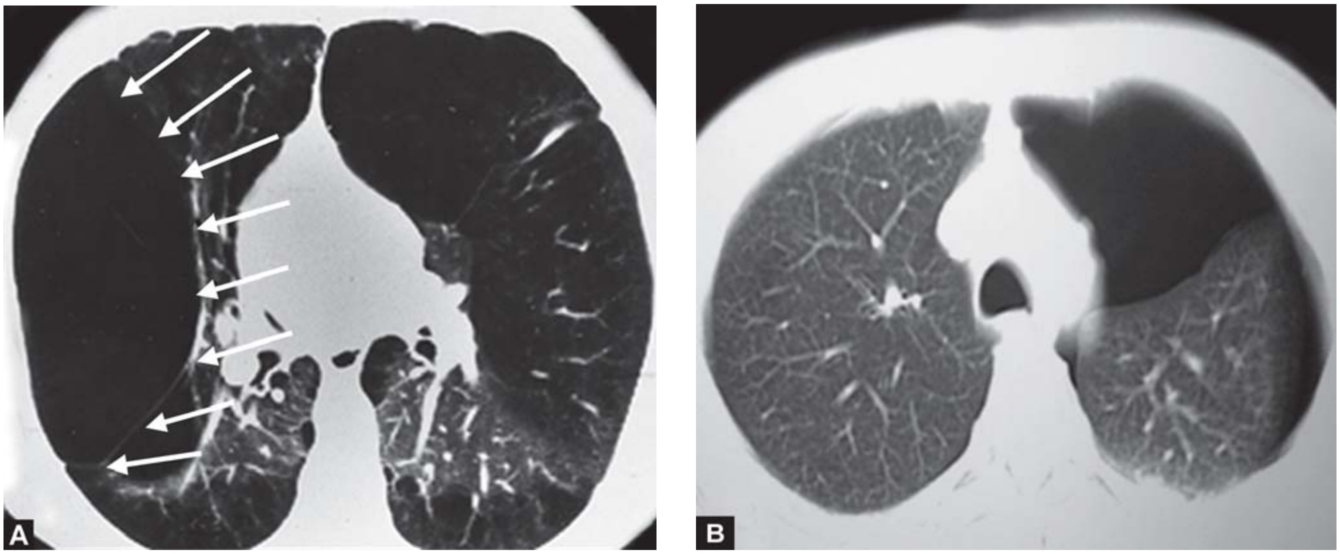
Though the above table is fairly exhaustive, almost every other pulmonary disease has been associated with SSP. In a study of 60 patients in north India, the most common etiology for SSP was identified as pulmonary tuberculosis followed by COPD and pyogenic infections. Acquired Immunodeficiency Syndrome (AIDS) associated pulmonary infections were seen in four (8.3%) patients with SSP.[6]

Clinical Manifestations

As lung function in these patients is already compromised, SSP often presents as a potentially life-threatening condition, requiring immediate action. In SSP, dyspnea is the most prominent clinical feature; chest pain, cyanosis, hypoxemia and hypercapnia, sometimes resulting in acute respiratory failure, can also be present. Diagnosis is confirmed on a posteroanterior chest radiograph; in bullous emphysema, the differential diagnosis with a giant bulla can be difficult, necessitating CT confirmation. The apparent pleural line with a large bulla is usually concave toward the lateral chest wall because it represents the medial border of the bulla, whereas the pleural line with a pneumothorax is usually oriented convexly toward the lateral chest wall (Figs 158.10A and B).

TABLE 158.2: Etiology of secondary spontaneous pneumothorax

Infection	*Malignancy*
Tuberculosis (most common cause in India)	Primary lung carcinoma
P. jiroveci pneumonia	Pulmonary metastasis (especially sarcomas)
Acute bacterial pneumonia	Complications of chemotherapy
Obstructive lung disease	Connective tissue disease
Chronic obstructive lung disease (COPD)	Rheumatoid arthritis
Asthma	Ankylosing spondylitis
Interstitial lung disease	Marfan's syndrome
Idiopathic pulmonary fibrosis [usual interstitial pneumonitis (UIP)]	Ehlers-Danlos syndrome
Nonspecific interstitial pneumonitis	Polymyositis/dermatomyositis
Eosinophillic granuloma	Scleroderma
Lymphangioleiomyomatosis	Other
Sarcoidosis	Catamenial pneumothorax
Langerhans cell granulomatosis	Pulmonary infarction
Radiation pneumonitis or fibrosis	Pulmonary hemorrhage
Histocytosis X	Pulmonary alveolar proteinosis
	Tuberous sclerosis
	Von Recklinghausen's disease
	Wegener's granulomatosis



Figs 158.10A and B: Comparison of bullous emphysema (A) and pneumothorax (B)

Management

SSP requires immediate air evacuation followed by prevention of recurrence at the first episode. All patients with SSP should be hospitalized. Awaiting recurrence prevention treatment, air evacuation can be achieved by simple manual aspiration in young (<50 years old) patients with small pneumothoraces, but most authors and guidelines recommend immediate insertion of a chest tube.[21] The evacuation of even a small pneumothorax can lead to a rapid improvement in symptoms. If respiratory failure occurs, necessitating mechanical ventilation, a chest tube should be placed immediately because the pneumothorax is likely to enlarge during mechanical ventilation (Fig. 158.11).

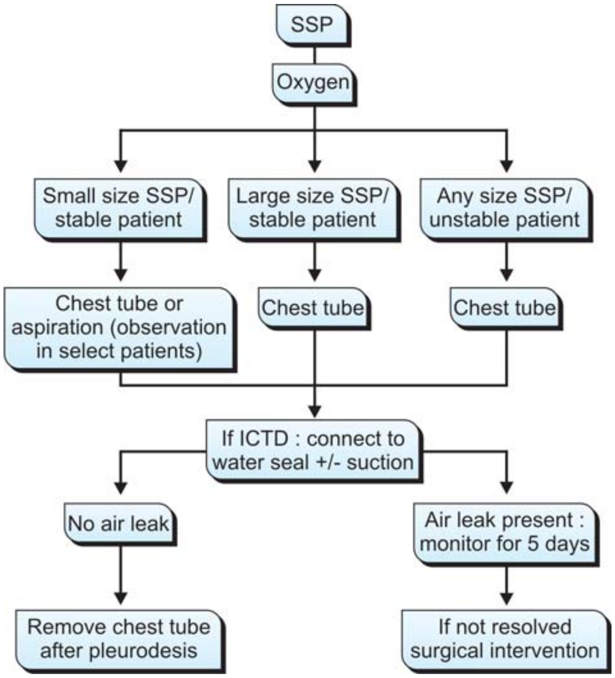

SSP
Oxygen
Small size SSP/ stable patient
Large size SSP/ stable patient
Any size SSP/ unstable patient
Chest tube or aspiration (observation in select patients)
Chest tube
Chest tube
If ICTD : connect to water seal +/- suction
No air leak
Air leak present : monitor for 5 days
Remove chest tube after pleurodesis
If not resolved surgical intervention

Fig. 158.11: Algorithm for management of secondary spontaneous pneumothorax[38]

Small bore chest tubes and even pigtail catheters are usually sufficient; large-bore chest tubes are recommended when large air leaks are suspected or when positive pressure ventilation is required. Persistent air leak is more common in SSP, particularly in the elderly. Recurrence prevention should preferably use a thoracoscopic approach; in case a visible air leak is present (e.g. a ruptured emphysematous bulla), it should be closed by electrocautery or stapling. In all cases, pleurodesis should be done using talc poudrage, pleural abrasion or partial pleurectomy. Patients in whom lung transplantation is a possibility in the future (e.g. cystic fibrosis, some cases of COPD), the transplant team should be consulted on whether to perform pleurodesis or not. Most transplant teams do not consider pleurodesis as a contraindication for transplantation.

Pneumothorax Secondary to Tuberculosis

In a study of 60 patients, tuberculosis (41%) was the most common etiology for SSP in India. SSP associated with tuberculosis should be treated with tube thoracostomy and often requires prolonged periods of chest tube drainage. Surgery should be delayed if possible till he or she has received antituberculous therapy for at least six weeks.

Pneumothorax Secondary to Pneumocystis in Patients with Acquired Immunodeficiency Syndrome

Pneumothorax in patients with AIDS is associated with multiple etiologies. Pneumocystis jiroveci, pyogenic infections, Kaposi's sarcoma, cytomegalovirus, pulmonary cryptococcus, coccidiomycosis and mycobacterial disease have all been associated with spontaneous pneumothoraces.[2] Most patients have a $CD4^+$ count less than 100 cells/mm^3. Approximately 5% of patients with AIDS who receive prophylactic pentamidine develop a spontaneous pneumothorax. This population also has higher risk of contralateral pneumothorax and iatrogenic pneumothorax because of frequent pulmonary procedures or need for ventilation. SSP associated with *P. jiroveci* is notoriously difficult to treat due to the necrotizing nature of the pneumonia. All patients with SSP, due to associated AIDS, should undergo tube thoracostomy. Heimlich valve or VATS is indicated if air leak persists for more than a few days.

Chronic Obstructive Pulmonary Disease (COPD) and Asthma

Pneumothorax is a well recognized, potentially lethal and often hard to treat complication of emphysema (39). COPD is the leading cause of SSP in the West, while it accounts for only 25% cases of SSP in India. Pneumothorax occurs in less than two percent of adults with acute asthma.

Cystic Fibrosis (CF)

Pneumothorax is a serious complication in patients with cystic fibrosis. Pneumothorax in CF patients is associated with a high rate of mortality and is an indicator of a poor prognosis. The risk of developing a pneumothorax increases as age increases and pulmonary function (FEV_1) decreases. The presence of *P. aeruginosa, Burkholderia cepacia*, and *Aspergillus* in the airways increases the risk of pneumothorax by causing increased inflammation, airway secretions and air trapping. Recurrence rates are high and hence preventive measures have to be taken with the first episode of pneumothorax.[40]

Catamenial Pneumothorax

Pneumothorax that occurs in conjunction with menstruation is called catamenial pneumothorax. Respiratory symptoms usually develop within 24–48 hours of the onset of the menstrual flow.[41] Catamenial pneumothoraces are more common on the right side. This is due to transperitoneal migration of endometrial tissue from the pelvis through small defects in the right diaphragm. Left-sided and even bilateral pneumothoraces have also been reported. Catamenial pneumothoraces tend to be recurrent unless there is a therapeutic intervention.

The treatment of catamenial pneumothorax is aimed at treating endometriosis, by suppressing the ectopic endometrium. This can be attempted by suppression of ovulation with oral contraceptives or by suppression of gonadotropins with danazol or gonadotropin-releasing hormone to produce a medical oophorectomy. Alternative treatments include thoracoscopy with stapling of blebs, closure of diaphragmatic defects and parietal abrasion or pleurectomy, or chemical pleurodesis.

Iatrogenic Pneumothorax

Iatrogenic pneumothoraces are more common than primary and secondary spontaneous pneumothoraces combined. The leading cause of iatrogenic pneumothorax is transthoracic needle aspiration. Pneumothorax is more likely if the patient has underlying COPD, if the lesion is deep within the lung, or if the angle of the needle route is wide. Other causes are transbronchial biopsy, thoracentesis, pleural biopsy, central vein catheterization, ventilation with high levels of positive end-expiratory pressure, tracheostomy, intercostal nerve block, mediastinoscopy, liver biopsy and cardiopulmonary resuscitation.[23]

Diagnosis of iatrogenic pneumothorax is often delayed, which should make physicians vigilant. Small and asymptomatic iatrogenic pneumothoraces often do not need any treatment, and resolve spontaneously. In larger or symptomatic pneumothoraces, simple manual aspiration or placement of a small catheter or chest tube attached to a Heimlich valve is usually successful. Larger tubes may be necessary in emphysematous patients or when mechanical ventilation is indicated.

Traumatic (Non Iatrogenic) Pneumothorax

A traumatic pneumothorax can result from either penetrating or nonpenetrating chest trauma. In penetrating injuries, the object penetrating the chest disrupts the visceral pleural surface prompting air to enter from the lung or allows air entry through the breached chest wall. With blunt chest trauma, pneumothorax is either due to a rib fracture lacerating the visceral pleura or due to abrupt elevation in the alveolar pressure causing alveolar rupture. Air may then dissect toward either the visceral pleura or the mediastinum. A pneumothorax develops when either the visceral or the mediastinal pleura ruptures.

Traumatic pneumothoraces may be occult, not seen on chest radiograph but found by additional imaging. A substantial number (29 to 72%) are occult, emphasizing the need for a high index of suspicion and early routine computed tomography in all chest and multitrauma patients.[42] Thoracic ultrasonography, which can be done at the bedside as part of an extended focused assessment for trauma patients can detect most (92 to 100%) pneumothoraces.

Most traumatic pneumothoraces should be treated initially with tube thoracostomy. If the patient has an occult pneumothorax or if the distance between the lung and chest wall is less than 1.5 cm, tube thoracostomy is probably not indicated unless the patient is receiving mechanical ventilation. Fracture of the trachea or a major bronchus, and traumatic rupture of the esophagus are uncommon causes of traumatic pneumothorax and an immediate thoracotomy is indicated. Rupture of the esophagus is accompanied by hydropneumothorax and the pleural fluid amylase concentration is raised. Mortality approaches 100%, if surgical treatment is not carried out promptly.

Tension Pneumothorax

Tension pneumothorax is present when the intrapleural pressure exceeds atmospheric pressure throughout expiration and frequently during inspiration. Most patients suffering a tension pneumothorax are receiving positive pressure to their airways, either during mechanical ventilation or during resuscitation.[23] Tension may also develop in spontaneously breathing patients, in the presence of a one-way valve process permitting air to enter the pleural space during inspiration but not exit during expiration.

Presentation is abrupt with sudden deterioration in the cardiopulmonary status of the patient. Decreased cardiac output due to impaired venous return and profound hypoxia due to ventilation-perfusion mismatch results in severe cardiopulmonary compromise. Patients with tension pneumothorax present with severe distress, displaying cyanosis, diaphoresis, tachycardia, hypotension and labored breathing. Treatment should not be delayed pending radiographic conformation, especially in a mechanically ventilated patient. When the diagnosis is suspected, the patient should immediately be given a high concentration of supplemental oxygen to alleviate the hypoxia. A large-bore (14- to 16-gauge) catheter with needle should be immediately inserted into the pleural space through the second anterior intercostal space. This confirms the diagnosis by usually eliciting an audible rush of air from the pressurized pleural space. Alternatively, the needle may be fitted with a partially sterile-water filled syringe and introduced into the pleural space until air is aspirated. Marked bubbling after the syringe plunger is removed confirms the diagnosis. Placement of the needle through the lateral fifth intercostal space may be safer, though the second anterior space had been previously advocated. Immediately thereafter, intercostal tube drainage should be placed.

Summary

Primary spontaneous pneumothorax is an important cause of sudden occurrence of chest pain and acute breathlessness in young adults. Secondary spontaneous pneumothorax outnumbers PSP in the general population. Prompt treatment relieves patient of his symptoms and can be life saving. Simple aspiration is the preferred initial method of drainage. Recurrence rates after first episode of PSP is 30 and 40 to 80% in SSP. Effective recurrence prevention can be done by chemical pleurodesis in resource constrained settings. Thoracoscopic intervention is preferred when available.

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Malignant Pleural Effusions

Srinivas Rajagopala, George D'Souza

INTRODUCTION

Malignant pleural effusions (MPE) constitute the second most common cause of exudative pleural effusions in the developing countries. On the other hand, malignancy is the most common cause in the developed countries, where the incidence of tuberculosis is low.[1-3]

ETIOLOGY OF MALIGNANT EFFUSIONS

About 50 to 65% of MPE are associated with lung and breast cancer,[1] while 25% are associated with lymphoma, gastrointestinal and genitourinary cancers. Sarcomas (including melanomas), germ cell tumors and prostatic carcinoma together account for about 10% of all MPE[4] while the primary source of malignancy is unknown in the remaining 7 to 15% of patients. The diagnosis of pleural malignancy is the first indication of cancer in about 10% of effusions.[5] Primary pleural malignancy is an uncommon cause of malignant pleural effusion and metastatic malignant pleural effusions are 25-fold common than mesotheliomas even in areas where the latter are relatively common.[6] Pleural effusion in a patient with lung cancer is a poor prognostic marker and the recent TNM classification has upstaged these patients to stage 4A.[7]

In India, no systematic data exists on the proportion of different etiologies of exudative pleural effusions in routine clinical practice. A retrospective review of 236 exudative pleural effusions from our institution over a one-year period (2005-2006) showed that tuberculosis (66.9%, N=158) was followed by malignancy (13.1%, N=31) as the most common causes of exudative pleural effusions (unpublished data). A second retrospective analysis over a five months period (January-May 2010) of 64 exudative effusions (20% of total admissions over that period) showed that malignancy (36%) was the most common cause of exudative pleural effusion; tuberculosis (34%), parapneumonic effusions/empyemas (17%) and pulmonary thromboembolism (6.25%) were the other common causes (unpublished data). With the virtual epidemic of lung cancer in India,[8,9] clinicians will increasingly face the challenge of diagnosing and managing patients with malignant pleural effusions.[10] Bidi smoking and biomass fuel use continue to fuel this epidemic in India.[11] Most patients with lung cancer present with advanced disease in India and the one-year survival has been reported as 9.8%.[12] Approximately half of all patients with metastatic lung cancer develop a malignant pleural effusion and have a significant reduction in quality of life because of the effusion.

Pleural effusions are present in 15% of patients of lung cancer at diagnosis, 50% of patients develop effusion during their disease course.[13] Adenocarcinomas are most frequently associated with malignant pleural effusions, although effusions may be seen with all the histopathological types of cancer.[14] Anti-p53 positivity increases the risk of pleural effusion in patients with carcinoma lung.[15] Breast cancer is the second most common cause, the time from the initial diagnosis to development of effusion is usually two years, but can extend up to 20 years. About 43% of patients with disseminated disease develop pleural effusions. The effusion is usually ipsilateral (70%) but can be contralateral (20%) or bilateral (10%).[16] Pleural effusions are also common in both Non-hodgkin Lymphoma (NHL) and Hodgkin Lymphoma (HL). About 40% of NHL and 16% of patients with HL have an associated effusion. Effusions in HL are associated with mediastinal lymphadenopathy and in NHL with evidence of disease elsewhere. About 3% of effusions related to HL and 20% of effusions related to NHL are chylothoraces.[17]

PATHOGENESIS OF METASTASIS AND EFFUSIONS

Pleural metastases occur by several mechanisms like pulmonary vascular invasion with tumor emboli to the visceral pleural surface with subsequent seeding of the parietal pleura, direct tumor invasion, hematogenous metastases to the parietal pleura from extrapulmonary primaries, and lymphatic involvement.[18] In lung cancer, pulmonary artery emboli and ipsilateral visceral pleura invasion (invasion beyond the elastic layer including invasion to the visceral pleural surface) is the first step.[19] Tumor seeding of the parietal pleura always follows visceral pleural involvement.[20] Pleural metastases may be present without associated effusion.[18,20] In one autopsy series of disseminated malignancy, pleural metastases were seen in 29% and pleural effusions were present in less than half of these patients.[18] Pleural lavage during thoracostomy for lung cancer surgery correlates with visceral pleural involvement and a positive lavage is associated with shortened survival.[21]

Malignant pleural effusions (malignant cells identified in pleural fluid or pleural tissue with associated effusion) are formed by several mechanisms, which may be direct or indirect (Table 159.1). Increased pleural permeability secondary to production of Vascular Endothelial Growth Factor (VEGF) is largely responsible for the development of MPE.[22,23] Lymphatic blockade in the parietal pleura stoma and at the lymph nodes also contributes to generation of MPE; pleural involvement and intrathoracic lymphadenopathy correlate with pleural effusions related to malignancy in autopsy studies.[18,20] In general, direct involvement of pleura by the malignancy makes it inoperable and the treatment approaches are predominantly palliative. However, "paramalignant" causes of effusion, especially pneumonia, pulmonary embolism and atelectasis may be operative in about 17% of cases and this should be ruled out before palliation alone is considered.[24]

CLINICAL PRESENTATION

Malignant pleural effusions may occur in a patient with diagnosed malignancy or may be the first sign of disseminated malignancy. In the first instance, clinical evaluation proceeds to confirm that the pleural cytology is positive and the symptoms guide the patient management; in the latter instance, clinical evaluation proceeds to evaluate the etiology of the effusion. Once the pleural cytology or histology is positive, a search for the primary malignancy has to be made to guide further management.

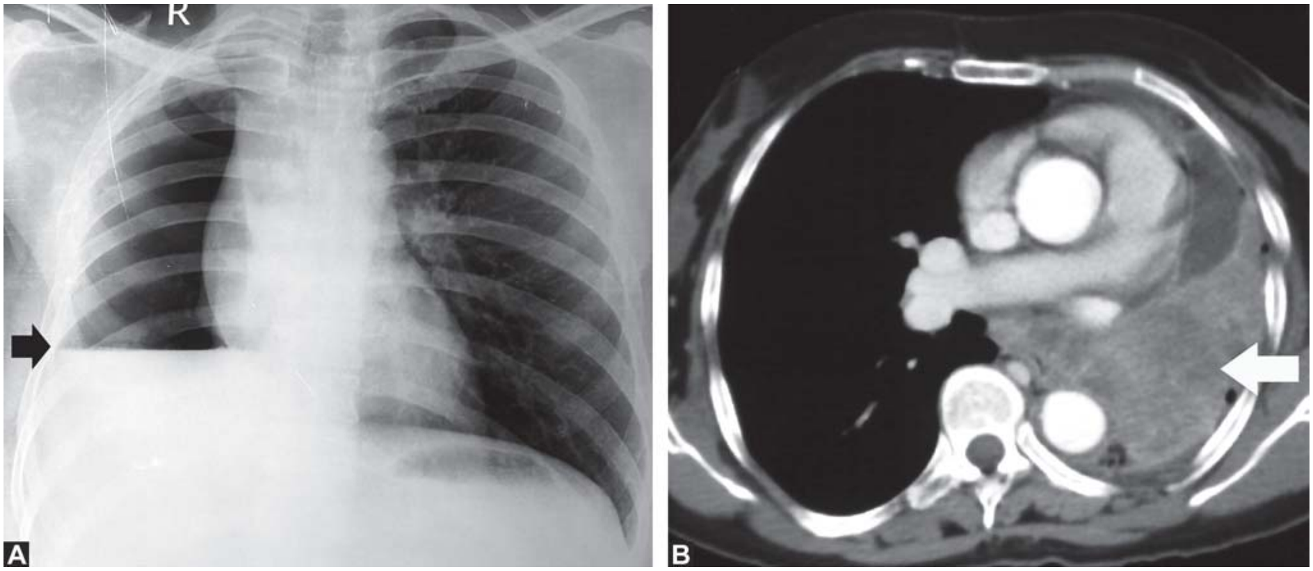
In either case, breathlessness is the most common presenting symptom in patients with MPE, occurring in more than half of the patients. The pathogenesis of dyspnea from a large pleural effusion appears to be related to decreased chest wall compliance, contralateral mediastinal shift, decreased ipsilateral lung volume and reflex stimulation from the chest wall and lung parenchyma. Nonproductive cough may also be caused by the presence of a pleural effusion. Both dyspnea and cough are relieved promptly by thoracentesis; failure of improvement suggests tumor infiltration of lung or pleura or another associated medical condition as the etiology of the pleural effusion.

Patients may also complain of systemic symptoms such as malaise, anorexia and weight loss which is related to the advanced stage of malignancy. A constant dull, aching chest pain may be present; however, this is more common in patients with mesothelioma.[24] Chest pain is related to malignant involvement of the parietal pleura, ribs and other intercostal structures. Patients with benign causes of their effusions are more likely to describe "pleuritic" chest pain. The presence of hemoptysis suggests an endobronchial growth as the primary etiology. A history of smoking and occupational exposure to asbestos may suggest the diagnosis of MPE. Symptoms of more than a month, absence of fever and serosanguineous fluid on thoracocentesis also favor the possibility of malignancy.[25]

When an effusion is the only sign of malignancy and the primary is unknown, the evaluation should include computed tomography of thorax, abdomen and pelvis and mammography in women.[26] Bronchoscopy is always negative when the chest-Computed Tomography (CT) does not demonstrate an abnormality.[26] Any abnormality in this evaluation (34% of 42 patients, all had lung primary) is confirmed by further invasive testing. If these are negative, no additional tests are required and the patient is managed as per Carcinoma of Unknown Primary Syndrome (CUPS) protocol.

RADIOLOGICAL FINDINGS

At presentation, patients with MPE typically have an effusion occupying half to two third of the hemithorax. While small effusions are seen in about 10%, an additional 10% present with a massive pleural effusion. Massive effusions are malignant in etiology in 55 to 70% of cases.[27]



Figs 159.1A and B: Composite image of chest radiograph (A) showing right-sided hydropneumothorax following thoracocentesis and lung entrapment due to a thick visceral pleural peel. The computed tomography image (B) shows a large intra-bronchial mass, loculated effusion and ipsilateral mediastinum

A massive effusion is associated with contralateral shift of the mediastinum. When there is an absence of contralateral mediastinal shift with an apparent large pleural effusion, bronchogenic carcinoma involving the ipsilateral mainstem bronchus (Fig. 159.1A), malignant mesothelioma, fixation of the mediastinum due to malignant lymph nodes or lung entrapment by extensive pleural malignancy should be suspected (Fig. 159.1B). Multiloculation at presentation is unusual in malignant effusions (unlike parapneumonic effusions) because of the high fibrinolytic activity of the metastatic tumor lesions.[28] Chest radiographs of patients with lung primary and an effusion often demonstrate the presence of associated abnormalities; these might sometimes be apparent after a therapeutic thoracocentesis.

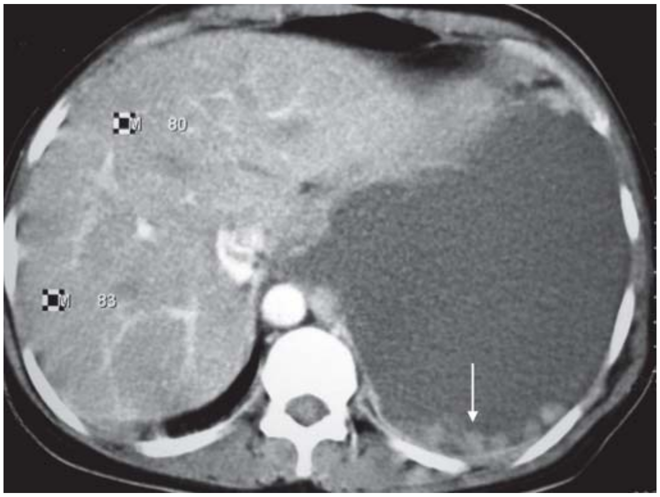
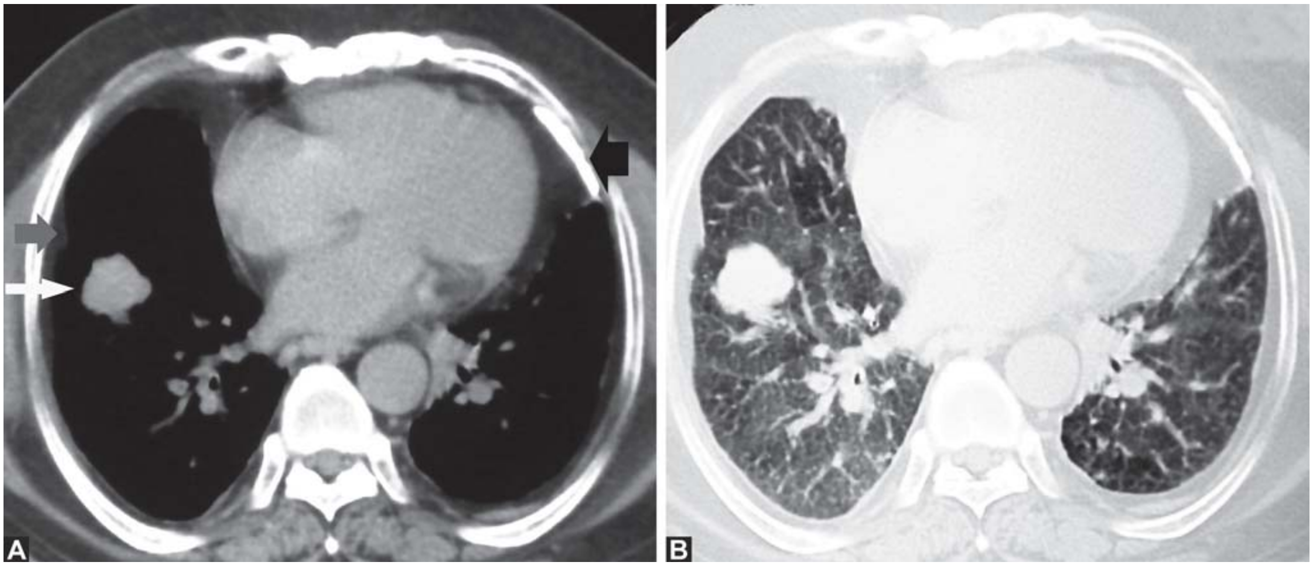
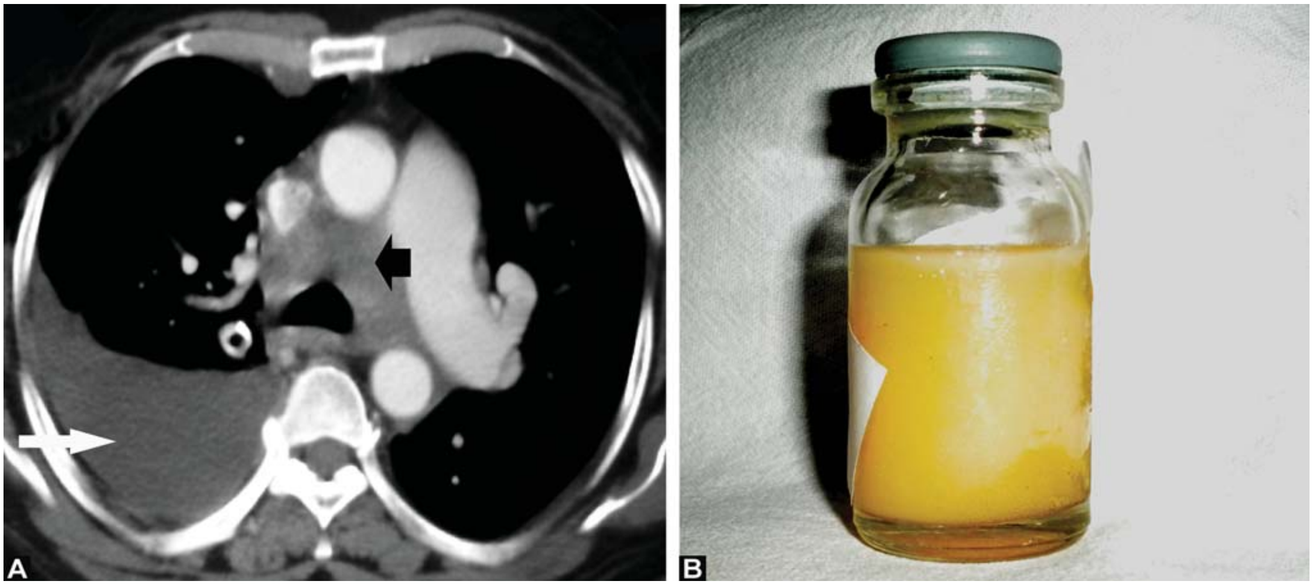


Fig. 159.2: Computed tomography showing left-sided effusion and multiple pleural nodules. Pleural biopsy showed adenocarcinoma

Computerized tomography of the chest should include upper abdomen to enable visualization of possible adrenal and hepatic metastasis. The diagnosis of malignant pleural thickening is favored by the presence of parietal pleural thickening of greater than 1 cm, circumferential pleural thickening, nodular pleural thickening and mediastinal pleural thickening (specificity 94 to 100%).[29] CT of the chest may be helpful in the evaluation of patients with malignant effusion by demonstrating pleural abnormalities (Figs 159.2 and 159.3A and B), mediastinal lymphadenopathy (Figs 159.4A and B), parenchymal disease, distant metastases, chest wall and airway involvement that cannot be detected on standard chest radiograph. CT appearances of mesothelioma may be very similar to metastatic pleural effusion. Presence of concomitant pleural plaques (20%), asbestosis, extensive chest wall invasion, circumferential nodular lung encasement, pleural thickening with irregular pleura-pulmonary margins, inter-fissure thickening and pleural thickening with superimposed nodules should suggest mesothelioma.[30,31] Magnetic resonance imaging is



Figs 159.3A and B: Composite image of computed tomography showing pleural calcification (left, black arrow) and a nodule (black arrow) in the right lower lobe with a minimal right-sided effusion. Fine needle aspiration and immunohistochemistry from the nodule confirmed adenocarcinoma



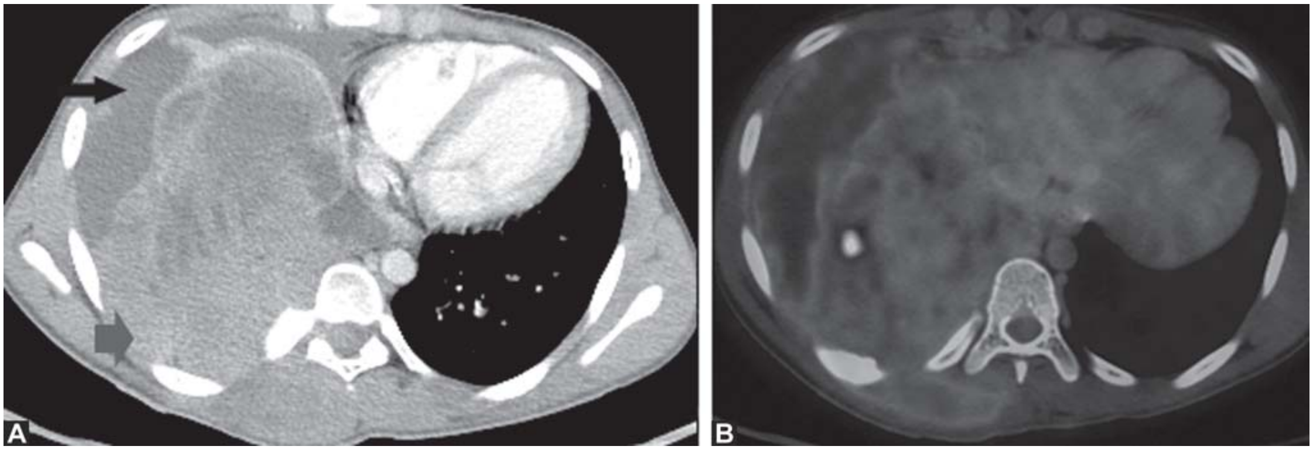
Figs 159.4A and B: Composite image of computed tomography (left) showing right moderate pleural effusion (black arrow) and mediastinal lymphadenopathy (white arrow). Thoracocentesis suggested a chylothorax (triglyceride 150 mg/dl and cholesterol of 45 mg/dl, right) and mediastinoscopic biopsy confirmed lymphoma.

not commonly performed in patients with MPE; it may be helpful in evaluating chest wall involvement. Positron emission tomography may be helpful in evaluating the extent of pleural involvement in malignant mesothelioma but does not offer additional information of routine use in patients with MPE (Figs 159.5A and B).

DIAGNOSIS

Pleural Fluid Analysis

Malignant pleural effusions can be serous, hemorrhagic or grossly bloody while malignant disease is the most



Figs 159.5A and B: Composite image of computed tomography (left) showing right moderate pleural effusion (black arrow) and a large right lower lobe mass (red arrow). CT-guided biopsy established the diagnosis of Askin's tumor. Positron Emission tomography images (right) shows an area of increased uptake in the right lower lobe corresponding to the mass.

TABLE 159.1: Mechanisms for formation of pleural effusions in relation to malignancy

1. *Direct*
   - Increased capillary permeability from direct pleural invasion
   - Lymphatic obstruction due to malignant lymphadenopathy
   - Disruption of thoracic duct or its major tributaries (chylothorax)[@]
2. *Indirect (Paramalignant)*[$]
   - Bronchial obstruction with atelectasis
   - Bronchial obstruction with pneumonia
   - Lung entrapment by malignancy (thick visceral pleural involvement)
   - Hypoalbuminemia (serum albumin <1.5 g/dl)
   - Pulmonary embolism
   - Malignant pericardial involvement
   - Superior vena cava syndrome
   - Radiation therapy
     - Early (<6 months): Pleuritis 6 weeks to 6 months after radiation
     - Late (>6 months)
       - Mediastinal fibrosis
       - Constrictive pericarditis
       - Superior vena cava obstruction
   - Chemotherapy (Methotrexate, cyclophosphamide, mitomycin, procarbazine, bleomycin)

[@] Most commonly seen with lymphomas
[$] Do not indicate nonoperability when seen with carcinoma lung

common cause of hemorrhagic effusion. About 50% of MPE are nonhemorrhagic and have red blood cell counts of <10,000 cells/ µl. The pleural fluid is almost always an exudate but these effusions may occasionally fulfill light's criteria by an elevated Lactate Dehydrogenase (LDH) only. It is suggested that this finding is due to increased cell turnover being the source of the elevated LDH, without increased vascular permeability needed to produce pleural fluid with increased protein concentration. If the analysis suggests a transudate (<5%), then "paramalignant" causes must be considered (Table 159.1). Nucleated cell count is typically low, generally <3,000/µl, composed mainly of lymphocytes, macrophages and mesothelial cells. The lymphocyte differential count mostly varies from 50 to 70% of all cells. The presence of pleural eosinophilia does not negate the possibility of pleural malignancy and the prevalence of malignancy is similar in both eosinophilic and noneosinophilic effusions.[32]

The pleural glucose concentration is lower than 60 mg/dl in approximately 20% of MPE. Impaired glucose transfer to pleural fluid and glucose utilization by tumor burden contributes to the observed low-glucose levels.[33] Lactic acid generated by anaerobic glycolysis in the pleural space and impaired carbon dioxide movement from the pleural space are responsible for low pH generation. A low pleural fluid pH (<7.30) and a low pleural fluid glucose (<60 mg/dl) are markers of advanced disease in the pleural space with increased tumor burden;[34] this is also associated with a decreased survival,[35] a higher sensitivity of diagnosis by initial cytologic examination and less successful pleurodesis. Using a dichotomous level of 7.15 yields an Odds Ratio (OR) of 4.46 (95% CI 2.69-7.45) for failure of pleurodesis.[36] Using multi-level LR's provide better information than using a dichotomous L.R of <7.2 or ≥7.2.[37] However, pleural fluid pH is not an accurate predictor of pleurodesis failure (positive predictive value of 45.7% only for pH <7.2) or survival (LR 1.7, 95% CI 1.20–2.41 at three months) and should not be used in isolation for predicting these outcomes.[36-38] Successful pleurodesis in 88% despite pH of <7.3 and in 40% with a pH below 7 with thoracoscopic talc pleurodesis has been reported.[39] Increased amylase concentration is seen in 10–14% of patients with MPE, especially adenocarcinoma lung and ovary, usually due to increased salivary isoenzyme concentration.[40] The routine assay of amylase is unhelpful in the diagnosis of exudates of undetermined etiology and should be measured only if there is a pre-test suspicion of acute pancreatitis, chronic pancreatic disease or esophageal rupture.[41]

Pleural Cytology

The diagnosis of MPE is established by demonstrating malignant cells in the pleural fluid or in the pleura tissue. Pleural fluid cytology is diagnostic in up to 60% of patients with MPE depending on the tumor load and the histopathological type of the primary malignancy. Pleural cytology is rarely positive in squamous cell carcinoma because bronchial obstruction and lymphatic involvement are frequent causes of pleural effusion in this setting. A sample submitted for cytology need not exceed 50 ml in quantity.[42] Cell-block and cytology smear analysis increases the yield of positive tests and enable immunohistochemistry. A positive cytology establishes malignancy, but provides no information about the site of primary. This is evaluated by subsequent imaging, endoscopy or markers by immunohistochemistry (PSA, CA-125).

Pleural Biopsy

The sensitivity of percutaneous blind pleural biopsy using Abrams' biopsy needle varies between 40–75%, depending upon the extent of parietal pleural involvement, number and adequacy of biopsies and operator experience. If blind biopsy is performed before cytology, one third of patients, who could otherwise be diagnosed, will be missed. The low yield of percutaneous biopsy is because of the initial lesions which tend to establish on the visceral pleura followed by metastases along the mediastinal and diaphragmatic pleura. Further, the involvement may be patchy and missed on blind biopsy. Percutaneous blind biopsy is still used when the cytology is negative and thoracoscopy is unavailable. Computed tomographic-guided cutting needle biopsy is superior to blind Abrams needle biopsy with a yield of 87% versus 47% (N=50, P=0.02, 74% had mesothelioma).[43] Computed tomography-guided percutaneous pleural biopsy has a yield similar to thoracoscopic biopsy and may be performed when confirmation of the diagnosis (without the need for pleurodesis) is the dominant clinical problem.

Medical thoracoscopy has a yield exceeding 95% for malignancy; further, this can be combined with complete drainage of the effusions, adhesiolysis and talc poudrage which has a greater percentage of successful pleurodesis (see below). Medical thoracoscopy can be performed using local anesthesia with conscious sedation in an endoscopy suite using nondisposable rigid instruments, making it less invasive and cheaper than video-assisted thoracoscopic surgery. The diagnostic yield and accuracy of thoracoscopy for malignant effusion exceeds 90%.[44,45] It is also safe and associated with low peri-procedure mortality (<0.5%).[46]

Tumor markers like Carcinoembryonic Antigen (CEA), Carbohydrate Antigens (CA) 15-3, 19-9, 549 and 72-4, neuron-specific enolase, SCC antigen, Cytokeratin 19 Fragments (CYFRA21-1) and Sialyl State-specific Mouse Embryonic Antigen (SSEA-1) have been evaluated to separate benign and malignant effusions. In general, these markers are not specific and have no role in daily practice.[47] In lymphoma, the clonality of lymphocytes demonstrated by flow cytometry on fluid samples establishes the diagnosis.

Immunohistochemistry is routinely used to differentiate adenocarcinoma from mesothelioma. Metastatic adenocarcinomas stain positive with CEA, MOC-3.1, B72.3, Ber-EP4 and BG-8, whereas mesotheliomas (and benign mesothelial cells) stain positive with calretinin and cytokeratin. A panel of four markers is usually employed in clinical practice.[14] Staining for Thyroid Transcription Factor-1 (TTF-1) in fluid and tissue can help establish pulmonary origin of adenocarcinomas.[48]

MANAGEMENT

The initial step is to establish malignancy and the site of the primary (Fig. 159.6). This guides subsequent chemotherapy and/or hormonal therapy and radiotherapy. The major indication for palliative treatment in patients with a malignant pleural effusion is the relief of dyspnea. The main considerations affecting management decisions include the patient's degree of breathlessness, functional status, duration of expected survival, type of primary tumor (expected response to

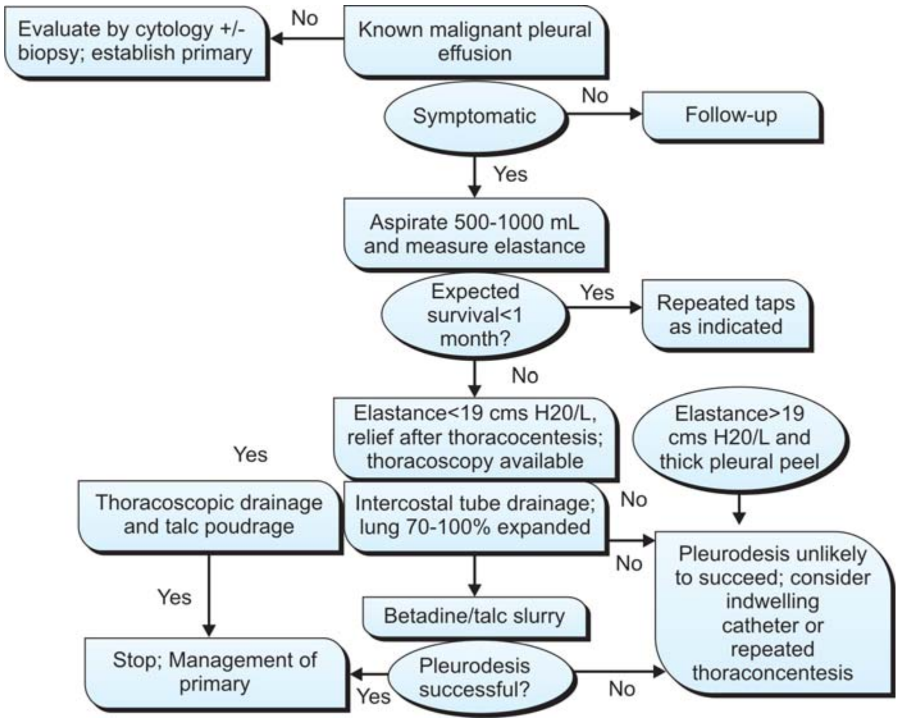

Evaluate by cytology +/- biopsy; establish primary
No
Known malignant pleural effusion
Symptomatic
No
Follow-up
Yes
Aspirate 500-1000 mL and measure elastance
Expected survival<1 month?
Yes
Repeated taps as indicated
No
Elastance<19 cms H20/L, relief after thoracentesis; thoracoscopy available
Elastance>19 cms H20/L and thick pleural peel
Yes
Thoracoscopic drainage and talc poudrage
Intercostal tube drainage; lung 70-100% expanded
No
No
Pleurodesis unlikely to succeed; consider indwelling catheter or repeated thoraconcentesis
Yes
Betadine/talc slurry
Stop; Management of primary
Yes
Pleurodesis successful?
No

Fig. 159.6: Flow-chart of evaluation and management of a patient with suspected malignant pleural effusion

chemotherapy) and lung expansion following thoracocentesis. The following modalities are used in isolation or combined as the clinical situation dictates (Fig. 159.6).

Observation

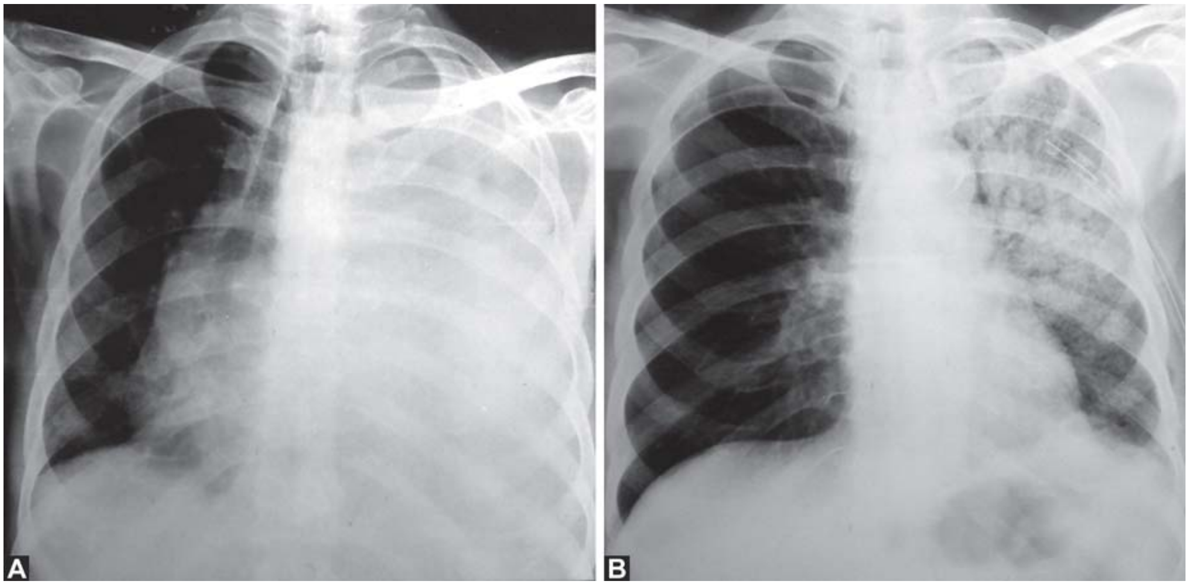
Observation is appropriate when patients are asymptomatic and neither therapeutic thoracocentesis nor pleurodesis are indicated in patients with asymptomatic mild-moderate effusions.

Chemotherapy and Radiation

Malignant pleural effusions from small-cell lung cancer, breast carcinoma and lymphoma may respond favorably to chemotherapy alone. If the effusion is mild-to-moderate, a trial of chemotherapy may be performed as a modality to control the effusion. In chylothorax from lymphoma, mediastinal radiation is effective. However chemotherapy is not useful in isolation to control the effusion, in most patients with MPE secondary to carcinoma lung. Anti-VEGF antibody bevacizumab has recently been approved for first-line treatment of non-small cell lung cancer. Pleurodesis should precede this treatment since VEGF is essential for successful pleurodesis.[49] In patients undergoing systemic chemotherapy, pleural effusions should be aspirated before chemotherapy is given because the antineoplastic drugs may accumulate in the pleural space and lead to increased systemic toxicity. Pleurodesis always precedes chemotherapy because the intercostal drain may become a potential nidus of infection.

Therapeutic Thoracentesis

Therapeutic thoracentesis is performed in all dyspneic patients with MPE for relief of breathlessness. Lack of improvement of dyspnea after thoracentesis implies an alternative associated condition like lymphangitic carcinomatosis, atelectasis, tumor embolism or thromboembolism. In our unit, the initial therapeutic thoracocentesis is always combined with pleural manometry and pleural elastance measurement (see the section on physiology of pleural diseases). Caution should be exercised when draining >1.5 L in a single session because of the potential of Reperfusion Pulmonary Edema (REPO) (Figs 159.7A and B). Using pleural manometry and limiting the procedure when pressure falls to -20 cms H_2O can guide safe thoracentesis in this setting. The amount of fluid evacuated by pleural aspiration should also be



Figs 159.7A and B: Composite image of chest radiographs of a patient with massive left-sided pleural effusion (left). Subsequent to thoracoscopy and intercostal tube drainage, the patient developed re-expansion pulmonary edema (right). The patient was managed with diuretics and oxygen and recovered at 48 hours.

guided by the presence of cough or chest discomfort. Mechanisms proposed for REPO include reperfusion injury of the underlying hypoxic lung, increased capillary permeability and local production of neutrophil chemotactic factors such as interleukin-8.[50] Caution must be exercised especially when the underlying lung has been collapsed for more than a week and large (>1.5 L) volumes are being drained as reperfusion edema complicates 2 to 7% of large volume thoracocentesis.[50] Re-expansion edema can also complicate thoracoscopic drainage of effusions.[51]

Therapeutic thoracocentesis alone has a high rate of symptom recurrence at one month, therefore, alternate options must be explored in all symptomatic patients. Therapeutic thoracentesis is used as the sole therapeutic option in advanced disease, poor performance status, tumors associated with a poor survival and pleural manometry studies suggesting lung entrapment. Repeated thoracocentesis in a patient who should undergo pleurodesis should be discouraged as this lead to formation of adhesions and hinders complete pleural evacuation (and subsequent pleurodesis).

Pleurodesis

Pleurodesis is a treatment that aims to produce symphysis of the pleural surfaces by chemical or mechanical means for symptom relief. The aim of pleurodesis in patients with malignant pleural effusions is to prevent re-accumulation of the effusion and the symptoms. Pleurodesis occurs through diffuse inflammation and local activation of coagulation with fibrin deposition. High intrapleural fibrinolytic activity,[52] high tumor burden and concomitant use of steroids[53] and possibly Non-Steroidal Anti-Inflammatry Drugs (NSAIDs),[54] reduce the effectiveness of pleurodesis. The initial event is injury to the pleural surfaces, followed by subsequent development of fibrosis with the obliteration of the pleural space. However, the mechanism of pleurodesis is highly complex, involves the intrapleural procoagulant-fibrinolytic milieu and angiogenesis pathways and differs from agent to agent.

Patient Selection, Initial Preparation and Procedure

Large pleural effusions are first drained incrementally with a maximum of 1.5 L on the first occasion. The intercostal tube is then clamped and any remaining fluid is drained 1.5 L at a time at two-hourly intervals. The procedure is stopped when cough, chest discomfort or vasovagal symptoms occur and re-started after an interval of 12–24 hours. The sine qua non for successful pleurodesis is an apposition of the pleural surfaces. While the exact amount of apposition required for a successful pleurodesis is unknown, it is usual to attempt pleurodesis after at least 50 to 70% apposition is visible on frontal radiographs.[2] Suction may be applied if apposition does not occur; however, this is usually unnecessary and excessive use of suction may increase the risk of reperfusion edema. Lack of apposition may be due to a thick visceral peel ("lung entrapment"), pleural loculations, proximal large airway obstruction or a persistent air leak. If pleural loculations are evident, then thoracoscopic drainage and pleurodesis or image-guided drainage of loculi may be done followed by pleurodesis.

Presence of proximal airway obstruction is a relative contraindication for intercostal tube drainage (and pleurodesis; Fig. 159.2). Suction is attempted for incomplete lung expansion due to persistent air leak. When suction is applied, the use of high-volume low-pressure systems is recommended with a gradual increment in pressure to about -20 cm H_2O.[2] Mild sedation with midazolam is achieved just prior to pleurodesis with 3 mg/kg (21 ml of 1% solution for a 70 kg male, maximum of 250 mg) lignocaine instilled intrapleurally just prior to the sclerosant. This achieves good analgesia with safe peak serum levels of lignocaine.[55] The chemical sclerosant is then instilled in the pleural space either through an intercostal tube or during thoracoscopy with an atomizer, following complete drainage of the effusion. The intercostal drain is clamped for an hour after the procedure.

Choice of Sclerosing Agent

An ideal sclerosing agent must have high molecular weight and chemical polarity, low regional clearance, rapid systemic clearance, a steep dose-response curve and should be well tolerated with minimal or no side effects. The choice of a sclerosing agent will be determined by the efficacy, availability, safety, ease of administration, number of administrations to achieve a complete response and cost. Despite the evaluation of a wide variety of agents, to date no ideal sclerosant exists. The use of sclerosants increases the probability of successful pleurodesis [RR 1.20 (95% CI 1.04 to 1.38), based on five studies with a total 228 subjects].[56] Pleurodesis practices vary widely from region to region around the globe.[57]

When different sclerosants are compared, talc is the most effective with a RR of effusion nonrecurrence of 1.34 (95% CI 1.16 to 1.55,10 studies, N=308) in favor of talc compared with bleomycin, tetracycline, mustine or tube drainage alone.[56,58] Talc mediates pleurodesis by antagonizing intrapleural VEGF by endostatin induction.[59] Talc slurry is well tolerated and chest pain and fever are the most common side effects seen.[58] Several reports of fatal acute respiratory distress syndrome (ARDS, 1–9% incidence) occurring after talc pleurodesis, mainly from American centers, suggested that talc may not have a good safety-efficacy profile.[60] Review of experience with talc pleurodesis from rest of the world literature, however, suggests that this toxicity may be related to the use of talc preparations with particles <15 µm in size (N=558, 0% incidence of ARDS with graded talc).[61] The small particles may escape into the systemic circulation through the parietal pleural pores, causing a marked systemic inflammatory response and ARDS. When graded talc (small particles <10 µm removed) was compared to mixed talc (mean diameter <15 µm) in randomized trial (N=48), a greater increase in the A-a gradient, a decrease in the PO_2, an increase in the C-reactive protein and a higher incidence of fever was seen.[62]

In summary, graded talc as slurry or poudrage is the most widely used and the most effective agent for pleurodesis currently. Problems with use of medical talc in India include its unavailability, cost and need for appropriate sterilization prior to use. Sterilized commercial talc (face talc, Johnson and Johnson) which has been batch analyzed for impurities (asbestos) and particle size has been used for pleurodesis effectively during thoracoscopy[63] or as slurry in India. This is another acceptable option for pleurodesis provided that batch analysis and sterilization are ensured.

Iodopovidone is an iodine-based topical antiseptic. It is extensively absorbed from mucosal surfaces with a 100-fold increase in serum iodine concentration. Iodopovidone undergoes minimal metabolism and is excreted unchanged. Several series using iodopovidone have shown no evidence of clinically evident thyroid abnormalities,[64] but caution must be exercised in patients with pre-existing hypersensitivity or thyroid disease. A solution containing a mixture of 20 ml 10% iodopovidone and 80 ml normal saline (Microshield, Johnson and Johnson) through the intercostal drain is used to create pleurodesis.[65] A success rate of 64.2–100% [summary success of 90.6% (95% CI, 86.4 to 93.8%)] has been reported, comparable to talc.[64,66] Pain is the most common side effect observed. Iodopovidone has been widely used in India including at our center, is safe, cheap, effective and widely available. Given these advantages, iodopovidone is likely to become the agent of choice for medical pleurodesis in India. Larger studies are however required, given the current database is formed by six studies (including 265 patients) only.[67]

Tetracycline was widely used in the past; however, the production of parenteral tetracycline has ceased in most countries and this agent is no longer available in India for pleurodesis. Filtered oral forms of tetracycline (35 mg/kg) or doxycycline (10 mg/kg) re-constituted in saline produce pleurodesis and have the potential as safe, inexpensive and effective agents for pleurodesis.[68] Filtered oral tetracycline is used in some Indian centers as the first choice (personal communication), but published large studies on efficacy in humans is lacking.

Bleomycin is an antineoplastic agent used in pleurodesis. Its mechanism of action is predominantly as a chemical sclerosant similar to talc. Bleomycin has a success rate (defined as nonrecurrence of effusion) of about 60% (55 to 85%). The recommended dose is 60,000 units intrapleurally. Bleomycin is expensive and relatively ineffective compared to talc for achieving pleurodesis. Nitrogen mustard and mitoxantrone are other antineoplastic agents, which have been used for successful pleurodesis and are cheaper alternatives to bleomycin.

Silver nitrate causes caustic injury to the mesothelium and results in pleural adhesions and pleurodesis. Silver nitrate was one of the first agents used for pleurodesis in concentrations varying from 1 to 10% and has a success rate of 75 to 90%. Severe pain and large exudative effusions may complicate its use. Given its low cost and wide availability, there is an interest in the use of low-concentration (0.5%) silver nitrate for pleurodesis.[69]

Quinacrine is an antimalarial agent that has been used for pleurodesis in Scandinavian countries with a success rate of 64 to 100% (N= 98). Pain, fever, nausea and mental status changes are common and hence widespread use of this agent is unlikely.[70]

Dried killed *Corynebacterium parvum*, an anaerobic gram-positive bacterium, has been used for pleurodesis with an overall success rate of 76% (169 patients, nine publications). However, its availability is limited and is not used extensively for this indication. OK-432 is obtained from the SU strain of *Streptococcus pyogenes* and is both immune-stimulating and cytotoxic and has been used with success rate of 70 to 80%. It has been considered as the agent of choice in Japan.

The search for more effective and safe agents for pleurodesis is ongoing. Transforming growth factor-β is a unique cytokine with potent profibrotic as well as anti-inflammatory activity. It upregulates collagen production and does not cause any inflammatory pleural response in animal models. It appears to be a more effective pleurodesis agent than talc in animals and human trials are awaited.[71]

Thoracoscopic Poudrage versus Intercostal Tube Drainage and Pleurodesis

Thoracoscopic talc poudrage is more effective when compared to talc slurry with a relative risk of nonrecurrence of 1.19 (95% CI 1.04 to 1.36, two studies, N=112) in favor of thoracoscopic pleurodesis. However, the evidence-base of the superiority of talc poudrage is weak; several trials suggest that talc slurry is as efficacious as poudrage.[72,73]

Other Issues in Pleurodesis

Small bore drain (10 to 14 Fr) insertion is generally easier to perform, causes less discomfort to the patient and is equally effective as larger drains (24 to 32 Fr); therefore a small drain is the initial choice for effusion drainage and pleurodesis.[74,75] Traditionally, pleurodesis was performed once drain output was <150 ml/day and the lung is fully expanded. The chest drain is removed once the output is <150 ml/day post-pleurodesis. This leads to longer hospital stays and greater costs. Rapid pleurodesis involves placing a 9-14 Fr catheter under guidance, achieving complete drainage and then attempting pleurodesis immediately. Fluid drainage is monitored for 12 hours post-procedure and the pleural catheter is removed if fluid output is <100 ml; otherwise, a second pleurodesis is performed after 24 hours. If loculations or fluid reaccumulation is detected, sonographically guided thoracentesis and pleurodesis through the thoracentesis needle is performed. This has been shown to be effective and can be performed with small drains in <24 hours.[76,77] The amount and duration of fluid draining after sclerosant instillation does not indicate pleurodesis success,[78] and the length of stay is significantly reduced when the chest drain is removed at 24 hours (4 versus 8 days). In the absence of excessive fluid drainage (greater than 250 ml/day), the intercostal tube is removed within 24–48 hours of pleurodesis.

The use of rotation and position change to disperse sclerosants after instillation through the chest drain is not supported by evidence. Unlike mesothelioma, malignant seeding of biopsy sites and drain site is extremely uncommon in metastatic pleural effusions and routine radiation to these sites is not recommended.[2]

When loculated pleural effusion prevents complete drainage and pleurodesis, the choice of procedure depends on the patient's performance status. If the performance status is good, thoracoscopic drainage and talc pleurodesis is the procedure of choice. Surgical pleurectomy and pleurodesis is an alternative where thoracoscopy is not available, but is seldom done.[79] Another alternative in resource-constraint settings is fibrinolysis of multiloculated effusions, followed by pleurodesis.[80] There are no large studies at present to guide patient selection and judge outcomes with this intervention currently; however, multiloculated effusions with poor performance status and trapped lung in resource-constrained settings may be situations for this modality.[81]

LONG-TERM AMBULATORY PLEURAL DRAINAGE

Incomplete lung re-expansion due to a thick visceral pleural peel (lung entrapment) prevents pleural apposition and prevents successful pleurodesis. Unlike patients with "trapped lung", these effusions are exudative, associated with ongoing pleural malignancy or inflammation and may increase in size.[82] The best management option for this situation is the insertion of a tunneled pleural catheter. This is 15.5 F silicone rubber catheter, 66 cm in length, with fenestrations along the proximal 24 cm and is inserted into the pleural space using the Seldinger technique under local anesthesia. A one-way valve prevents air from entering and permits drainage into a vacuum bottle at regular intervals. When compared to doxycycline pleurodesis for recurrent symptomatic effusion, indwelling catheters have shorter hospital stays (1 versus 6.5 days), lesser late recurrences (13% versus 21%, P=0.446) and comparable improvement in dyspnea and the quality of life. Further, 46% (N=42) achieved spontaneous pleurodesis at a median of 26.5 days.[83] This initial experience has subsequently been confirmed by other authors. Malignant seeding of the tract and occurrence of infection are rare with appropriate care.[84] If the indwelling catheter is used as the first line of management,[85] patients with significant drainage after two weeks should be offered chemical pleurodesis through the catheter.[1]

PROGNOSIS

The predictors of survival in terms of decreasing importance include the performance status of the patient, the site of the primary lesion and the stage of malignancy. The performance status is significantly associated with mortality and the median survival is 1.1 months with a Karnofsky score <30 and 13.2 months with a score >70.[86] The median survival of a patient with MPE varies from 3 to 12 months, depending on the stage and the type of underlying malignancy; in general, this is shortest with carcinoma lung and longest with ovarian carcinoma.[87] As discussed above, poor correlation exists between biochemical characteristics (including pH) of pleural fluid and survival.

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Malignant Pleural Mesothelioma

Arun S Shet, George D'Souza

INTRODUCTION

Mesothelioma is an insidious neoplasm arising from the mesothelial surfaces of the pleural and peritoneal cavities, the tunica vaginalis or the pericardium. Eighty percent of all cases are pleural in origin. The predominant cause of malignant mesothelioma is inhalational exposure to asbestos, approximately 70% of cases of pleural mesothelioma being associated with documented asbestos exposure. Due to limited availability of data based on which one can formulate evidence based guidelines, this chapter incorporates practical and updated guidelines on the management of mesothelioma. These guidelines are generally made on the basis of expert opinion unless otherwise stated in the text. For a discussion on peritoneal, pericardial and tunica vaginalis origin mesothelioma, the reader is directed to other sources in the literature.

EPIDEMIOLOGY

The incidence of mesothelioma in the United States peaked in the year 2000 is on the decline with an annual incidence estimated as approximately 3,300 cases per year. However, the incidence is increasing in many other places in the world, particularly in the Great Britain and Europe, where a peak of up to 2,450 deaths per year are expected around the year 2015. The incidence of mesothelioma in the more developed countries is falling due to recent legislation aimed at reducing asbestos exposure in the workplace and the general environment. On the other hand, mesothelioma incidence rates are predicted to increase dramatically in the less developed countries secondary to the poor regulation of asbestos mining and the proliferation of industrial and household utilization of asbestos.

The annual incidence of malignant pleural mesothelioma in India is now known. India imports nearly 100,000 metric tons of asbestos per year (2005 data), and small-scale asbestos (chrysotile and tremolite) mining and milling contributes nearly 5–10% of the total national usage.[1,2] More recent studies suggest that the consumption of asbestos in India has increased greatly (IBAN report) to approximately 300,000 tons per year (2007).

Risk Factors

Asbestos

Asbestos, a group of hydrated magnesium silicate fibrous minerals, have closely been linked with the epidemiology and natural history of malignant mesothelioma.[3,4] There are two major types of asbestos: (1) serpentine and (2) amphibole. Ninety percent of the asbestos currently used in the United States is the Canadian chrysotile, a serpentine fiber that is reportedly less carcinogenic.

There appears to be a dose-response relationship between asbestos exposure and mesothelioma. This is best illustrated by the cohort study of 4,659 people living in an Australian city that produced crocidolite asbestos but who did not directly participate in its mining or milling; the incidence of mesothelioma increased significantly with greater environmental exposure, based upon the neighborhood and duration of residence.[5]

Recent studies indicate that environmental, non-occupational exposure to asbestos can also contribute to an increased risk of mesothelioma. In certain rural areas in Turkey and Bulgaria, soil contains remarkably high levels of tremolite asbestos fibers, many cases of mesothelioma in these regions appear to be secondary to long-term non-occupational asbestos exposure.[6,7] A role for non-occupational exposure to asbestos was also supported by a study from California in which an increased incidence of mesothelioma was associated with proximity to naturally occurring asbestos deposits.[8]

Persons at high risk of mesothelioma can be identified by tracing the processing and commercial uses of asbestos. Workers with high levels of asbestos exposure include miners, millers and producers of asbestos products and laborers who install plumbing, boilers and heating equipment in ships, factories and homes. The risk extends to workers who may not handle asbestos directly but are in proximity to the material, such as carpenters, electricians, and welders in shipyards. Thus, clinicians evaluating suspected malignant mesothelioma patients should take a detailed exposure history emphasizing the period 20–50 years before diagnosis and including possible household contact exposure.

According to the United States Geological Survey, India was the third largest consumer of absestos (302,139 tonnes in 2007) after China and Russia. However, unlike Russia, both China and India are not signatories to the International Labour Organization asbestos convention. Thus, it is likely that there will be an increase in asbestos related lung injury including mesothelioma in these rapidly industrializing countries, both due to increased consumption of asbestos and to lack of regulations regarding its use. Based on a survey of asbestos exposed workers, clinical asbestos-related diseases-pleural changes, pulmonary fibrosis, bronchogenic carcinoma and diffuse malignant mesothelioma are expected to occur in workers from mining, milling and manufacturing as well as in those with secondary exposures to asbestos-containing materials, including construction and maintenance workers, users of asbestos-containing consumer products and the occupants of asbestos-containing buildings.[1] Thus, the increased consumption of asbestos in India will eventually lead to substantial morbidity and mortality of which a part will be due to malignant mesothelioma.

Radiation Therapy

Radiation therapy ionizing radiation to supradiaphragmatic fields is a likely risk factor for the subsequent development of mesothelioma, with a long latent period between the initial treatment and the diagnosis of the second malignancy. The data are more convincingly in favor of increased risk for patients with lymphomas[9,10] and testicular cancers[11] who have been exposed to radiation as opposed to radiated patients with breast cancer[12,13] where the data are somewhat more conflicting.

Viral Oncogenes

Several lines of evidence have implicated the Simian Virus 40 (SV40) as a cofactor in oncogenesis related to mesothelioma.[14] SV40 is an oncogenic virus in human and mammalian cell systems. Sequences of DNA of the virus have been found in lymphomas, brain and bone tumors and mesotheliomas. However, there is data suggesting that SV40 virus may have been a contaminant of injectable polio virus vaccines approximately 30–50 years ago and that the presence of this virus in tumors may not necessarily be causal. Thus the putative role of SV40 in mesothelioma is controversial and its ultimate role in viral oncogenesis remains somewhat unclear and unproven.

Nanomaterials

There is an increase in the use of nanomaterials in several industries. Data from animal models implicated carbon nanotubes in the development of peritoneal mesothelioma.[15] Thus, with an increasing use of the organic and inorganic nanoparticles substances, it is likely that we will see the development of nanomaterial related pulmonary disease even if there is no increase in mesothelioma in humans.

PATHOGENESIS

Mesothelial cells form the lining of the parietal and visceral pleura where they normally facilitate the free movement of the lung during the process of respiration. Any form of injury to these cells can result in proliferation that occurs in response to the release of local growth factors. Asbestos can induce changes in these cells by several processes that can ultimately lead to malignant proliferation (Fig. 160.1). One of these mechanisms is by irritation as a result of physical properties. The shape and ratio of length to width determine how deeply into the lung these fibers can penetrate and indirectly affects their likelihood of inducing cancer. This irritative process can span from pleural plaques to a frank mesothelioma like process. Similarly, asbestos fibers can pierce individual cells and cause rupture of the mitotic spindle apparatus disrupting mitosis, resulting in chromosomal damage to the cells. Another form of injury induced by asbestos is the production of reactive oxygen species, which causes oxidant stress and damage to DNA, proteins and lipids. Finally, asbestos can also induce phosphorylation of kinases, promoting cellular activation and proliferation.

Several features noted in the mesothelioma cell suggest that there are multiple pathways that lead to oncogenesis. For instance, mesothelioma cells exhibit dysregulated growth, increased expression of telomerase and loss of certain tumor suppressor genes (p16, p14, NF-2 Merlin). Additionally, there is evidence for an antiapoptotic phenotype, increased angiogenesis and matrix interactions along with the release of growth promoting cytokines that exert paracrine effects. Thus, the development of mesothelioma appears to be a culmination of several events that act in concert to produce the eventual clinical phenotype exhibited by patients with mesothelioma (Fig. 160.1).

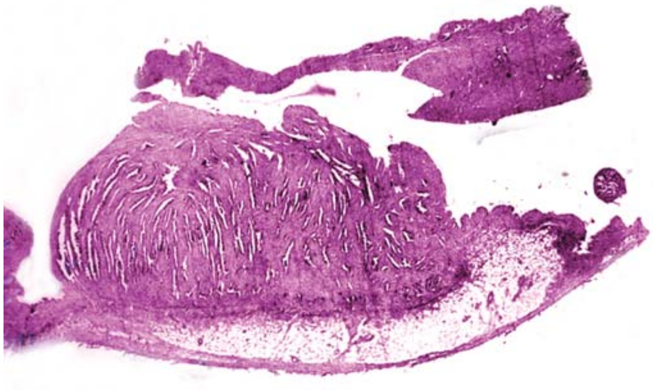

Fig. 160.1: Pleural nodule of mesothelioma situated perpendicular to the visceral layer of pleura [H & E x 100]

Pathology

Early stage MPM due to its slow growth can present as multiple small nodules that occur characteristically on the parietal pleura but can also involve the visceral pleura. Eventually, these nodules coalesce to form a thickened rind of tumor that fuses the parietal and visceral pleurae. At a more advanced stage, the tumor typically encases the entire lung and extends along the interlobar fissures resulting in a thick rind of tumor that can reach diameters of several centimeters or more, despite only minimal invasion of the underlying lung parenchyma. The consistency of the tumor can vary from firm to gelatinous. Adjacent structures can be involved at an early stage, with invasion of the chest wall, pericardium and diaphragm, and a majority of patients will have mediastinal lymph node involvement at autopsy (Fig. 160.2).

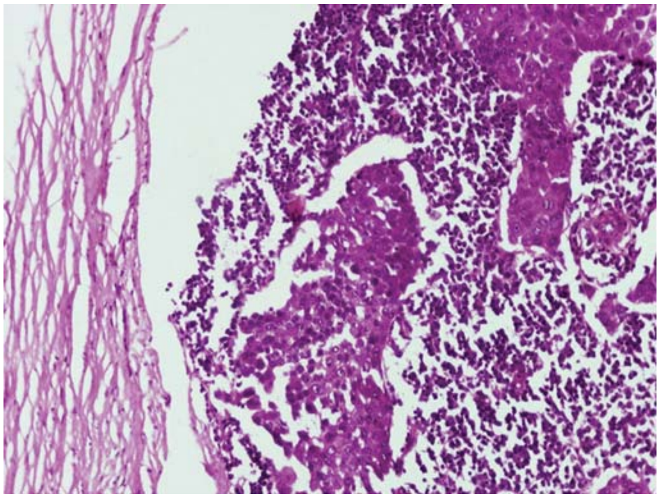

Fig. 160.2: Photomicrograph confirming the metastases of pleural mesothelioma in sinusoids of a cervical lymph node [H & E x 250]

Histologically, mesothelioma is typically classified into three broad histologic subtypes: (1) epithelioid; (2) sarcomatoid and (3) biphasic (mixed). The epithelioid variant is the most common, comprising about 60% of all mesotheliomas. Typical histological appearances of this subtype include tubulopapillary, acinar (glandular), adenomatoid and solid epithelioid patterns. In addition to reactive mesothelial hyperplasia, the differential diagnosis includes metastatic carcinomas and other epithelioid tumors. Sarcomatoid mesotheliomas are composed of malignant spindle cells, which may mimic malignant mesenchymal tumors, such as leiomyosarcoma or synovial sarcoma. Desmoplastic mesothelioma, which consists of bland tumor cells between dense bands of collagenous stroma, is considered to be a subtype of sarcomatoid mesothelioma (Fig. 160.3). In addition to fibrous pleurisy, the differential diagnosis includes sarcomatoid carcinoma and other sarcomas. Biphasic or mixed mesotheliomas have epithelioid and sarcomatoid features, but multiple tissue sections or larger samples may be needed to demonstrate both components.

There is no single marker that has sufficiently high sensitivity and specificity for malignant mesothelioma, and it is, therefore, standard practice for pathologists to employ a panel of markers (both positive and negative). Pancytokeratin stains are very useful in diagnosis and will stain the vast majority of mesothelioma. If the tumor is pancytokeratin negative, then the screening panel should

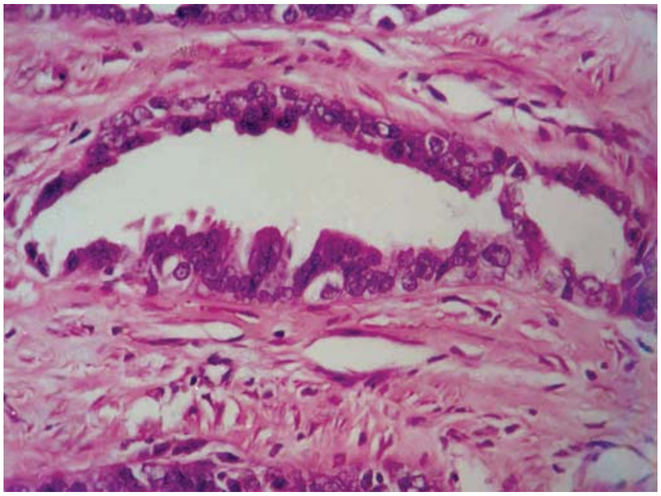

Fig. 160.3: Note the glandular epithelium of the neoplastic component sitting directly on the underlying stroma without the intervening basement membrane [H & E x 400]

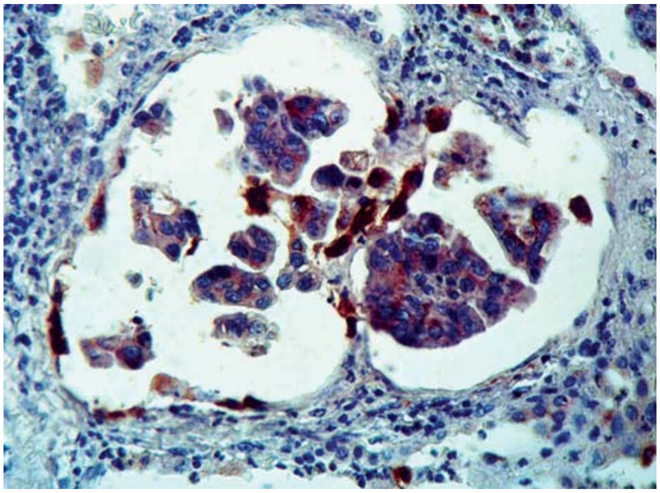

Fig. 160.4: Immunohistochemistry confirming the mesothelioma expressing positivity for calretinin [H & E x 400]

be broadened to include stains to exclude lymphoma, melanoma, angiosarcoma or epithelioid hemangioendothelioma. For epithelioid mesothelioma, common positive immunohistochemical markers that can be used to support a diagnosis of pleural mesothelioma include calretinin, CK5/6, the Wilms' tumor-I (WT1) antigen (nuclear staining) and D2-40 (podoplanin). For sarcomatoid or biphasic pleural mesothelioma cytokeratin reactivity does not necessarily differentiate malignant mesothelioma from other sarcomas, particularly if the cytokeratin staining is focal. Multiple cytokeratin antibodies, such as AE1/3, CAM5.2 (or CK 18) and CK7, should be used since cytokeratin expression can be focal, weak or variable. Electron microscopy, which used to be the gold standard for mesothelioma diagnosis, is now largely replaced by immunohistochemistry (Fig. 160.4).

Although the published literature has limited pathological series from India, single center experience from the pathology department at St. Johns National Academy of Health Sciences during 1969–1991 revealed a predominance of epithelial type mesotheliomas.[16]

CLINICAL PRESENTATION

Mesothelioma most commonly presents in the fifth to seventh decades of life. A large proportion of patients diagnosed at an earlier age have a history of childhood exposure to asbestos. The most frequent presenting symptoms of pleural mesothelioma are dyspnea and nonpleuritic chest pain. Rarely, asymptomatic patients present with a unilateral pleural effusion that is found incidentally on routine chest radiograph. Common physical findings at the time of diagnosis include unilateral dullness to percussion at the lung base, palpable chest wall masses and scoliosis toward the side of the malignancy.

The clinical presentation may also be accompanied by a variety of described paraneoplastic syndromes: (a) Disseminated intravascular coagulation; (b) Migratory thrombophlebitis; (c) Thrombocytosis; (d) Coombs-positive hemolytic anemia; (e) Hypoglycemia and (f) Hypercalcemia associated with secretion of a parathyroid hormone-like peptide. Several prognostic factors have been identified of which the retrospective review series by the surveillance, epidemiology and end results program of 1,475 patients including age, sex, stage, treatment and geopgraphical area of residence.[17] Based on these and other factors, prognostic scores have been developed and prospectively validated by both the Cancer and Leukemia Group B (CALGB) and the European Organization for Research and Treatment of Cancer (EORTC).[18–20] Several of these prognostic scores have served as the basis for the design of randomized controlled chemotherapy trials in good performance patients.[21] Often, the identification of these prognostic factors (Table 160.1) provides some guidance in determining the patient's eligibility for chemotherapy or best supportive care in a limited resource setting.

In general, the disease is staged using the TNM based Union Internationale Contre le Cancer (UICC) classification (Table 160.2), although the major drawback

TABLE 160.1: Factors indicating good or poor prognosis at the time of presentation

Factor	*Good prognosis*	*Poor prognosis*
Interval since diagnosis*	Symptoms < 2 months prior to diagnosis	Symptoms > 2 months prior to diagnosis
Age†	Age under 75 years	Age > 75 years
Sex*	Female	Male
Performance status†*	Performance status 0/Good	Performance status 1–2/Poor
Chest pain† or pain*	Absent	Present
Laboratory WBC* Platelets† LDH†	< 8300/µL< 400,000 /µL< 500 IU/L	> 8300/ìL> 400,000 /—L> 500 IU/L
Histology*	Epitheloid	Non-epitheloid
Stage*	Stage I–II disease	Stage III–sIV

*EORTC: European Organization for Research and Treatment of Cancer Studies[18, 20]

†CALGB: Cancer and leukemia group B studies[19]

TABLE 160.2: TNM based Union Internationale Contre le Cancer (UICC) classification

TNM	
TX	Primary tumor not assessable
T0	No evidence of primary tumor
T1a	Tumor limited to ipsilateral parietal mediastinal, diaphragmatic pleura; no involvement of visceral pleura
T1b	Tumor involving ipsilateral parietal mediastinal, diaphragmatic pleura, with focal involvement of viscera pleural surface
T2	Tumor involving any of the ipsilateral pleural surfaces with one of the following: confluent visceral pleural tumor, invasion of diaphragmatic muscle or invasion of lung parenchyma
T3	Tumor involving any of the ipsilateral pleural surfaces with one of the following: invasion of the endothoracic fascia, invasion into mediastinal fat, solitary focus of tumor invading the soft tissues of the chest wall, or nontransmural involvement of the pericardium (locally advanced but resectable)
T4	Tumor involving any of the ipsilateral pleural surfaces, with at least one of the following: diffuse or multifocal invasion of soft tissues of the chest wall, any involvement of rib, invasion through the diaphragm to the peritoneum, invasion of any mediastinal organ, direct extension to the contralateral pleura, invasion into the spine, extension to the internal surface of the pericardium, pericardial effusion with positive cytology, invasion of the myocardium, invasion of the brachial plexus (locally advanced but unresectable)
NX	Regional lymph nodes not assessable
NO	No regional lymph node metastasis
N1	Metastases to the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases to the subcarinal or ipsilateral mediastinal lymph nodes
N3	Metastases to the contralateral mediastinal or internal mammary lymph nodes, or anysupraclavicular node metastasis
MX	Presence of distant metastases not assessable
M0	No distant metastasis
M1	Distant metastasis present

Stage grouping:

Stage I			
A	T1a	N0	M0
	T1b	N0	M0
B	T2	N0	M0
	T3	Any N	M0
Stage II	Any T	N1	M0
Stage III	Any T	N2	M0
	T4	Any N	M0
	Any T	NN3	M0
Stage IV	Any T	Any N	M1

of any staging system in MPM is the uncertainly in defining the T and N extent of disease by current imaging techniques. There are several staging systems including one that has been recently devised by members of the International Mesothelioma Interest Group which has been approved by the UICC. In the absence of any clear agreement as to which staging system is the most appropriate, it appears that the TNM based UICC classification is currently the most widely accepted standard despite the above mentioned limitations.

Natural History

Mesothelioma exerts its morbidity and mortality via inexorable local invasion. Patients typically develop shortness of breath and chest pain as the tumor gradually obliterates the pleural space and replaces any pleural fluid. As the tumor spreads, deoxygenated blood is shunted through the encased lung, leading to fatigue, dyspnea and hypoxemia that is often refractory to supplemental oxygen. Further growth of the tumor results in localized invasion and any of the following symptoms depending on the site of the original growth (dysphagia, hoarseness, cord compression, brachial plexopathy, Horner's or superior vena cava syndrome). While unusual, metastases may occur to the opposite lung, brain and other extrathoracic sites. Extension of the malignancy into the abdominal cavity may occur, particularly in patients who have prolonged survival after primary aggressive therapy of their thoracic disease, and spread throughout the abdomen in a manner similar to primary peritoneal mesothelioma may be observed. In such patients, invasion of liver and other organs is rare, but bowel obstruction can be a problem.

DIAGNOSTIC APPROACH

Malignant mesothelioma is often misdiagnosed initially and patients may be subjected to multiple consultations and tests before the correct diagnosis is established. Although thoracentesis or closed pleural biopsy often can establish the diagnosis of pleural malignancy, it may not provide enough tissue to distinguish mesothelioma from lung adenocarcinoma. Closed pleural biopsy is also not sufficiently reliable to define the histological subtype of mesothelioma, a potentially important factor in choosing therapy. In addition, negative results do not exclude a diagnosis of mesothelioma. Although rarely indicated, surgical intervention (via video thoracoscopic biopsy or open thoracotomy) has a higher diagnostic yield. In a study of 188 consecutive patients during 1970–1993, video-assisted thoracoscopic (VATS) biopsy was diagnostic in 98% of cases, compared with 26% for thoracentesis alone and 39% for fluid cytology and closed pleural biopsy.[22] For an approach to patients with MPM, the algorithm given in Fig. 160.5 is a good starting point. Most patients presenting to our institution with MPM present with advanced disease and do not have good performance scores. Thus, a majority may not go through a complete three step assessment for the role of multimodality therapy (Fig. 160.6). Instead, based on the presence or absence of certain prognostic markers, we would elect for chemotherapy or best supportive care based on the performance score.

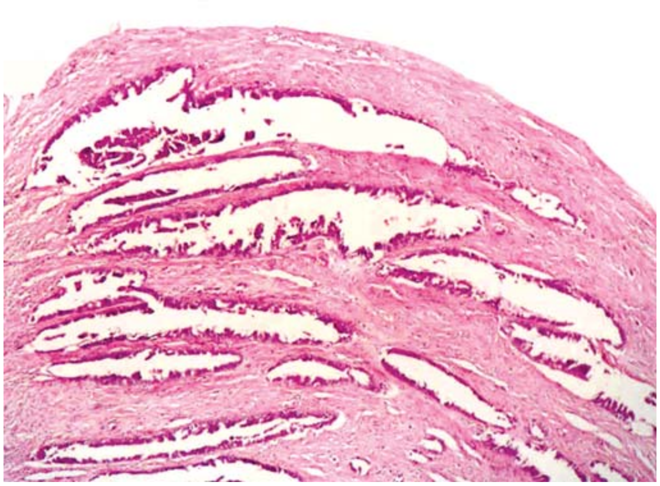

Fig. 160.5: Classical presentation of the glands at right angles to the underlying pleura [H & E x 250]

Cytopathological and Histopathological Diagnosis

Once a sample of pleural fluid or tissue is obtained, a group of immunohistochemial markers is important in diagnosing malignant mesothelioma. Malignant mesothelioma is characterized by the presence of staining for EMA, calretinin, WT1, cytokeratin 5/6, HBME-1 (an anti-mesothelial cell antibody) or mesothelin (more than 85% of epithelioid mesotheliomas). The absence of staining for certain markers (carcinoembryonic antigen; thyroid transcription factor-1; the tumor glycoproteins B72.3, MOC-31 and Ber-EP4; and the epithelial glycoprotein BG8) is particularly useful in narrowing down the differential diagnosis.

Tumor Markers

A role for tumor markers has not yet been well established in mesothelioma although several markers

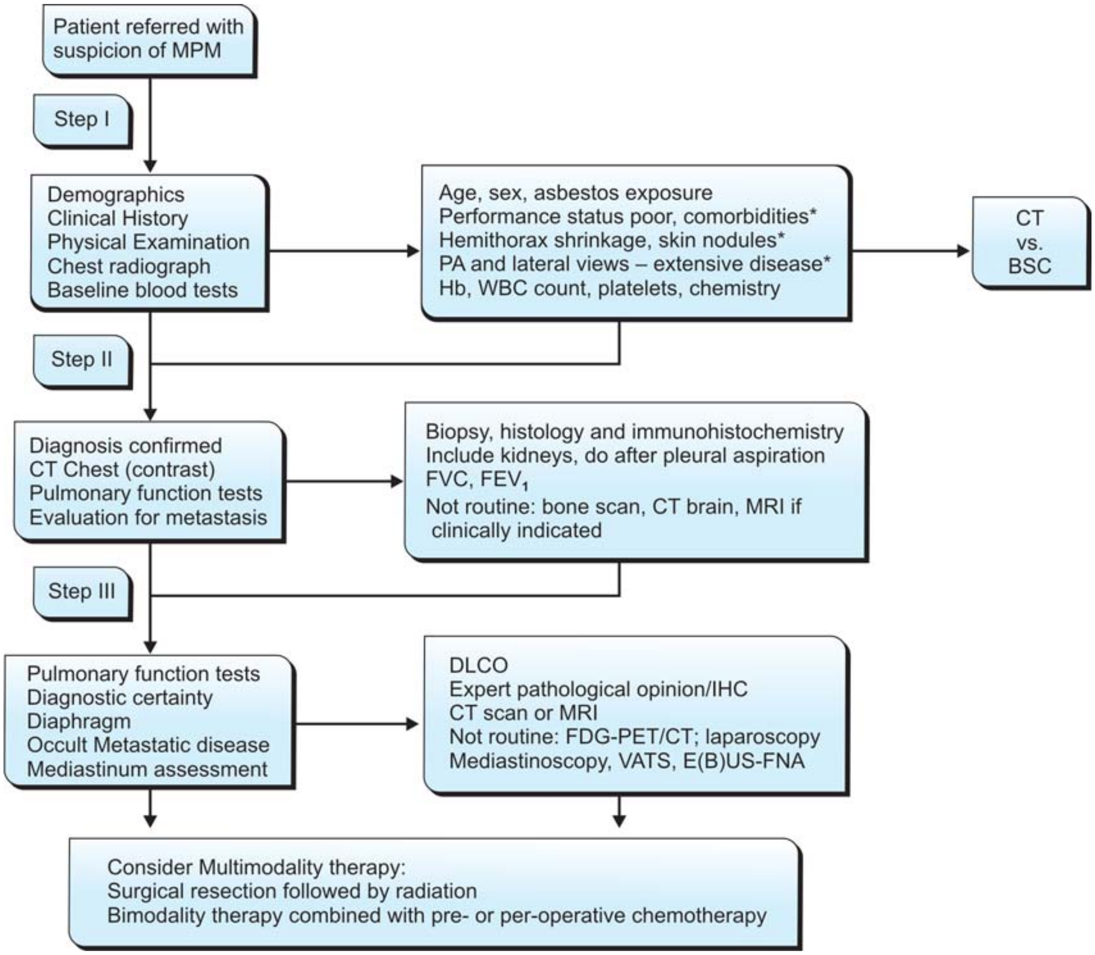
Patient referred with suspicion of MPM
Step I
Demographics
Clinical History
Physical Examination
Chest radiograph
Baseline blood tests
Age, sex, asbestos exposure
Performance status poor, comorbidities*
Hemithorax shrinkage, skin nodules*
PA and lateral views – extensive disease*
Hb, WBC count, platelets, chemistry
CT vs. BSC
Step II
Diagnosis confirmed
CT Chest (contrast)
Pulmonary function tests
Evaluation for metastasis
Biopsy, histology and immunohistochemistry
Include kidneys, do after pleural aspiration
FVC, FEV1
Not routine: bone scan, CT brain, MRI if clinically indicated
Step III
Pulmonary function tests
Diagnostic certainty
Diaphragm
Occult Metastatic disease
Mediastinum assessment
DLCO
Expert pathological opinion/IHC
CT scan or MRI
Not routine: FDG-PET/CT; laparoscopy
Mediastinoscopy, VATS, E(B)US-FNA
Consider Multimodality therapy:
Surgical resection followed by radiation
Bimodality therapy combined with pre- or per-operative chemotherapy

Fig. 160.6: Approach to malignant pleural mesothelioma (MPM)
*Indicates reasons to consider best supportive care (BSC) or chemotherapy (CT)

have been assessed in the past. Two recently identified serum biomarkers that appear to have a potential include Serum Mesothelin Related Protein (SMRP) and osteopontin.[23,24] The SMRP levels are elevated in 84% of patients with malignant mesothelioma compared with less than 2% in patients with other pulmonary or pleural diseases. These markers may have utility as an adjunct to cytopathological or histopathological diagnosis but currently are not available as clinical tools in our setting.

TREATMENT

Surgery

Surgery for malignant pleural mesothelioma can be diagnostic, palliative, or rarely, curative in intent. The vast majority of patients have locally advanced disease, advanced age or other comorbid medical illnesses, precluding aggressive surgical intervention. Thus, surgical intervention for potential cure is only possible in a small percentage of patients with localized disease. Additionally, less than 25% of those eligible for aggressive surgical intervention will be alive at five years, and even fewer will be disease-free. Although associated with substantial morbidity, surgery has resulted in palliating the major symptoms of the disease, although a survival benefit has been seen in selected patients.

Pleurectomy and extrapleural pneumonectomy have been used to try to definitively treat the primary tumor, although neither of these approaches has been shown to increase survival. These procedures can be considered in patients to obtain symptom control, especially for lung entrapment syndrome. However, both of these procedures are associated with substantial morbidity, and thus should be performed only at centers with considerable experience.[25]

In general, the consensus is that surgery, whether debulking or radical resection, is best performed in conjunction with other forms of treatment (chemotherapy and radiotherapy or other investigational therapy).[26] Among surgically treated patients with MPM, the only long-term survivors have undergone extrapleural pneumonectomy as part of multimodality therapy.[27] Operative mortality is approximately 5% for radical surgery in experienced centers[28] but morbidity is 50%.

Pleurodesis

By far, the most common and bothersome symptom in mesothelioma is persistent dyspnea from large, unilateral pleural effusions. A reasonable palliative approach is complete drainage of the pleural effusion (by tube thoracostomy or video thoracoscopy) and introduction of an irritative agent into the pleural space (by injection or insufflation) to produce pleurodesis.

Instillation of agents (tetracycline, doxycycline, bleomycin, talc), pleurectomy, pleuroperitoneal shunting and radiation are other treatments that have been described for malignant pleural effusions. The general recommendations for pleurodesis are to use sterile talc and perform this procedure early in the course of disease. A simple and cheap option for pleurodesis, which is widely available, is to use the solution of povidone iodine mixed with 10% lidocaine and 100 mg hydrocortisone. Our experience shows that this is an effective and inexpensive approach to manage resistant pleural effusions. Thoracoscopic application (poudrage) may be more successful than other methods of pleurodesis (e.g. by tube thoracostomy), because of the presence of bulky tumor or “trapping” of the lung by a thick visceral pleural peel of tumor which compromises the efficacy of pleurodesis.

Chemotherapy

Although previously results of chemotherapy were disappointing and survival rates less than 10 months, the appearance of several new antineoplastic agents has resulted in improvements in objective response rates and overall survival.[29] Evaluation of the effectiveness of chemotherapy requires adequate definitions of response. Both the objective response rate (as measured on CT scan by a decrease of greater than 30% in the thickness of the pleural rind perpendicular to the rib cage) and progression-free survival have been used as surrogates for efficacy in all the phase III studies to date in MPM patients.

Single Agent Chemotherapy

Cisplatin, gemcitabine, permetrexed, anthracycline, vinca alkaloids have all been shown to have substantial activity in the setting of phase II studies; however, cisplatin is the most active single agent and forms the back bone for combination chemotherapy regimes.

Combination Chemotherapy

Three randomized clinical trials have established that platinum-based dual agent chemotherapy significantly prolongs survival compared to single agent chemotherapy or best supportive care.[20,29,30]

Permetrexed/cisplatin: In the single-blinded EMPHACIS trial, 456 patients were randomly assigned to cisplatin (75 mg/m^2) plus either permetrexed (500 mg/m^2) or a placebo, both given once every three weeks. The median survival was significantly longer for the combination (12.1 vs 9.3 months), as was the time to progression (5.7 vs 3.9 months) and the objective response rate (41% vs 17%). All parameters favored the combination therapy group, including global quality of life, pain, dyspnea, fatigue, anorexia and cough. In a multivariate regression analysis of prognostic factors derived from this trial, factors predictive of overall survival were therapy group, vitamin supplementation group (those receiving both B12 and folic acid), Karnofsky performance status (90–100 vs 70–80), less advanced disease stage, non-mesothelioma histological subtype and white blood cell count (≥ 8200/µL vs lower values). Permetrexed/carboplatin combination has been studied in the phase II setting and appears to have similar efficacy compared with permetrexed/cisplatin and can be used in the setting where cisplatin nephrotoxicity is a concern.

Raltrexed/cisplatin: The efficacy of this combination was studied in a phase III trial in which 250 patients were randomly assigned to raltitrexed (3 mg/m^2) plus cisplatin (80 mg/m^2, both in 21 day cycles) or the same dose of cisplatin alone. In the 213 patients with measurable disease, the combined therapy group had a higher objective response rate. Survival in all randomized patients was significantly increased with the combination regimen: the median survival was 11.4 versus 8.8 months with single agent and the one-year survival was 46 versus 40%. Thus, first line combination chemotherapy including cisplatin and pemetrexed or raltitrexed demonstrates greater activity than cisplatin alone in phase III studies, with higher response rates and improved survival. Any combination of this doublet-based chemotherapy is currently considered the standard therapy for first line treatment of MPM.

Although the scientific rationale for chemotherapy and the evidence base supporting such therapy has been conclusively demonstrated in the setting of randomized controlled trials, the utility of such chemotherapy may be questioned in a limited resource setting where patients pay out of pocket. Furthermore, despite statistically significant improvement in overall survival, in the setting of limited resources, whether such marginal improvements in survival offer any meaningful value to the patient is something that may need to be assessed sensitively by both patient and physician. Overall, a very careful evaluation of the socioeconomic status, overall performance status and patient willingness for chemotherapy may help further delineate patients that would benefit most from chemotherapy.

Second Line Chemotherapy

Several second line agents have been shown to have a response in the setting of mesothelioma that is unresponsive to primary combination chemotherapy. The available data are rare (only 6 phase II studies) and do not allow for the proposal of any specific agent or schedule. In our setting we tend to recommend best supportive care for such patients, as they tend to have a Karnofsky performance status of less than 70 once they have failed first line therapy. Exceptionally well preserved patients in whom financial status does not impact treatment decisions may elect to undergo salvage therapy in which case our most preferred agent is permetrexed or vinorelbine.[31] Ideally, such patients should be enrolled in a clinical trial to assess the role of such therapy in a scientific manner.

Radiotherapy

Malignant mesothelioma is traditionally resistant to radiotherapy.[32] Furthermore, the diffuse nature of the tumor prevents localized radiation therapy. However, local radiotherapy can be delivered to surgical sites with questionable margins or to prevent seeding of tumor and can also be used to palliate symptoms. Fractionated radiotherapy using intensity modulation is the technique that has shown some success and is generally used after surgical resection of malignant melanoma. Other radiotherapeutic approaches have also been tried but the results have been disappointing.

Novel Approaches

Molecularly targeted therapies (thalidomide,[33] bevacuzimab, geftinib,[34] imantinib,[35] and erlotinib[36]), immunotherapy (interferon and interleukins[37]), and gene therapy have been investigated with varying but limited degrees of success. Most of these therapies have not yielded dramatic results although with the small numbers that have been studied assessment of results tends to be somewhat conflicted. In general, such treatments should be attempted only in the setting of a clinical trial.

Palliative Therapy

Recurrent pleural effusions are best controlled by the removal of all fluid, with the use of suction when required, followed by chemical or surgical pleurodesis. There are several types of pain in patients with malignant mesothelioma. Local involvement of the chest wall causes somatic pain. Intercostal nerve or vertebral invasion causes neuropathic pain. Organ invasion causes more diffuse visceral pain. Opiates typically provide adequate pain relief for the duration of action of the drug (4 hours for liquid morphine and 12 hours for sustained-release morphine). Special attention should be paid to initiating patients on medications that prevent constipation.

Somatic pain often responds to a nonsteroidal anti-inflammatory drug given in addition to an opiate. In general we used paracetamol before going to more effective non-steroidal anti-inflammatory agents such as naproxen. The cycloxygenase 2 (etoricoxib) inhibitors are especially useful and have little or no side effects. Neuropathic pain requires the addition of an anticonvulsant, such as carbamazepine, gabapentin or sodium valproate. Some patients require procedural pain relief, such as intrathecal analgesia or nerve block however, in our setting this is not commonly an approach that is taken. Palliative radiotherapy aimed at pain relief may be considered in cases of painful chest wall infiltration or nodules.

Dyspnea due to fluid accumulation or encasement of the lung by tumor is common. Typically this is difficult to treat and can be addressed using a combination of therapies including blood transfusions (anemia), diuretics (fluid overload), centesis (effusion), and oxygen. Other measures that have been shown to be helpful in the setting of lung cancer,[38] such as creating a stream of air across the face, self help breathing techniques and yoga, may be tried.

Psychosocial factors are important in the palliation of malignant mesothelioma. In the setting of limited resources, it is especially important to pay attention to palliative care provided in the form of a team of doctors and non-medical staff including, surgeons, chest physicians, oncologists, pain and palliative care specialists, psychologists and physiotherapists to ensure that this occurs in a timely and meaningful manner.

Prevention

A key method of prevention of cancer in general is population based screening to detect disease at an early stage and improve prognosis by more effective medical or surgical treatment. This would seem like an attractive strategy in mesothelioma where the time to develop invasive cancer seems to be at least a decade, if not more. To date however, the inadequate performance of potential screening methods[39] and the low prevalence of disease do not seem to justify large scale screening programs.

Aside from screening, public health policy related to occupational health exposures in limited resource countries needs to improve to reduce the potential future burden of asbestos related illness including mesothelioma.[2] Several issues may need to be resolved before prevention of mesothelioma becomes a reality in the Indian setting. For instance, the occupational exposure standard is still 2 fibers/ml of air (compared to the United States occupational safety and health administration guidelines: 0.2 fibers/ml of air for fibers >5 µm in length). The Health and Safety Legislation Act does not cover 93% of workers in the unorganized sector where asbestos exposures are extremely high and workers remain uninformed and untrained in dealing with asbestos exposure. Furthermore, mesothelioma is not recognized as an occupational disease in India and the latest cancer registry data have no information on mesothelioma.[2] Industrial hygiene assessment is seldom carried out and pathologists do not receive training in identifying mesothelioma histopathologically. Greater awareness and advocacy among health care professionals and public health policy experts may enforce changes that result in prevention as a better strategy than cure.

Criteria to Consider Multimodality Therapy

1. Biopsy proven non-sarcomatoid MPM
2. Clinical stage T1-3, N0-1, M0
3. Patients fit for pneumonectomy (adequate cardiovascular reserve)
4. Patients with good performance status (fit to receive chemotherapy)
5. Patients fit to receive radical hemithorax radiation

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Section

21

PULMONARY MANIFESTATIONS OF SYSTEMIC DISEASES

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161

Pulmonary Involvement in Collagen Vascular Disease

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INTRODUCTION

Collagen vascular diseases can involve any part of the thorax including the lung parenchyma, pleura, airways, blood vessels, lymph nodes, lymph channels, chest wall musculature and the diaphragm. In these multisystem disorders, the lung involvement can be a part of the multisystem illness or it may be the only manifestation of the systemic illness. Occasionally, the lung involvement may herald the onset of the systemic illness. In most cases, however, the pulmonary involvement is detected during the course of the collagen vascular illness. The following discussion encompasses important pulmonary manifestations of the principal collagen vascular diseases (Table 161.1).

TABLE 161.1: Key facts of thoracic involvement in collagen vascular disease (CVD)

1. Any part of the thorax can be affected by collagen vascular disease.
2. Thoracic manifestations may precede, occur concurrently or follow the course of collagen vascular disease.
3. Thoracic manifestations of CVD may be indistinguishable from secondary infections and toxicities caused by the drugs used for treating CVD.
4. Rheumatoid arthritis-related lung disease is more common in men.
5. Thromboembolism frequently occurs in systemic lupus erythematosus patients.
6. Malignancy may complicate the course of scleroderma and dermatomyositis; lymphoma may occur in the patients with Sjogren’s syndrome.
7. A normal chest X-ray does not exclude parenchymal lung disease; lung functions and High Resolution Computed Tomography (HRCT) are often required.
8. Smoking exacerbates collagen vascular disease and alveolar hemorrhage.

RHEUMATOID ARTHRITIS

Rheumatoid Arthritis (RA) is a systemic autoimmune process that primarily affects the joints, and can also involve other organs, including the lungs and pleura, eyes, skin, heart and peripheral nerves. Pleuropulmonary disease is more common in the patients with RA who have severe chronic articular disease, high titers of rheumatoid factor, subcutaneous nodules, cutaneous vasculitis, myopericarditis, ocular inflammation and Felty’s syndrome. Pleuropulmonary abnormalities associated with the rheumatoid process are many and the differential diagnosis is wide[1,2] (Table 161.2).

Pleural Involvement

Pleural involvement can cause pleural effusion, empyema, chylothorax, pleural thickening, fibrothorax and lung entrapment. Autopsy studies have reported pleural disease in 38 to 73% of the patients with rheumatoid arthritis; however, only 2 to 21% patients with pleural disease have symptoms and only 5% have radiological evidence of pleural inflammation.[3-5] Pleural effusion can be caused by inflammation or by necrosis, cavitation and rupture of a nodule into the pleural space. Pleural disease has a remarkable predilection for men, although RA is more common in women in a ratio of 2:1 to 3:1. Pleural involvement mostly remains sub-clinical or asymptomatic. When symptoms occur, dyspnea, fever and chest pain are most common. Physical examination may reveal a pleural friction sound and diminished breath sounds over the affected lung field.

TABLE 161.2: Pulmonary complications of rheumatoid arthritis

Tissue involved	*Manifestation*
Pleura	Effusion Empyema Pleural thickening Calcification Pneumothorax
Parenchyma	Necrobiotic nodules Caplan's syndrome Pneumonitis Interstitial fibrosis Bronchiolitis Obliterans Organizing Pneumonitis (BOOP) Apical bullous disease
Airways	Airway obstruction Bronchiolitis Bronchiectasis
Blood vessels	Vasculitis Pulmonary hypertension
Thoracic muscle cage	Dyspnea, muscle weakness

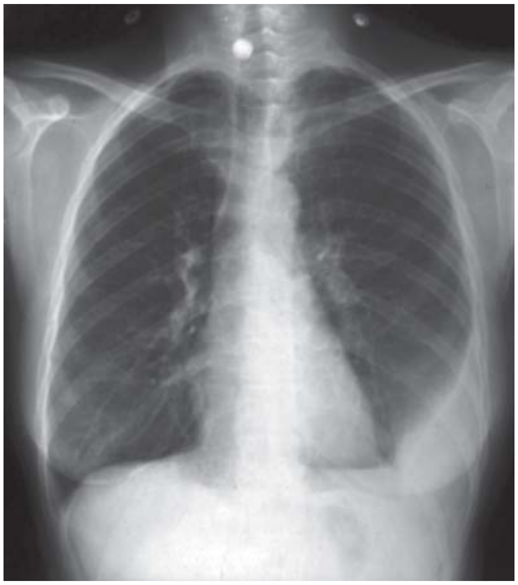


Fig. 161.1: A left-sided pleural effusion in a woman with rheumatoid arthritis for more than ten years. Pleural fluid glucose was 20 mg/ml. She was asymptomatic. No treatment was given

Thoracentesis should be performed in patients who have RA and a pleural effusion. Pleural fluid analysis usually reveals a white cell count less than 5,000/mm^3, a pleural fluid glucose of less than 0.3 g/L, a pleural fluid glucose to serum glucose ratio less than 0.5, a pH less than 7.3 and high pleural fluid LDH level (i.e. > 700 IU/L). Low glucose levels are nonspecific and may occur in tuberculosis and malignant mesothelioma. Less commonly, patients with RA and a long-standing pleural effusion may develop cholesterol effusion, known as a pseudochylous or chyliform effusion. Cholesterol effusions have the appearance of an empyema, but are sterile. The milky appearance is due to an elevated cholesterol level (always >65 mg/dL and sometimes over 1000 mg/dL); cholesterol crystals, identifiable with polarized light, may also be present. Cytological examination of rheumatoid pleural fluid often reveals slender or elongated or round multinucleate macrophages and giant multinucleated cells and ragocytes or "RA cells".[6,7]

Rheumatoid pleuritis and pleural effusions commonly resolve spontaneously (Fig. 161.1). The reported useful treatment options include Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), glucocorticoids (oral or intrapleural), pleurodesis and decortication. When treatment is required due to the presence of pleuritic chest pain or the size of the effusion, the initial choice is an NSAID, such as indomethacin. In refractory cases of pleural effusion, a moderate dose of oral glucocorticoids, e.g. 10-20 mg of prednisone daily, may be beneficial. If the patient is intolerant of the side effects due to systemic glucocorticoids, intrapleural glucocorticoids, e.g. 120-160 mg of depo-methylprednisolone acetate can be tried. Use of chemical pleurodesis and decortication is reserved for refractory effusions and fibrothorax.

Interstitial Lung Disease

In Walker's series comprising of 516 cases, only 8 (2%) had radiographical evidence of Interstitial Lung Disease (ILD).[3] A much higher prevalence is detected by pulmonary function testing. As many as 41% of patients with RA have restrictive impairment and reduced diffusion capacity.[8] High resolution computed tomography can identify the clinically silent lung disease. A higher prevalence of ILD occurs in men then in women. Other risk factors include smoking, high titers of RF, alpha-1 anti-trypsin variants, subcutaneous nodules and prominent joint manifestations.[9] Diffuse pulmonary fibrosis of RA has features similar to those seen in Idiopathic Pulmonary Fibrosis (IPF) patients. However, the rheumatoid pulmonary fibrosis is a separate entity, because the lungs of these patients, in addition to the usual changes of IPF, show specific features of hyaline collagen nodules, often with necrosis, along with a surrounding palisade of fibroblasts[10-12] (Fig. 161.2).

The symptoms of rheumatoid ILD are nonspecific, namely: dyspnea, dry cough and basal lung crepitations. Finger clubbing may also be present.

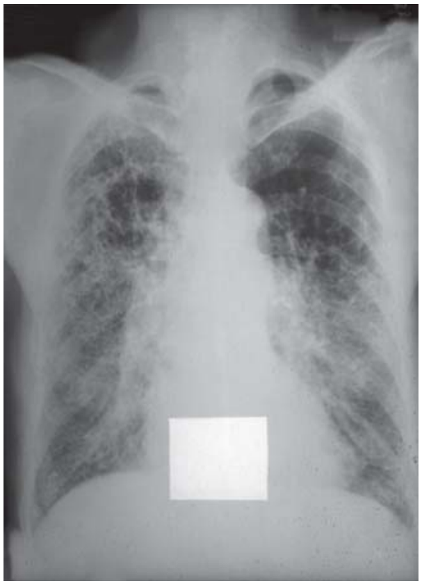


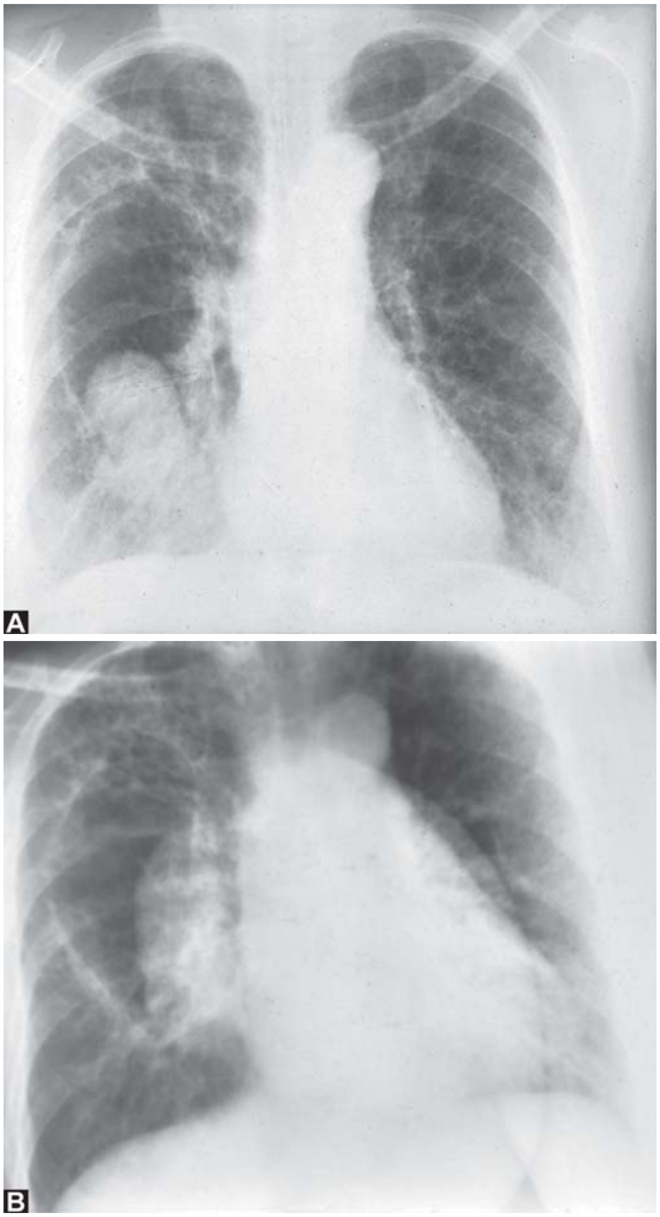
Fig. 161.2: Posteroanterior view of the chest in a patient with rheumatoid arthritis showing extensive interstitial disease with honeycombing and cystic changes

In established cases, chest X-ray films show small lungs with diffuse bilateral reticulonodular infiltrates with lower lobe predominance. Progression of the disease results in cystic spaces, honeycombing and fibrosis. HRCT of the chest shows similar lesions, but with higher sensitivity.[13] Erythrocyte Sedimentation Rate (ESR) is usually raised and serum rheumatoid factor is positive (Figs 161.3A and B).

Rheumatoid ILD has a better prognosis and slower rate of deterioration than IPF. Spontaneous remission can occur. No optimal therapeutic approach has been established for RA related ILD. Often corticosteroids are used as the first-line treatment. Initial dose of prednisone is 1 mg/kg per day for 6-8 weeks with subsequent tapering based on clinical and lung function monitoring. Response to corticosteroids is variable. Drugs, like methotrexate, azathioprine, cyclophosphamide, have been used alone and in combination with prednisone. Cyclosporine has been proved beneficial in selected cases. Bronchoalveolar Lavage (BAL) fluid lymphocytosis indicates a good response to treatment, whereas BAL neutrophilia portends a poor prognosis.[13]

Rheumatoid Nodules

Rheumatoid nodules are the specific pulmonary manifestation of RA. The prevalence of pulmonary rheumatoid nodules is not clear. In one series, only 2 of 516 patients showed radiological evidence of nodules.[3] However, a study of open lung biopsies from 40 patients with suspected lung disease found that rheumatoid nodules were the most common abnormality present in 13 patients; 8 out of these 13 patients had multiple nodules[10] (Figs 161.4 and 161.5). There are two types of rheumatoid lung nodules: Intrapulmonary necrobiotic nodules and Caplan's syndrome.



Figs 161.3A and B: A posteroanterior and right decubitus chest X-ray films showing a large cavity and with an aspergilloma. The patient has history of rheumatoid arthritis for more than 40 years

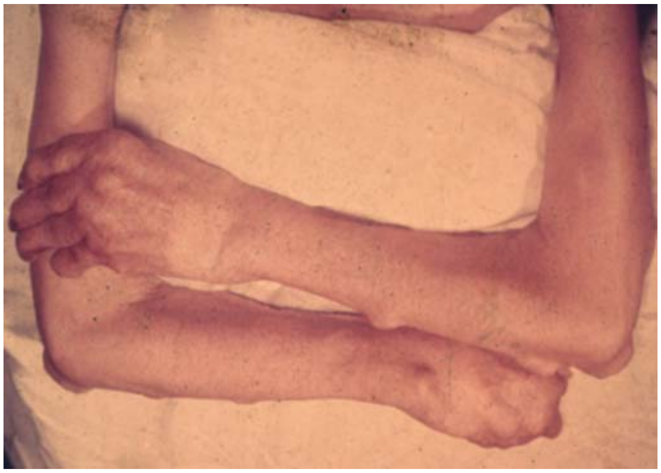


Fig. 161.4: A 60-year old man with advanced rheumatoid arthritis and many subcutaneous nodules. He has high rheumatoid factor titer. He is the type of rheumatoid arthritis patient who is prone to developing pulmonary nodules and interstitial fibrosis

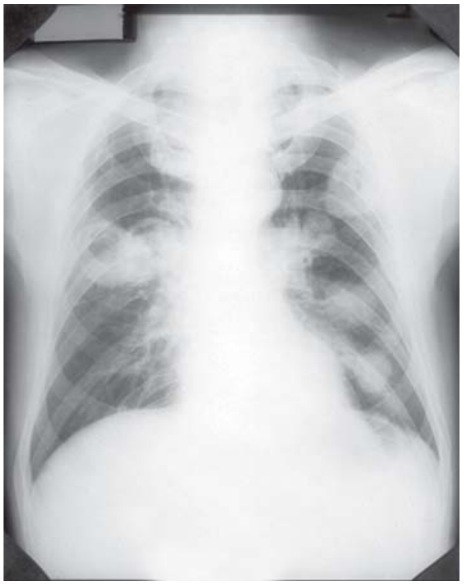
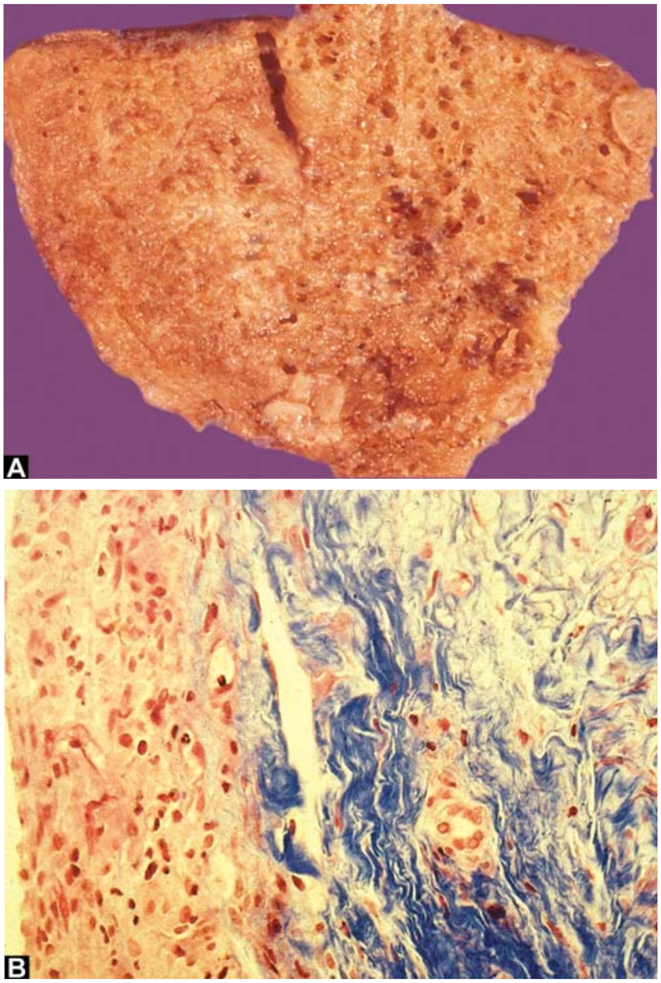


Fig. 161.5: A posteroanterior view of the chest of a patient with rheumatoid arthritis showing multiple solid and cavitary pulmonary nodules

Necrobiotic Nodules

These may occur in any part of the lung, but are generally frequent in subpleural areas and in association with interlobular septa. The histology of a rheumatoid pulmonary nodule is similar to that of rheumatoid nodules at other sites, with central necrosis, palisading epithelioid cells, a mononuclear cell infiltrate and vasculitis. These nodules may shrink, disappear, cavitate or become fibrotic. The prognosis is good (Figs 161.6A and B).



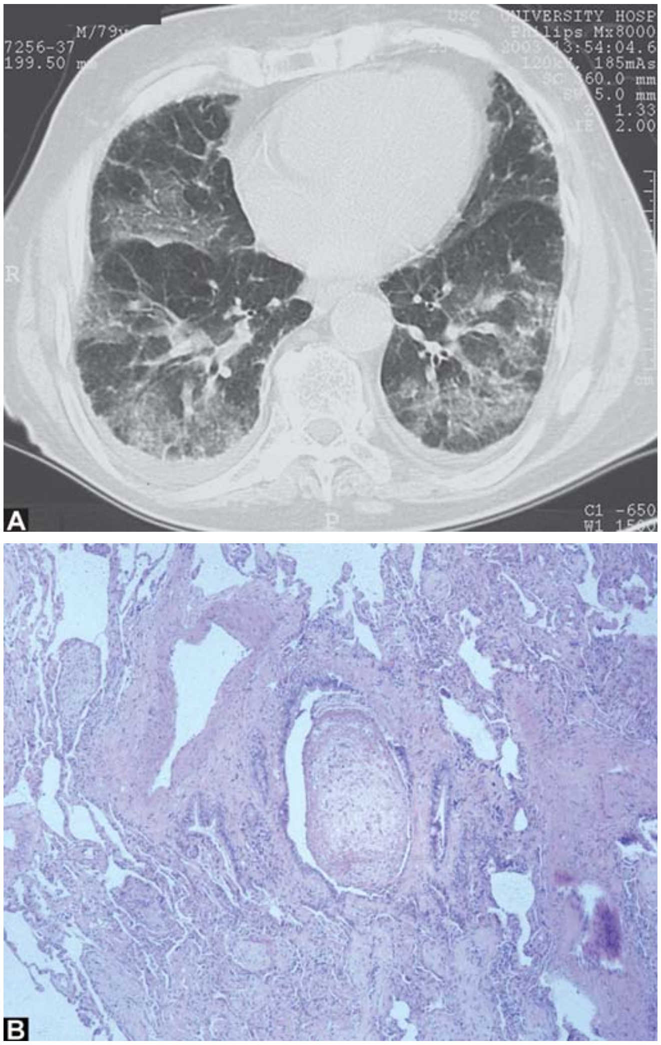
Figs 161.6A and B: (A) Gross appearance of rheumatoid pulmonary nodules; (B) Histolgical appearance with palisading inflammatory cells and fibrosis in a rheumatoid nodule

Caplan's Syndrome (Rheumatoid Pneumoconiosis)

In 1953, Caplan first reported the occurrence of lung nodules in coal miners who also had rheumatoid arthritis. Caplan's syndrome can also occur in patients with RA exposed to both asbestos and silica. Histologically, the findings are similar to necrobiotic nodules, but are surrounded by pigmented cells. There is no effective treatment for Caplan's syndrome. The prognosis is good.[14]

Organizing Pneumonia

Organizing Pneumonia (OP), also known as BOOP or Cryptogenic Organizing Pneumonitis (COP) is a proliferative bronchiolitis. In a study of open lung biopsies from 40 patients with parenchymal lung disease and RA, OP was the second most common pathological



Figs 161.7A and B: (A) A CT showing peripheral and lower lobe patchy infiltrates characteristic of bronchiolitis obliterans organizing pneumonia (BOOP). It can occur in any collagen vascular disease; it responds nicely to treatment. (B) A lung biopsy showing typical Mason bodies causing obstruction of BOOP (HE X 100)

manifestation, following rheumatoid nodules.[10] In other series it was the most common ILD after Usual Interstitial Pneumonitis (UIP) and Nonspecific Interstitial Pneumonitis (NSIP).[11, 12] Patients with RA complicated by OP present with cough, dyspnea, malaise, weight loss and fever. Crackles are noted on physical examination. Diagnosis may occasionally be made with a transbronchial lung biopsy, but more commonly an open or thoracoscopic lung biopsy is required. The biopsy demonstrates patchy intraluminal polypoid plugs of immature fibroblast tissue within respiratory bronchioles (Figs 161.7A and B).

The prognosis of OP is generally good, but spontaneous improvement is rare. Most patients with OP respond rapidly to oral glucocorticoid therapy. Therapy with prednisone is usually initiated with 1-1.5 mg/kg per day (using ideal body weight) to a maximum of 100 mg/day given as a single oral dose in the morning for 4-8 weeks. If the patient becomes stable or is improved, the prednisone dose is gradually tapered to 0.5-1.0 mg/kg per day (using ideal body weight) for another 4-6 weeks. Prednisone is gradually tapered to zero if the patient remains stable or is improved after 3-6 months. The patient should be monitored with chest radiographs and pulmonary function testing every 6-8 weeks during the first year, and therapy should be reinstituted aggressively at the sign of any recurrence.

If the patient cannot tolerate corticosteroids, cyclophosphamide (1-2 mg/kg per day given as a single daily dose) is recommended. Start with 50 mg daily and slowly increase the dose over 2-4 weeks, not exceeding 150 mg/day. A trial of 3-6 months is usually required.

Airway Obstruction

Upper Airway Obstruction

Upper airway disease is more common in women and in patients with long-standing RA. Direct laryngoscopy and CT scanning demonstrate that 54 to 75% of patients have cricoarytenoid abnormalities. A rheumatoid nodule on the vocal cord or vasculitis involving the recurrent laryngeal or vagus nerves may cause obstruction. Early symptoms of upper airway disease may include a hoarse voice, odynophagia, tenderness of the throat and pain on coughing or speaking. Diagnosis of upper airway obstruction is made by laryngoscopy and inspiratory and expiratory flow volume loops.

Small Airway Obstruction

The prevalence of small airway obstruction and bronchial hyper-responsiveness in patients with RA remains unestablished, because studies have been confounded by the presence of smoking or RA-ILD. In non-smoking subjects, a prevalence of 0 to 24% has been reported.

Obliterative Bronchiolitis

Obliterative bronchiolitis (OB) is a rare and usually fatal condition characterized by progressive concentric narrowing of membranous bronchioles. An OB is more common in women patients with positive rheumatoid factor test and Sjögren's syndrome (Fig. 161.8). It can also occur in patients with RA who receive d-penicillamine, gold and sulfasalazine treatment. Patients typically present with the rapid onset of dyspnea and dry cough.

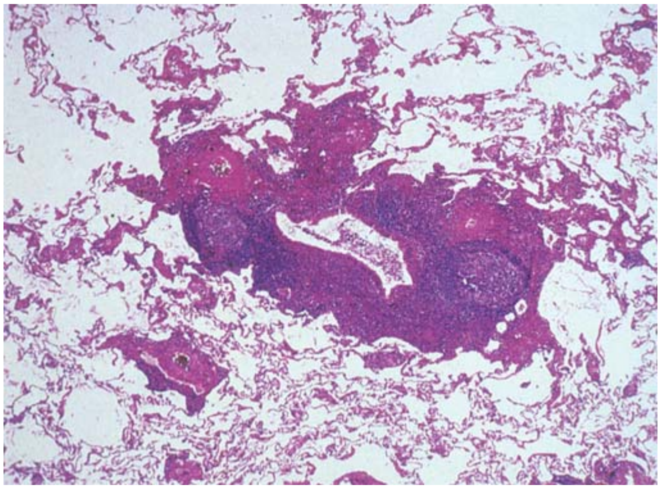


Fig. 161.8: Rheumatoid bronchiolitis (HE X120)

Fever, weight loss and malaise are generally not present. Physical examination may reveal inspiratory crackles and a mid-inspiratory squeak. Lung function changes include airflow obstruction, normal Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) and hypoxemia. A trial of high dose corticosteroids, prednisone (in the dosage of 1-1.5 mg/kg per day) is indicated.[15,16]

Bronchiectasis

Although an association between bronchiectasis and RA has been noted, it does not appear to be clinically significant in most patients.[17]

Apical Bullous Disease

Apical fibrotic and cavitary lesions similar to those in ankylosing spondylitis have been reported in patients with RA.[18]

Thoracic Cage Involvement

Abnormalities of thoracic cage mobility, similar to those seen with ankylosing spondylitis, can occur.

Pulmonary Hypertension

Pulmonary arterial hypertension is rare in patients with RA. Its clinical manifestations and prognosis are similar to those with idiopathic pulmonary arterial hypertension in the absence of RA. Secondary pulmonary hypertension usually associated with severe ILD has also been reported in patients with RA.[19]

Lung Cancer

The risk of developing lung cancer may be slightly greater in patients with RA than in the general population.[20,21]

TABLE 161.3: Pulmonary complications of progressive systemic sclerosis (SSc)

Common

1. Non-specific interstitial pneumonitis
2. Usual interstitial pneumonitis/fibrosis
3. Pulmonary hypertension
4. Alveolar cell carcinoma
5. Pleural thickening

Uncommon

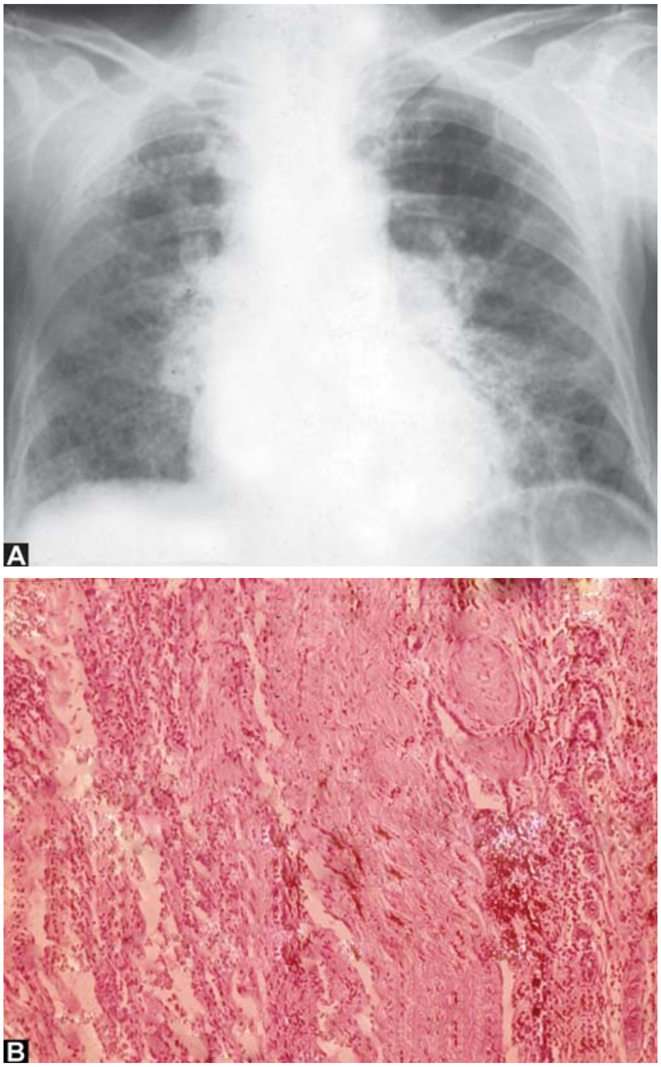
1. Pleural effusion
2. Pneumothorax
3. Bronchiectasis
4. Lung cancer
5. Vascular aneurysm

SCLERODERMA

More than 80% of patients with systemic sclerosis have lung involvement. ILD and pulmonary hypertension are the two major pulmonary complications. Other less common pulmonary complications include pleural effusions, aspiration pneumonia, spontaneous pneumothorax, bronchiectasis, hemoptysis, drug-induced pneumonitis and lung cancer[22,23] (Table 161.3).

Interstitial Lung Disease

The reported prevalence of ILD in patients with SSc varies. ILD is detected early by HRCT and in autopsy series. The early development of ILD occurs in African-American patients and in the patients with skin disease, high serum CPK levels, hypothyroidism and cardiac involvement.[24] Early SSc-ILD frequently causes no symptoms. When present, the most common symptoms are fatigue, breathlessness and dry cough. Chest pain is infrequent; hemoptysis is rare. The most characteristic physical sign is presence of bilateral fine inspiratory crackles rales at the lung bases. The symptoms, physical findings and radiographic characteristics of SSc-associated ILD are similar to other types of ILD.[25,26] The classic radiographic features of established ILD comprise of symmetric, reticular opacities. These are usually most pronounced at the lung bases (Figs 161.9A and B). Thin section (3 mm or less) HRCT scanning of the lung can demonstrate the character and distribution of fine structural abnormalities not seen on chest radiographs[27] (Fig. 161.10). The extent of ILD seen on HRCT, inversely related to Forced Vital Capacity (FVC) is a predictor of survival. The FVC is reduced and there is a proportional reduction of the Forced Expiratory Volume in One Second (FEV_1). The FEV_1/FVC ratio remains normal. The Total Lung Capacity (TLC), Functional Residual



Figs 161.9A and B: (A) Posteroanterior chest X-ray film showing difuse fine nodular and honeycombing in an adult with progressive systemic sclerosis; (B) Lung biopsy specimen from the patient shows extensive fibrosis

Capacity (FRC) and residual volume (RV) are decreased in ILD. The patients with SSc who have a near-normal FVC at initial presentation have low-risk for progression to severe lung disease. Diffusion capacity is reduced in over 70% of the patients and its decrease correlates with the severity of ILD seen on HRCT. A reduction in DLCO accompanied by relatively normal spirometry and lung volumes suggests pulmonary vascular disease. The value of the Six-Minutes Walk Test (6MWT) is more limited in SSc, as it does not discriminate well between patients with lung involvement and those without.[28]

The common pathological patterns of SSc-associated ILD are NSIP and UIP. The most frequently noted histopathological finding on lung biopsy in SSc is fibrotic NSIP. Intimal thickening of pulmonary arteries and resulting luminal narrowing is often found in post-mortem lung specimens. Lung biopsy is rarely indicated in SSc associated lung disease.[29,30]

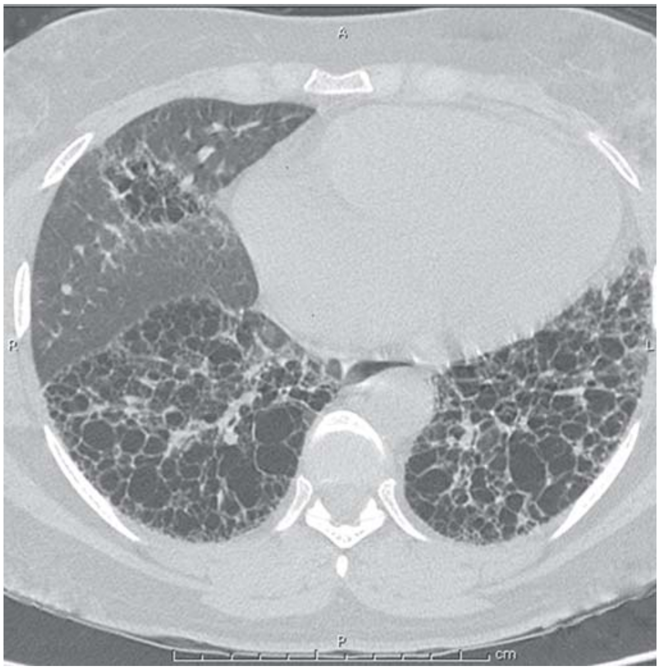


Fig. 161.10: HRCT showing honeycombing and dilated esophagus in a scleroderma patient

Bronchoalveolar lavage fluid in patients with SSc-associated ILD shows increased numbers neutrophils, eosinophils, lymphocytes and mast cells. The clinical significance of these findings is controversial. In a study of 158 patients with early SSc-associated ILD, there was no difference in the change in FVC after 12 months when patients with BAL-defined alveolitis were compared to patients who had a normal BAL. The levels of KL-6, a glycoprotein, found predominantly on type II pneumocytes and alveolar macrophages are elevated in the serum of patients with SSc-associated ILD.[31]

Pulmonary Arterial Hypertension

The prevalence of PAH in SSc varies 7 to 50%. It may occur as an isolated pulmonary complication of SSC, or can coexist with ILD. It may also be associated with the CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias). Early PAH is asymptomatic, but dyspnea on exertion is the most common initial symptom. Patients with advanced PAH may have chest pain due to right ventricular angina, and near-syncope or syncope on exertion due to reduced cardiac reserve. On physical examination, advanced PAH may be associated with a prominent a-wave in the jugular venous pulse, a loud pulmonic second heart sound, and a right ventricular gallop. The murmur of tricuspid regurgitation is common and may be accompanied by a palpable right ventricular lift or heave.[32]

On a chest radiograph, PAH produces an enlarged pulmonary artery and attenuation of the smaller pulmonary vessels. The presence of PAH may be suspected if pulmonary function tests show a significant decrease in DLCO (less than 65% of the predicted value) in the presence of normal spirometry.[33]

Doppler echocardiography permits estimation of pulmonary artery pressures when tricuspid regurgitation is present. The test cannot be relied upon to exclude PAH in high-risk patients due to its limited sensitivity and technical limitations. Right heart catheterization is the gold standard for identification and evaluation of PAH.[34]

A new screening test for PAH in SSc is measurement of serum levels of Brain Natriuretic Peptide (BNP) and/or N-terminal pro-brain natriuretic peptide (NT-proBNP). Elevated NT-proBNP levels have a sensitivity and specificity of 90% respectively for the presence of PAH.[35-37]

Aspiration Pneumonitis

Gastroesophageal reflux, present in most patients, may cause recurrent aspiration of gastric contents and lung injury.[38]

Pleural Disease

Pleural effusion and spontaneous pneumothorax are rare complications.[39,40]

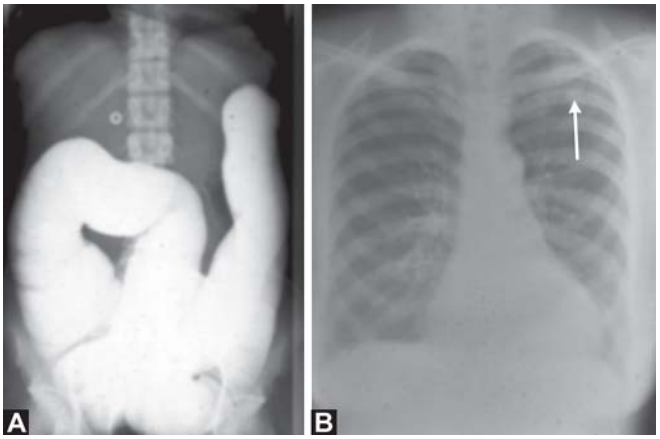
Bronchiectasis

Cylindrical bronchiectasis is a common finding on HRCT scanning of the lungs of patients with SSc. In one study comprising 22 patients, bronchiectasis was present in 59% of cases.[41,42]

Lung Cancer

The risk of lung cancer is increased in SSc patients with diffuse skin involvement (Figs 161.11A and B).

Corticosteroids have no effect on the course of established ILD in scleroderma. Colchicine suppresses the release of fibroblast growth factors *in vitro* from alveolar macrophages, but does not affect the scleroderma lung disease. Cyclophosphamide significantly improves dyspnea and lung functions.[43,44]



Figs 161.11A and B: A rare complication of pulmonary fibrosis in scleroderma. The patient has smooth colon. Because of the loss of haustral markings. There is a small lung nodule in the left upper lobe which on biopsy turned out to be an alveolar cell carcinoma

SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is characterized by lymphocytic infiltration of the lacrimal and salivary glands. It can exist as a primary disorder or as a secondary condition associated with other autoimmune diseases such as rheumatoid arthritis, Systemic Lupus Erythematosus (SLE) and scleroderma. The typical symptoms of SS are dryness of the eyes (keratoconjunctivitis sicca) and dryness of the mouth (xerostomia).[45]

Primary Sjögren's syndrome (pSS) primarily affects women between 50 and 70 years of age. The prevalence of pulmonary disease in SS has not been established, and the reported incidences vary greatly. In one study the prevalence of respiratory disease in patients with pSS was found to be as high as 75%.[46]

An ILD, the most common lung abnormality in SS, occurs in about 25% of all patients. It is particularly seen in patients who have both glandular and extraglandular features of SS. The most common type of ILD in pSS is NSIP[47] (Table 161.4).

Dyspnea and dry cough are two principal symptoms; the presence of bibasilar crackles is the most frequent sign. Asymptomatic patients can have detectable abnormalities on pulmonary function testing or HRCT. The chest radiograph may be normal, or may show a fine reticular or nodular pattern with basilar prominence on

TABLE 161.4: Pulmonary complications of Sjögren's syndrome

1. Non-specific interstitial pneumonitis
2. Usual interstitial pneumonitis
3. Lymphocytic interstitial pneumonitis
4. Pulmonary lymphoma
5. Diffuse pulmonary amyloidosis

TABLE 161.5: HRCT features of pulmonary Sjögren's syndrome

1. Interstitial lung disease
    - Ground glass attenuation
    - Interlobular thickening
    - Honeycombing
2. Airway involvement
    - Bronchial thickening
    - Bronchiectasis
    - Centrilobular nodules
3. Thin-walled cysts

chest radiograph in 10 to 20% of cases. The HRCT is more sensitive than chest radiograph for interstitial disease[48-50] (Table 161.5).

In patients with interstitial opacities on chest radiograph, pulmonary function tests commonly reveal a restrictive pattern with a low diffusing capacity.[49] The combination of a restrictive defect and a low DLCO appears to be more common in pSS than in sSS. Anti-Ro antibody positive patients have significantly lower diffusing capacity than anti-Ro antibody negative patients.[51]

In patients without clinical or radiographical evidence of pulmonary disease, BAL may show evidence of inflammation. A pure lymphocytic alveolitis is common; neutrophil predominance is also observed in some cases. A wide spectrum of histological changes, including a mild inflammatory response, NSIP, end-stage fibrosis, honeycombing and OP, is seen. A feature common in SS is lymphocytic infiltration causing follicular bronchiolitis, LIP, nodular lymphoid hyperplasia and lymphoma. Occasionally, in SS, lung biopsy specimens may reveal noncaseating granulomas, a finding suggestive of sarcoidosis.[52-54]

The treatment of SS and ILD remains empiric, since no controlled studies have been performed. In symptomatic patients with SS and ILD and functional deterioration, the standard treatment is oral prednisone in the dosage of 1 mg/kg per day with subsequent tapering, continued for at least six months. The patients who do not improve with systemic glucocorticoids should receive azathioprine, cyclophosphamide and cyclosporine.[55,56]

SYSTEMIC LUPUS ERYTHEMATOSUS

During the course of their illness, most patients with SLE show signs of pulmonary involvement (Table 161.6). Chest pain, cough, and dyspnea are often the first symptoms. Pleural inflammation may cause chest pain in the absence of a friction rub or radiographic evidence of a pleural effusion. The pain is often aggravated by deep breaths and change of position. Chest pain may also arise from the inflamed muscles and the connective tissue.[57]

Pleural Disease

The effusions, when present, are small, recurrent and often bilateral. The pleural fluid is an exudate with elevation of pleural fluid LDH. The total white cell count is low and pleural fluid glucose concentration is only slightly lower than serum blood levels. The complement levels and protein concentration are characteristically low in lupus effusions. Pleural disease and pain in SLE generally responds well to local heat, NSAIDs and topical analgesics. If there is no response within a few days, moderate to high dose steroids will generally be effective. Immunosuppressive agents are rarely indicated. Fibrothorax and lung entrapment are rare.[58,59]

Acute Lupus Pneumonitis

Acute lupus pneumonitis occurs in 1 to 12% of the patients and is characterized by fever, cough (sometimes with hemoptysis), chest pain, dyspnea, basilar rales and pulmonary infiltrates especially in the lower lung fields. Pleural effusion is present in about 50% of the patients.[60] Pathological examination in lupus pneumonitis reveals

TABLE 161.6: Pulmonary manifestations of SLE

1. Acute lupus pneumonitis
2. Chronic lupus pneumonitis
3. Vanishing lung syndrome
4. Alveolar hemorrhage
5. Cryptogenic organizing pneumonia
6. Pleural effusion
7. Linear atelectasis
8. Acute reversible hypoxemia
9. Veno-occlusive disease
10. Adult respiratory distress syndrome
11. Pulmonary hypertension

TABLE 161.7: Common clinical features of pulmonary hypertension

1. Right ventricular heave or lift
2. Jugular venous distention
3. Prominent A and V venous waves
4. Fixed split pulmonary 2nd sound
5. Right ventricular gallop
6. Tricuspid regurgitation murmur (systolic)
7. Pulmonary insufficiency murmur (diastolic)
8. Enlarged liver
9. Ascites
10. Peripheral edema

TABLE 161.8: HRCT patterns of lupus pneumonitis

1. Ground-glass attenuation (NSIP pattern on biopsy)
2. Reticular-linear pattern (UIP pattern on biopsy)

acute alveolar wall injury, alveolar hemorrhage, alveolar edema, hyaline membrane formation and immunoglobulin and complement deposition (Table 161.7). The diagnosis of alveolitis may be made by the presence of late inspiratory crackles, and abnormalities on CT scanning, 67 gallium scintigraphy or BAL (Table 161.8). It is difficult to clinically separate acute lupus pneumonitis from alveolar hemorrhage. An increased DLCO is suggestive of alveolar hemorrhage. Video-assisted thoracoscopic biopsy or open lung biopsy may be necessary. The patients with lymphocytosis on BAL have the best prognosis, whereas, the predominance of eosinophils or neutrophils in lavage fluid portends high mortality rate. Lupus pneumonitis developing in the postpartum period has a poor prognosis.[61,62]

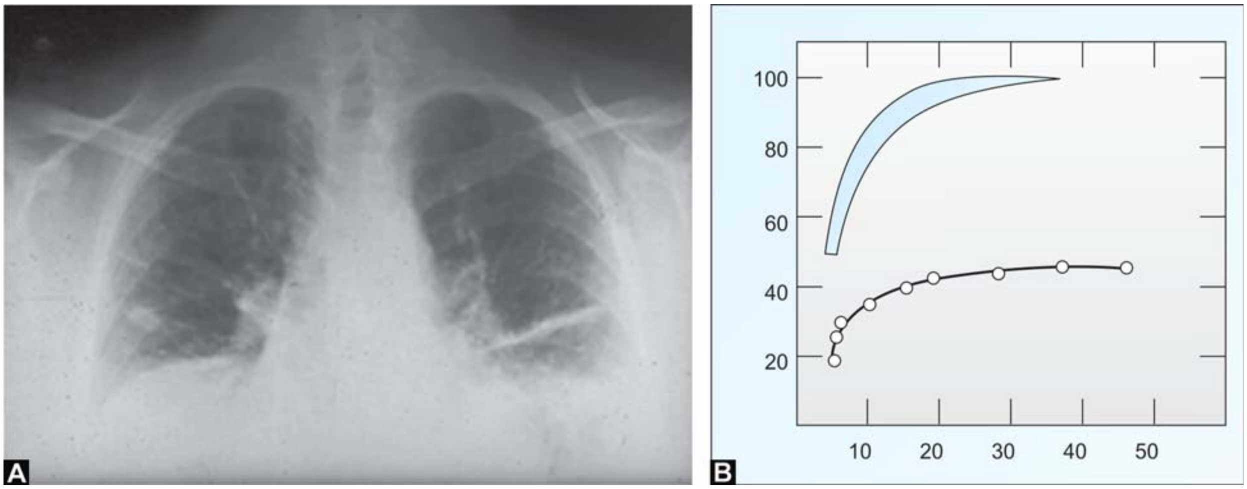
Acute lupus pneumonitis, however, needs prompt and aggressive treatment with prednisone around 1-1.5 mg/kg per day in divided doses. If no response is seen within 72 hours, the administration of intravenous pulse glucocorticoids (one gram of methylprednisolone per day for three days) and addition of slower acting immunosuppressive drugs, such as cyclophosphamide, should be considered.[63]

Chronic Lupus Pneumonitis

Chronic (fibrotic) lupus pneumonitis occurs in less than 10% of patients with longstanding SLE, and those with anti-Ro antibodies are more likely to develop chronic pneumonitis. These patients frequently suffer from chronic non-productive cough, dyspnea and recurrent pleuritic chest pain. Pulmonary function studies show a restrictive pattern with reductions in lung volumes, DLCO and arterial blood oxygen tension.

Chest radiographs reveal changes of chronic pneumonitis. The HRCT, BAL and 67-gallium scintigraphy are the important tools to diagnose lupus pneumonitis. In undiagnosed cases, lung biopsy may become necessary (Figs 161.12A and B).

Treatment of chronic lupus pneumonitis is begun with oral prednisone in a dose of 1 mg/kg per day. Patients treated with glucocorticoids tend to improve slowly and stabilize with time. Symptomatic improvement may not always be reflected in DLCO improvement. Immunosuppressive agents are considered if no



Figs 161.12A and B: (A) A chest X-ray film showing small lungs and linear basilar atelectasis in a patient with systemic lupus erythematosus. (B) The lung function graph shows reduced lung compliance

TABLE 161.9: Histopathology features of lupus pneumonitis

1. Nonspecific interstitial pneumonitis
2. Usual interstitial pneumonia
3. Lymphocyic interstitial pneumonitis
4. Alveolar wall thickening
5. Alveolar septal immune-complex deposits
6. Type-II pneumocyte hyperplasia

response is seen within a few months of beginning steroid therapy. The optimal choice of immunosuppressant is uncertain, but cyclophosphamide, azathioprine or mycophenolate have all been utilized.[64,65]

Pulmonary Hypertension

Mild-to-moderate pulmonary hypertension occurs in more than 50% of the patients. Dyspnea, chest pain and chronic nonproductive cough are the frequent symptoms. Fatigue, weakness, palpitations and edema may also occur. Physical findings are similar to pulmonary hypertension from any other cause (Table 161.9). Laboratory abnormalities include hypoxemia, enlarged pulmonary arteries with clear lung fields on chest radiography, reduced lung volumes and a reduced carbon monoxide diffusing capacity and electrocardiographic evidence of right ventricular hypertrophy. The typical histopathological features of lupus-induced pulmonary hypertension include plexiform angiomas, thickening of the muscular wall of the pulmonary arteries, and immunoglobulin and complement deposition in the arterial walls.[66,67]

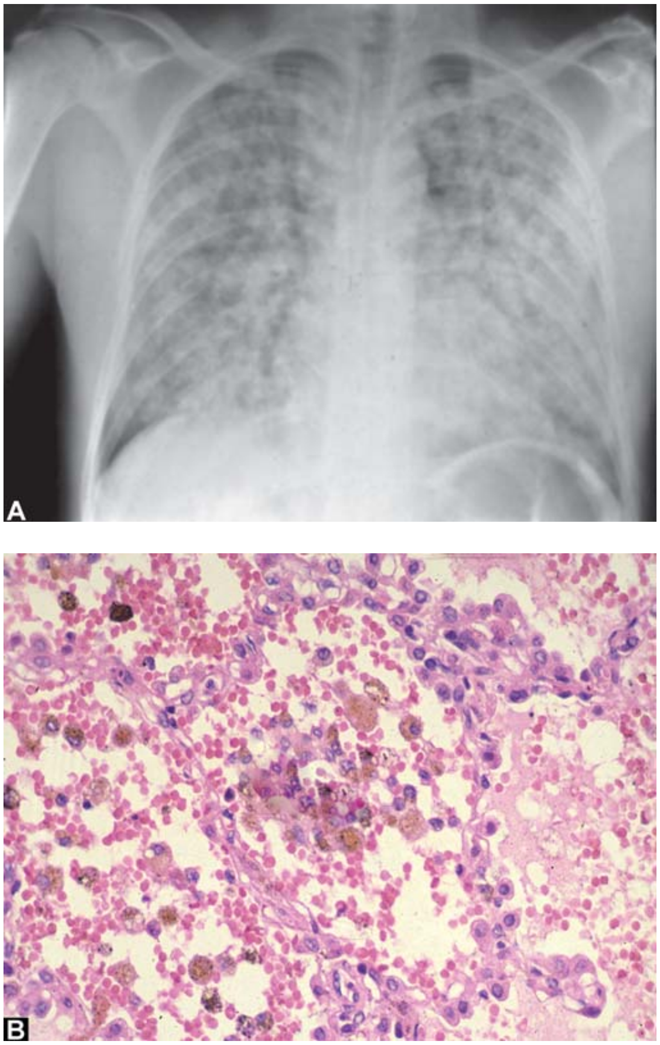
The management of patients with secondary pulmonary hypertension and SLE is similar to that in idiopathic pulmonary arterial hypertension.

Vanishing Lung Syndrome

This syndrome is characterized by dyspnea, pleuritic chest pain and a progressive decrease in lung volume without any significant lung or pleural disease on chest CT. The most likely cause of VLS is a myositis or myopathy that affects the diaphragms. However, some patients with VLS may have normal diaphragmatic muscle strength. The syndrome should always be considered in patients with SLE who have dyspnea, clear chest X-rays, and elevated diaphragms. Corticosteroids, theophylline, and/or immunosuppressive therapy may improve symptoms and pulmonary function.[68]

Pulmonary Hemorrhage

Alveolar hemorrhage is uncommon complication in SLE. Rarely, it may be the presenting manifestation of SLE, but most commonly it occurs during the course of an already diagnosed lupus.[69,70]



Figs 161.13A and B: (A) A chest X-ray film showing diffuse alveolar densities in a patient with SLE and hemoptysis. The patient was anemic and had an elevated single-breath diffusing capacity for carbon-monoxide; (B) A bronchoscopic biopsy in alveolar hemorrhage shows only blood and the test is of little value

The patient complains of dyspnea, hemoptysis and cough. Chest X-ray films may reveal bilateral alveolar infiltrates. Pulmonary magnetic resonance imaging may suggest hemorrhage, since the paramagnetic effects of iron in hemorrhagic blood result in preferential T2 shortening. The BAL yields bloody fluid with hemosiderin-laden macrophages. A significantly elevated diffusing capacity for carbon monoxide may be strongly suggestive of pulmonary hemorrhage; the diagnosis can be established definitively by lung biopsy.

High dose corticosteroids, cyclophosphamide, plasmapheresis, antibiotics and mechanical ventilation have improved survival rate (Figs 161.13A and B).

Cryptogenic Organizing Pneumonia (COP)

The COP (also known as BOOP) is a pathological entity characterized by the formation of plugs of fibrous tissue in bronchioles and alveolar spaces. Dry cough and multiple infiltrates on chest X-ray are two main clinical features. The diagnosis is confirmed by lung biopsy. Treatment with oral prednisone (1 mg/kg per day) is usually effective.[71]

Acute Reversible Hypoxemia

Acute hypoxemia as a manifestation of SLE is characterized by hypoxemia, a normal chest radiograph, and no evidence for pulmonary emboli. Plasma C3a levels are markedly elevated. In addition, up-regulation of adhesion molecules, such as E-selectin, VCAM-1 and ICAM-1, occurs suggesting that there is excessive complement activation and leukocyte-endothelial cell adhesion and leuko-occlusive vasculopathy. Glucocorticoids alone or with aspirin are effective.[72]

Pulmonary Veno-occlusive Disease (PVOD)

Pulmonary venoocclusive disease, a rare cause for pulmonary hypertension seen in SLE, is characterized by intimal fibrosis, occlusion of the pulmonary veins and edema in the interlobular septa. High resolution CT shows thickened interlobular septa, lymph node enlargement and ground glass opacities.[73]

Adult Respiratory Distress Syndrome

When Adult Respiratory Distress Syndrome (ARDS) develops, it is commonly due to bacteremia or sepsis with gram negative bacilli and more likely occurs in those who had been treated with glucocorticoids. It has a poor prognosis.[74]

DERMATOMYOSITIS (DM) AND POLYMYOSITIS (PM)

Four principal types of lung disease have been described in DM-PM[75,76] (Table 161.10).

Interstitial Lung Disease

When sought systematically in all patients, using techniques such as HRCT of the chest, the prevalence of ILD is about 40% in DM-PM. Several histological patterns of ILD occur in DM-PS[77,78] (Table 161.11).

Patients with ILD typically present with dyspnea and a nonproductive cough, fever and arthralgias.[64] Chest auscultation usually reveals dry bibasilar crackles. ILD can precede the diagnosis of myositis by months or years, or be the predominant feature at the time of presentation. The course of ILD varies amongst different patients (Table 161.12). In patients with symptomatic ILD, the pulmonary disease determines prognosis; it is worse than in the patients who do not have ILD. The prognosis and response to treatment are worse in patients with DM (Table 161.13).

TABLE 161.10: Clinical course of dermatomyositis/polymyositis related ILD

1. Acute fulminant disease with fever and respiratory failure
2. Slowly progressive disease lasting years
3. Asymptomatic disease with abnormal chest X-ray and abnormal functions

TABLE 161.11: Four types of lung disease in dermatomyositis/polymyositis syndrome

1. Interstitial lung disease
2. Respiratory muscle weakness
3. Infection
4. Drug-induced pneumonitis

TABLE 161.12: Histopathologic pictures dermatomyositis/polymyositis related lung disease

1. Non-specific interstitial pneumonitis
2. Usual interstitial pneumonitis
3. Bronchiolitis obliterans organizing pneumonia
4. Cellular interstitial pneumonia
5. Diffuse alveolar damage

TABLE 161.13: Factors suggesting good therapeutic response of DM-PM pulmonary disease

1. Young age
2. Polymyositis rather than dermatomyositis
3. Cryptogenic obliterative obstructive pneumonitis
4. High serum CK level at the time of onset of ILD
5. Alveolar infiltrate or ground glass attenuation
6. Little or no fibrosis on HRCT or lung biopsy

The diagnosis of ILD in DM and PM can be established by the clinical presentation, chest X-ray, high resolution CT scan and pulmonary function tests. The major radiographical finding is diffuse reticulonodular interstitial changes found predominantly in the lung bases (Fig. 161.14). Thin-section or high resolution chest CT is an excellent technique for characterizing nonspecific interstitial changes on chest X-ray. Typical patterns include ground glass opacification, basilar consolidation, septal thickening, honeycombing and

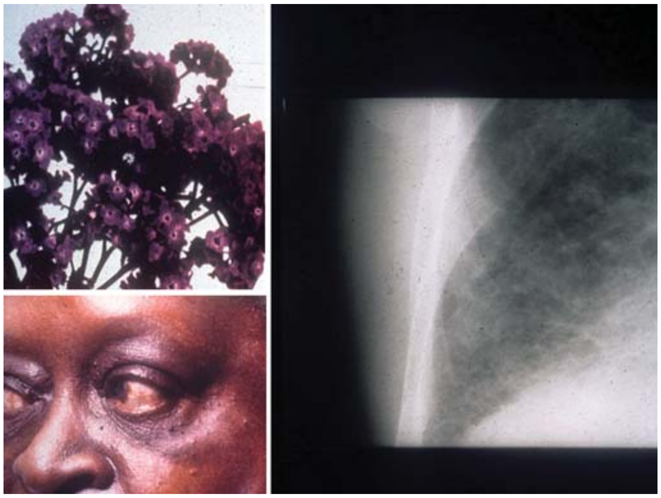


Fig. 161.14: A composite picture showing bluish purple hue of the face and fine nodular haziness of the lung in a patient with dermatomysitis

irregular linear opacities. The Jo-1 antigen, precipitating antibody to an acidic nuclear protein antigen is an important marker of the PM-DM associated ILD.[79,80]

Treatment of ILD in patients with myositis almost always requires glucocorticoids, regardless of whether pulmonary or muscle disease is the predominant feature of the patient's illness. No controlled trials of glucocorticoids have been undertaken; about 50% of myositis patients with ILD respond to corticosteroids.

Since ILD is a fatal disease, a second agent is added from the beginning of therapy in patients with DM or PM complicated by ILD. Options for this second agent in patients with mild ILD include azathioprine and methotrexate; azathioprine is preferred because of its favorable side effect profile. In patients with moderate to severe ILD cyclophosphamide is given. In patients with inexorable disease, rituximab and Intravenous Immune Globulin (IVIG) are the most commonly used treatment options.[81,82]

Respiratory Muscle Weakness

Respiratory muscle weakness occurs in 4 to 8% of patients with DM or PM. Typical inflammatory myopathic changes have been seen in the diaphragm, intercostal muscles and accessory muscles. Respiratory muscle weakness can cause mild dyspnea, linear or plate-like changes on chest X-ray, respiratory failure and hypercapnic coma. The patients with expiratory muscle strength less than 30% of normal and FVC less than 55% of predicted normal are prone for developing hypercapnia.

TABLE 161.14: Pulmonary manifestations of ankylosing spondylitis

1. Upper lobe fibrosis
2. Upper lobe cavities with fungus balls
3. Interstitial lung disease
4. Pleural effusion/thickening
5. Sleep apnea syndrome
6. Pneumothorax

Lung infection is common in DM and PM. Prophylaxis with trimmethoprim-sulfamethoxazole against *P. jirovecii* is given to the patients with DM or PM-ILD who are treated with high-dose glucocorticoids and immunosuppressive agents.

ANKYLOSING SPONDYLITIS

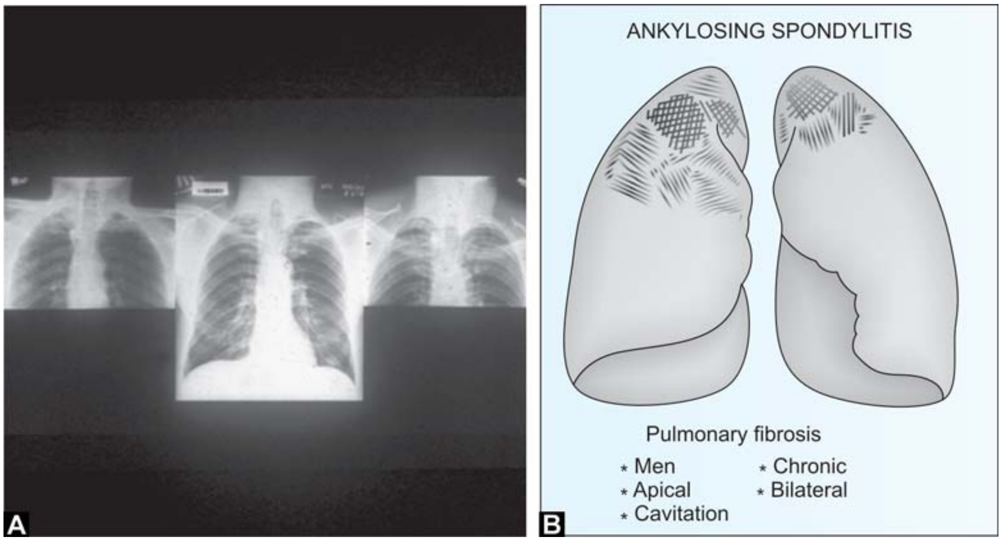
Ankylosing Spondylitis (AS) is a chronic progressive inflammatory rheumatic disease that affects primarily the sacroiliac joints and the axial skeleton. The disease is two to three times more common in men than in women, and is strongly associated with HLA-B27, a histocompatibility antigen I. A wide variety of pulmonary manifestations are seen in ankylosing spondylitis[83,84] (Table 161.14).

Upper Lobe Fibrosis

Upper lobe fibrosis is the most common extra-articular manifestation of AS. Occurring predominantly in men, the infiltrate may be unilateral, bilateral, acute or chronic, solid or cavitary. The cavities may become colonized with fungi or mycobacterial agents. In a study of 1,028 cases of AS seen in a tertiary referral centre over a 10-year period, 22 patients (2.1%) were found to have apical lung fibrosis on chest radiographs (Figs 161.15A and B). The HRCT imaging, however, reveals higher prevalence of apical fibrosis. The clinical significance of the HRCT abnormalities that are common in asymptomatic AS patients is uncertain[85-89] (Table 161.15).

TABLE 161.15: HRCT abnormalities in AS-related lung disease

1. Apical fibrosis
2. Thin-walled cavities
3. Fungus ball
4. Non-specific parenchymal abnormalities
5. Hilar/mediastinal adenopathy
6. Emphysema
7. Pleural changes



Figs 161.15A and B: A composite picture showing upper lobe lesions in a patient with ankylosing spondylitis

The pathogenesis of the apical fibrosis and other lung abnormalities seen in AS lesion is not known. Histological features include hyaline and elastic degeneration with interstitial fibrosis. Granulomas and vasculitis are absent. The lung function abnormality is restrictive in nature. Most of the patients are asymptomatic and treatment is not required. In symptomatic patients with active inflammation, non-steroidal anti-inflammatory agents have been used. The European League against Rheumatism has recommended the use of anti-TNF agents in AS patients with persistent activity, despite conventional treatment with non-steroidal drugs.[90-92]

Sleep Apnea Syndrome

The prevalence of sleep apnea syndrome is higher in AS patients then in general population. It has been suggested that AS predisposes to sleep apnea via different mechanisms that include restriction of the oropharyngeal airway due to cervical spine or temporomandibular arthritis, compression of medullary centers or by restrictive lung disease. Fatigue, a common symptom of AS, may be related to sleep apnea syndrome.[93]

Pneumothorax

A rare manifestation of pulmonary involvement in AS is due to rupture of fibrocystic foci. Due to the tendency of recurrence, prophylactic measures should be undertaken.[94]

Respiratory Muscle Weakness

Maximum inspiratory pressure, maximum expiratory pressure and maximum voluntary ventilation are reduced in AS. The respiratory muscle strength seems to correlate with diminished chest expansion.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

The pathogenesis and pathophysiology of MCTD are not well known. The clinical, radiological and physiological features of lung involvement in MCTD are similar to those observed in progressive systemic sclerosis in particular and other connective tissue diseases in general.[95,96]

Interstitial Lung Disease

The pathological features of ILD in MCTD are much like those seen in IPF, and include alveolarseptal infiltration by lymphocytes, plasma cells and type III collagen fibers. Corticosteroids and cytotoxic agents, such as chlorambucil and cyclophosphamide, are effective in acute inflammatory state.[97,98]

Pleural Effusion

Pleuritis occurs in about one-third of all the patients with MTCD. Occasionally, bilateral pleural inflammation is the initial event of MCTD; the fluid is usually exudative. Pleural thickening is uncommon.

TABLE 161.16: Principles of therapy in collagen vascular disease

1. Corticosteroids, cyclophosphamide, methotrexate and azathioprine and biological agents are the main drugs used
2. Rheumatoid arthritis-related ILD responds to corticosteroids and methotrexate
3. Corticosteroids are not useful in scleroderma-related lung disease; cyclophosphamide is the drug of choice
4. Acute lupus pneumonitis responds to corticosteroids
5. Collagen vascular disease-related BOOP/CP has good prognosis and responds to corticosteroids
6. Polymyositis-dermatomyositis related lung disease is fatal, corticosteroids and cyclophosphamide should be used

Pulmonary Hypertension

Progressive pulmonary hypertension is the most serious pulmonary complication of MCTD. It is often accompanied by severe systemic vasculitic lesions. In one study, out of all the patients studied, 67% had pulmonary hypertension. In these patients, elevated pulmonary vascular resistance was associated with impairment of diffusion capacity. Lung biopsy specimens reveal muscular hypertrophy of the small pulmonary arteries. Plexogenic angiopathy and intimal thickening of medium-sized arteries has been observed. Fatal pulmonary hypertension has been reported in MCTD patients.[99,100]

TREATMENT

Principle of therapy in collagen vascular diseases has been highlighted in Table 161.16.

CONCLUSION

Collagen vascular diseases form a heterogeneous group of autoimmune mediated inflammatory disorders. Pulmonary involvement is common. It is necessary to differentiate the primary lung disease related to the disease process from the super-imposed secondary infections and drug-induced changes. The treatment options are limited and include corticosteroids, immunosuppressive drugs and newer biological agents.

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Pulmonary Manifestations of Systemic Diseases: An Approach

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The lungs with their dual blood circulation and an open airway system exposed to the environment are liable to get involved in systemic diseases as well as in diseases of other organ systems. The spectrum of pulmonary manifestations due to systematic diseases are broad, accordingly, a major source of morbidity and mortality. This chapter is focused on important pulmonary manifestations of gastrointestinal and hepatic disorders.

ENDOCRINAL DISORDERS

Endocrine diseases can present with different respiratory symptoms. Respiratory problems may occur indirectly due to an increased risk of infection (as in diabetes) or due to upper airway obstruction secondary to goiter. Alterations in pulmonary function associated with disorders of the endocrine system can also occur due to the direct involvement of the respiratory system or its components.

Diabetes Mellitus

Diabetes is a systemic disease that produces structural and functional changes, particularly in the connective tissues, leading to end-organ damage in eyes, kidneys and nervous system. Microangiopathic processes and non-enzymatic glycosylation of tissue proteins at chronically high circulating glucose levels, together impair the collagen and elastin cross-linkage with reduction in the strength and the elasticity of connective tissue leading to functional derangement of end organs. Since the alveolar capillary network constitutes the largest microvascular organ in the body, it is highly susceptible to systemic microangiopathy. However, owing to a large physiological reserve of gas exchange, clinical manifestation and disability develop later in the lung than in the smaller microvasculature such as in the kidneys and the retina. In some cases, it may remain subtle and under recognized by both the endocrinologists and the chest physicians.

Diabetes can cause several clinical and functional respiratory complications (Table 162.1). Abnormal lung function can be detected in up to 73% of young asymptomatic type 1 diabetic patients.[1] Various cross-sectional studies have shown decreased Forced Vital Capacity (FVC), Forced Expiratory Volume in One Second (FEV_1) by 8-20% in both type 1 and type 2 diabetes mellitus consistent with modest restrictive defect without airway obstruction.[2-4] Similar observation of modest impairment is pulmonary function in a restrictive pattern has been observed in two recent systematic reviews of 74 studies involving more than 5000 patients

TABLE 162.1: Pulmonary complications of diabetes mellitus

Functional abnormalities
- ↓ Vital capacity
- ↓ Total lung capacity
- ↓ Diffusion capacity for carbon monoxide
- ↓ Inspiratory muscle strength
- ↓ Cough reflex

Sleep disordered breathing

Increase risk of infection
- Tuberculosis
- Fungal infections
- Legionella pneumonia

Aspiration pneumonia

However, longitudinal obser-vations over a 5- and 15-year follow-up period demonstrated that the rate of decline of FEV_1, and FVC is generally non-progressive in diabetic individuals in the long term, similar to that observed in non-diabetic subjects.[2,5] Similarly, reduction in total lung capacity and end expiratory lung volume of up to 30% below normal, which is inversely related to glycosylated hemoglobin levels, has been demonstrated in large cohorts of diabetes.[3,6,7]

Diabetic microangiopathy can also involve alveolar tissue and capillaries leading to reduction in alveolar gas transport, as manifested by reduced Diffusing Capacity of the Lung for Carbon Monoxide (DL_{CO}). Although a few studies have reported a normal lung diffusing capacity, majority of studies reported a reduced diffusing capacity among diabetic patients which is correlated with microangiopathy in other organs, duration of diabetes and microalbuminuria.[8-15] Based on available evidence, routine pulmonary function testing in diabetics is not warranted due to the small and clinically insignificant derangement in lung functions.

Subclinical autonomic dysfunction can occur within a year of diagnosis in type 2 diabetes and within two years in type 1 diabetes patients.[16] Reduced or absent cough reflex, diminished perception of inspiratory loading, sleep disordered breathing and aspiration are all associated with autonomic dysfunction in diabetic patients.[17-20] Clinically, there is depressed vagal tone manifested by blunted bronchodilator effect of anticholinergic agents and preservation of an intact end-organ response, supported by the findings of absent bronchoconstrictive response to cold-air provocation with normal or increased bronchial smooth muscle reactivity to direct stimuli with inhaled histamine.[21-23]

Diabetes mellitus with associated hyperglycemia is a risk factor for the development tuberculosis and is highlighted in several retrospective and prospective studies.[24-27] In the retrospective studies, the risk of acquiring tuberculosis in diabetes mellitus was as high as 4.8% compared to 0.8% risk in general population; type 1 diabetes mellitus was associated with 38 times more risk than in general population.[24] In countries with high incidence of tuberculosis, it is the most common complicating illness seen in diabetics.[25, 27] Surprisingly, the rate of infection with *Mycobacterium tuberculosis* is similar in both diabetics and matched controls as opposed to relative risk of 3.5 times higher in diabetics for development of pulmonary tuberculosis.[28] Routine screening for TB is recommended in a high prevalence country especially in children and adolescents with type I diabetes mellitus.[29]

Although clinical features, sputum positivity rate, response to anti-tubercular drugs are similar in diabetes mellitus and general population, radiological predilection for lower lung fields, tendency to cavitate and multilobar involvement are more frequently found in diabetics.[30, 31]

Thyroid Dysfunction

Thyroid hormones play a crucial role in lung development, surfactant synthesis and lung defenses. Consequently, both hyperthyroidism and hypothyroidism may alter the functions of respiratory system and result in several different clinical complications (Table 162.2). Both the excess and the deficiency of thyroid hormones can contribute to dyspnea and exercise limitation through the common mechanism of congestive heart failure or myopathy leading to respiratory muscle weakness and respiratory failure. Pleural effusion due to hypothyroidism *per se* or secondary to pericardial involvement may cause respiratory symptoms which resolve with treatment of hypothyroidism.

Obstructive manifestations, such as dyspnea, stridor, wheezing, hoarseness or cough produced by goiter, can occur by direct compression of the extrathoracic or intrathoracic trachea. Compression or irritation of the recurrent laryngeal nerves may result in airway obstruction due to vocal cord paralysis. Both the conditions remain obscured by other common causes of airway obstruction, unless specifically searched. The presence of dynamic obstruction can be demonstrated by the characteristic dampening of both the inspiratory and the expiratory curves on flow volume loop during lung function testing. One of the most consistent finding in hypothyroidism is its influence on the central ventilatory control. Both hypoxic ventilatory drive and hypercapnic ventilatory response are depressed in hypothyroidism. The blunting is more marked in

TABLE 162.2: Pulmonary complications of thyroid dysfunction

Functional abnormalities
- Characteristic dampening of inspiratory and expiratory flow volume loop in goiter
- ↓ Inspiratory muscle strength due to myopathy
- Blunted ventilatory response to hypoxia
- Blunted hypercapnic ventilatory response

Sleep apnea
- Central
- Obstructive

Pleural effusion
- Hypothyroid pleural effusion
- Hypothyroid associated effusion due to pericardial involvement

myxedema which can effectively be improved with thyroid hormone replacement.[32-34] Blunted ventilatory response is an important cause of increasing failure; approximately 3% of the mechanically ventilated patients who have weaning failure are subsequently detected to have hypothyroidism.[35]

In hypothyroidism, respiratory disturbances due to sleep apnea are observed in up to 50-100% of patients besides, the fact that the prevalence of hypothyroidism in sleep apnea is very low.[36,37] Both central apnea due to blunted ventilatory response to hypoxia and obstructive apnea secondary to deposition of mucopolysaccharides in the oropharynx and tongue leading to narrowing of upper airway during sleep can occur in hypothyroidism. Although hormone replacement leads to normalization of sleep apnea, a few patients may require continuous positive airway pressure support on the long-term basis.[38,39]

Acromegaly

Acromegaly is characterized by excessive bony growth, soft tissue hypertrophy and facial coarsening consequent to excessive release of growth hormone, most commonly from a pituitary adenoma. In patients with acromegaly, macroglossia, nasal polyps, oropharyngeal airway narrowing and vocal cord dysfunction are common features which predispose to respiratory disturbances and sleep apnea. Inspiratory pharyngeal collapse during sleep due to hypertrophy of parapharyngeal and retropharyngeal soft tissue and an enlarged tongue are some of the important causes of obstructive sleep apnea in acromegaly.[37] Neck circumference of greater than 41 cm and the circumference of the index finger of above 8.5 cm were found as good predictors of development of sleep apnea in acromegaly. Other respiratory problems which are commonly seen in acromegaly are extrathoracic airway obstruction, difficult intubation and vocal cord dysfunction.

GASTROINTESTINAL DISEASES

Due to close anatomical proximity and continuity of abdominal viscera to the thorax, any intra-abdominal pathology can secondarily involve the lungs, but more commonly few specific diseases have simultaneous and pronounced pulmonary manifestations.

Gastroesophageal Reflux Disease

TABLE 162.3: Pulmonary disorders associated with gastroesophageal reflux

- Chronic cough
- Bronchial asthma
- Aspiration pneumonia, lung abscess, bronchiectasis
- Vocal cord dysfunction
- Chronic bronchitis
- Idiopathic pulmonary fibrosis

Gastroesophageal Reflux Disease (GERD) may trigger, exacerbate or possibly cause many pulmonary diseases (Table 162.3). Despite extensive studies addressing the pathophysiological link between respiratory symptoms and reflux disease, the true relationship in the population remains uncertain. Patients with chronic cough and asthma have a high prevalence of GERD. Therefore, many guidelines recommend consideration of GERD in the routine work-up of patients with wheezing and chronic cough, whether the association is causal or casual is yet to be determined.

There is clear documentation of higher prevalence of GERD in asthma and chronic cough than in the general population with approximately 75-80% of asthmatics showing reflux symptoms.[40, 41] In addition GERD has been postulated as a potential trigger for asthma.[42] Mechanisms by which GERD leads to respiratory symptoms are:

- Microaspiration of frequent small volume aspirate from the proximal esophagus leads to laryngeal and/or tracheobronchial mucosal reaction and symptoms of hoarseness, cough or wheezing.
- Reflux of acid from the lower esophagus may lead to reflex activation of vagus nerve and bronchoconstriction. Common embryonic origin of the esophagus and lung, together with common vagal innervations of these organs, further supports this hypothesis.
- Gross aspiration of gastric contents may result due to the presence of an anatomical or physiological abnormality in the lower esophageal sphincter. These patients commonly present with aspiration pneumonia, lung abscess and bronchiectasis.

Furthermore, physiological alterations associated with asthma or its treatment may themselves promote gastroesophageal reflux. Transient lower esophageal sphincter relaxation and negative pressure generated during episode of coughing or bronchoconstriction and flattening of diaphragm secondary to hyperinflation are commonly seen in asthmatics and are associated with change in the pressure gradient between the thorax and the abdomen. Similarly, beta agonists and theophylline dilate the smooth muscle throughout the body including at the lower esophagus disrupting the gastroesophageal physiological barrier. Both of these factors may lead to GERD in asthma.

The presence of gastroesophageal reflux as an important trigger in patients with asthma has been recently disputed. It was shown in a large double-blind trial that silent GERD was not a likely cause of poorly controlled asthma.[43] Only a specific subgroup of patients with respiratory symptoms may respond to therapy for GERD, which should include a combination of antireflux measures such as the weight reduction, avoidance of meals before bedtime, eating low fat diet and acid suppressive therapy.

Acute Pancreatitis

Pulmonary complications are the most frequent and potentially the most serious systemic complications of acute pancreatitis. The spectrum of pulmonary sequelae of acute pancreatitis range from subclinical arterial hypoxemia to frank acute respiratory distress syndrome (ARDS)[44,45] (Table 162.4). When present, these sequelae are associated with significant mortality. Respiratory dysfunction precedes the occurrence of heart, liver and renal failure and is responsible for early deaths in severe acute pancreatitis.[46]

Arterial Hypoxemia and Respiratory Failure

During early stages of acute pancreatitis, subclinical arterial hypoxemia is a frequent occurrence. Several studies have demonstrated arterial hypoxemia ($PaO_2 < 80$ mm Hg) in up to 55 to 65% of patients during the first 48 hours without any obvious clinical or radiological abnormality, they are associated with significantly higher mortality.[47-50] The mortality rises to 14% at PaO_2 less than 60 mm Hg, from 6% at PaO_2 less than 70 mm Hg.[44] Similarly, in another study, mortality of 60% was observed in 22% patients of acute pancreatitis with severe respiratory insufficiency.[51] These studies clearly suggest that respiratory insufficiency, early in acute pancreatitis, is a predictor of poor outcome.

Hypoxemia in these patients is predominantly caused by ventilation perfusion mismatch resulting in right to left intrapulmonary shunting of approximately 30% of the cardiac output.[52] Changes in pulmonary vascular permeability and reduction in oxygen affinity of hemoglobin related to increase in circulating fatty acids are the other few mechanisms proposed for hypoxemia in acute pancreatitis.[52,53] Due to the subclinical nature and normal chest radiograph, a high index of suspicion and close monitoring are required to detect hypoxemia, especially during the first 72 hours. Supplemental oxygen is indicated to keep the arterial PaO_2 more than 70 mm Hg.

TABLE 162.4: Pulmonary complications of acute pancreatitis

- Pleural effusion
- Atelectasis
- Mediastinal abscess
- Pneumonitis
- Pulmonary infarction
- Acute respiratory distress syndrome

Acute Respiratory Distress Syndrome

The most serious pulmonary complication of acute pancreatitis is ARDS, seen in approximately 15–20% patients with an associated mortality of 50 to 75%.[48,54-56] Usually, persistent and refractory hypoxemia evolves to overt ARDS in 2–7 days, but may have rapid onset and course. Rapid appearance and progression to multilobar infiltrates is classically noted on chest radiography. Although the exact mechanism of lung injury is poorly understood, pancreatic enzymes and inflammatory mediators play a key role in its pathophysiology. Phospholipase A_2 binds to pulmonary capillaries and has the potential to induce the enzymatic degradation of phospholipid component of surfactant leading to increased vascular permeability and alveolar collapse.[57, 58] Free fatty acids released from triglycerides by pul-monary lipases lead to capillary and alveolar wall damage and alveolar edema.[59]

Standard supportive treatment for acute pancreatitis consists of nutrition maintenance, hemodynamic management and suppression of secretory function of pancreas. Management of lung injury with lung protective ventilation is similar to that for other forms of ARDS with an aim to maintain oxygen delivery to all organ systems. Specific treatments, such as protease inhibitors and antioxidants, targeted to pancreatic injury have failed to decrease the severity of the disease.

Pleural Effusion

Pleural effusion is a frequent complication of both acute and chronic pancreatitis with an associated mortality of 20 to 30%.[60] When present, the effusions are usually small, left sided, occasionally bloody and are indicators of severe disease.[61,62] Effusion is usually exudative, serosanguineous in appearance with high amylase, protein and lactate dehydrogenase. The main mechanisms proposed for effusion in acute pancreatitis are:

- *Increased permeability of lymphatics:* Pancreatic enzyme causes fluid leak that diffuses from peritoneal side to the pleural space through pores in the diaphragm.

- *Impaired lymphatic drainage:* High enzymatic content and exudate in the pleural fluid causes obstruction of the lymphatics.
- *Increased permeability of diaphragmatic capillaries:* Caused by inflammatory process in the adjacent pancreas.
- *Pancreaticopleural fistulae:* Secondary to leak and disruption of pancreatic duct.

Pancreatitis related effusions are usually self-limited and resolve spontaneously without any therapeutic intervention when the pancreatic inflammation subsides. Persistence of effusion indicates the occurrence of complications, like pancreatic abscess or pseudocyst formation. Symptomatic effusions may be drained with thoracentesis or tube thoracotomy, while chronic effusions often require drainage of the pseudocyst or of abscess, or excision of the fistulous tract.

HEPATIC DISORDERS

Hepatic Hydrothorax

In the absence of a coexisting cardiopulmonary disease, development of pleural effusion in cirrhosis of the liver with portal hypertension is termed as hepatic hydrothorax. It can complicate approximately 5-10% of cirrhotic liver irrespective of the underlying etiology.[63] Due to the pressure gradient between the abdominal and the pleural cavities, the fluid from the abdominal cavity moves to the pleural space via the small defects in the diaphragm. Additionally, intravascular volume expansion secondary to sodium retention and hypoalbuminemia contributes to the development of hydrothorax. The effusion is essentially a transudate with its origin in the peritoneal cavity. An exudative character of the fluid should raise the suspicion of tuberculous effusion or of secondary bacterial infection.

Sometimes, ultrasonography or nuclear scan is required to establish the presence of ascites.[64] In a majority, the effusion is small or of moderate size predominantly on the right side, but left sided, bilateral and massive effusion is not infrequent. In an appropriate clinical setting, similarity between the pleural and the peritoneal fluid establishes the diagnosis. Liver transplantation is the definitive treatment of choice. Transjugular intrahepatic portosystemic shunt, thoracoscopic repair of the diaphragmatic defect and pleurodesis are alternative options when definitive therapy is not feasible.

Hepatopulmonary Syndrome (HPS)

The association of liver disease with widespread intrapulmonary vasodilation and impaired arterial oxygenation is known as hepatopulmonary syndrome.[65,66] The coexistence of decreased lung compliance and reduced diaphragmatic motility due to massive ascites characteristically leads to hyperventilation and corresponding hypocapnia because of which increased alveolar-arterial oxygen gradient becomes the most sensitive method to detect pulmonary gas exchange disturbances.

Pathophysiology

The characteristic histopathological pulmonary vascular changes in HPS consist of dilated vessels at the precapillary, capillary and postcapillary levels leading to intrapulmonary shunting of mixed venous blood into the pulmonary vein.[67]

The precise pathophysiological mechanism underlying HPS remains uncertain. Excessive production or altered clearance of vasodilator molecule such as nitric oxide is considered as one of the mechanism for hyperkinetic circulation in HPS.[68, 69] Several mechanisms have been proposed for the gas exchange abnormalities seen in HPS:

- *Ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch:* It occurs in mild to moderate HPS due to the areas of preserved ventilation but profoundly increased perfusion. Impaired hypoxic pulmonary vasoconstriction seen in advanced liver disease contributes to this $\dot{V}/\dot{Q}$ mismatch.[70,71]
- *Increased intrapulmonary shunting:* It is the primary abnormality in severe HPS.
- *Diffusion-perfusion defects:* Oxygen from the alveoli fails to diffuse to oxygenate the hemoglobin.[72,73] Additionally, coexistence of hyperdynamic circulation leads to shorter transit time for red blood cells that would further aggravate diffusion induced gas exchange disturbance.

Clinical Features

Most patients have prominent clinical and functional features of advanced liver disease such as jaundice, ascites, palmar erythema, liver and splenic enlargements. Extensive cutaneous spider nevi which are seen more commonly in patients with HPS are considered as a cutaneous marker of both systemic and intrapulmonary vasodilatation.[70] Specific pulmonary features consist of dyspnea, platypnea, orthodeoxia, cyanosis and digital

TABLE 162.5: Diagnostic criteria for hepatopulmonary syndrome[66]

Essential features:
- Presence of chronic hepatic disease
- Normal or near normal chest radiography (with nodular basal shadowing)
- Pulmonary gas exchange abnormalities - ↑ (A - a)PaO_2 of ≥15 mm Hg with or without concomitant arterial hypoxemia (arterial PaO_2 <80 mm Hg)
- Positive contrast enhanced-echocardiogram or abnormal intravenous radiolabeled perfusion lung scan or both

Additional features:
- ↓ DLCO
- Dyspnea with or without platypnea and orthodeoxia
- Hyperkinetic circulatory state with normal or low pulmonary artery pressure

clubbing. Increased dyspnea in the upright position (i.e. platypnea) and orthodeoxia (i.e. decrease of PaO_2 ≥5% or >4 mm Hg from the supine to the upright position) are the characteristic, but not pathognomonic features of HPS.[74,75]

Diagnosis

In patient with chronic liver disease, presence of platypnea, orthodeoxia and clubbing strongly suggest a diagnosis of HPS (Table 162.5). Hyperkinetic circulation, systemic hypotension, low or normal pulmonary artery pressure with normal or low pulmonary vascular resistance are the characteristic hemodynamic features.

Two dimensional contrast-enhanced echocardiography provides a sensitive, noninvasive and qualitative screening tool to identify intrapulmonary shunting, now considered as the gold standard.[76,77] Demonstration of microbubbles (60–90 µm in diameter) of air in the left heart chambers within 3–6 beats of their visualization in the right heart chambers is almost diagnostic of this condition. In normal individuals, intravenously injected microbubbles are trapped in the pulmonary circulation and removed. Simultaneous appearance of microbubbles in the left heart chambers differentiates intracardiac from intrapulmonary shunts. The only limitation of this technique is its inability to differentiate between different forms of intrapulmonary vascular deformities.

Alternative demonstration of technetium-99m labeled macroaggregated albumin activity over extrapulmonary organs suggests right to left shunting, but the method is limited by its inability to differentiate between intracardiac and intrapulmonary shunting. In healthy individuals, only 3–6% of albumin macroaggregates pass through the pulmonary vasculature to organs like the brain, the kidney and the liver, but, in the presence of pulmonary vasodilatation, the shunt ratio is 10–71%.[78,79]

Treatment

Orthotopic liver transplantation has been shown as an effective measure for complete resolution of HPS in approximately 80% of the patients.[80-82] Alternatively, medical management with agents like bismesylate almitrine, long-term oxygen therapy and propranolol has been tried to reduce the shunt but the results are disappointing. A few centers have also tried palliative measures like embolization of pulmonary fistulas, portal decompression with transjugular intrahepatic portosystemic shunting.[83,84]

Portopulmonary Hypertension

Portopulmonary Hypertension (PoPH) is defined hemodynamically as an elevated mean Pulmonary Arterial Pressure (mPAP) >25 mm Hg, an increased pulmonary vascular resistance (PVR) greater than 240 dynes/sec/cm^5 and a normal pulmonary artery occlusion pressure (<15 mm Hg) in a patient who has portal hypertension with or without cirrhosis. The condition is both pathophysiologically and clinically different from HPS (Table 162.6). The prevalence of PoPH is around 0.61–2%, recent studies from orthotopic liver transplant centers show higher prevalence of 4 to 5%.

TABLE 162.6: Differentiation between hepatopulmonary syndrome and portopulmonary hypertension

	Hepatopulmonary syndrome	*Portopulmonary hypertension*
Causes	Liver disease with portal hypertension	Liver disease with portal hypertension
Pathophysiology	Pulmonary vasodilation	Pulmonary vasoconstriction
Symptoms	Platypnea, Orthodeoxia	Dyspnea, Edema
PaO_2	Hypoxemia, Orthodeoxia	Hypoxemia at late stages
Chest X-ray	Usually normal	Signs of pulmonary hypertension
Contrast ECHO	Late (>3–6 cardiac cycles) appearance of microbubbles in left atrium	Usually negative
Cardiac output	Increased	Normal or decreased
Pulmonary vascular resistance	Decreased	Increased
Shunt	>10%	Nil

Histopathologically, PoPH is characterized by medial hypertrophy, plexogenic and thrombotic pulmonary arteriopathy, indistinguishable from primary pulmonary hypertension.[85] The combination of vasoconstriction, vascular proliferative response and in situ microthrombosis underlie the increase in PVR seen in patients with PoPH. Portosystemic shunting of vasoactive agents like thromboxanes, serotonin and bradykinin due to altered hepatic metabolism is postulated as a possible mechanism for pulmonary arterial vasoconstriction.[86] Endothelial damage with vascular remodeling caused by excessive pulmonary blood flow and microvascular thrombosis may also contribute.

The clinical picture in PoPH is indistinguishable from that of primary pulmonary hypertension and appears late in the evolution of the disease. Predominantly, patients have exertional dyspnea. As the severity increases, peripheral edema, fatigue, abdominal bloating, palpitation and syncope may appear.

Prominent pulmonary artery and cardiomegaly are seen on chest radiography. Transthoracic Doppler echocardiogram is the screening procedure of choice in patients with liver disease and unexplained dyspnea. Features suggestive of PoPH on echocardiography include the elevation of right ventricular systolic pressure (calculated from the peak tricuspid regurgitant velocity using modified Bernoulli equation and an estimate of right atrial pressure), shortened pulmonary acceleration time, paradoxical septum motion, and right-ventricular hypertrophy and dilatation.[87] Using right ventricular systolic pressure cutoff of 40 mm Hg, Doppler echocardiography has a sensitivity and specificity of 80% and 96% respectively, but it cannot differentiate between elevated PVR and hyperdynamic circulation (low or normal PVR) as a cause of pulmonary hypertension.[88] Confirmation of the diagnosis of PoPH requires right heart catheterization which permits measurements of pulmonary artery pressure, PVR, pulmonary artery wedge pressure and of cardiac output.

Treatment aimed at lowering pulmonary artery pressure and resistance is indicated in all symptomatic patients. Diuretic administration is required for the associated cor pulmonale and volume overload. Anticoagulation is often contraindicated due to the associated hemorrhagic diathesis related to liver disease and its complications. Supplemental oxygen to maintain saturation above 90% is beneficial for all patients. Drugs with vasodilating and vasomodulating effects can be given but there are no randomized controlled trials specific to this population. Use of these drugs should be individualized depending upon the severity of the disease and prospects for liver transplantation.

Orthotropic liver transplantation can be beneficial in a highly selected subset of patients but the resolution of pulmonary hypertension after transplantation is not universal. Both intraoperative and immediate postoperative complications of liver transplantation are also high because of the associated comorbidities and deranged hemodynamics.

RENAL DISEASES

Chronic renal failure usually affects the lung indirectly by affecting the other organ systems of body such as through raised pulmonary venous pressure and anemia. A transient respiratory gas exchange abnormality following hemodialysis is also a frequent occurrence. The common renal complications are discussed under Table 162.7.

TABLE 162.7: Pulmonary complications of renal failure

Pulmonary edema
Pleural diseases
- Pleural rub
- Pleural effusion
- Fibrosing uremic pleuritis/Fibrothorax

Pulmonary calcifications
Sleep apneas
Hemodialysis-induced gas exchanges abnormalities

Pulmonary Edema

Subclinical or overt pulmonary edema is common in renal failure due to a number of different mechanisms:

- Fluid overload
- Hypoproteinemia with reduced plasma colloid pressure
- Depressed myocardial function
- Increased microvascular permeability

The characteristic distribution of edema in the more central part of the lungs is explained by the diversion of flow through the shortest arterial pathway. Hypertension, diabetes mellitus, anemia and ischemic heart disease commonly seen in end-stage renal disease may also adversely affect the heart.

Pleural Effusion

Pleural effusion is seen in approximately 3% of patients of renal failure.[89] The exact mechanism of pleural disease is not understood, it is probably similar to that of pericarditis seen in uremia. Almost half of the patients with pleural effusion are symptomatic with fever, chest pain, cough or dyspnea; the degree and severity of uremia have no correlation with the occurrence of effusion.[89] Both transudative or exudative effusion can occur; most commonly it is an exudate which is frequently serosanguineous or frankly hemorrhagic.[90,91] Lymphocytes are the predominant cells, pleural biopsy characteristically reveals chronic fibrinous pleuritis. Transudative effusions are seen in the fluid overload states and in congestive heart failure. Confident diagnosis of uremic pleuritis requires exclusion of other common causes of effusion like pleural infection especially tuberculosis, malignancy and pulmonary embolism.[92]

Effusion routinely disappears with dialysis in 4–6 weeks in most cases. In 25% of patients it may persist, progress or recur. In a small number of patients, progressive pleural thickening may lead to ventilatory defects and require surgical decortication.[93,94]

Hemodialysis-induced Pulmonary Gas Exchange Abnormalities

Arterial hypoxemia during dialysis is a common occurrence. A fall in arterial PaO_2 of 10–15 mm Hg is observed within few minutes of dialysis, reaches a plateau after 45–60 minutes and persists for the duration of dialysis.[95,96] Hypoxemia may occur due to several different mechanisms:

- Shift in oxyhemoglobin dissociation curve due to procedure related rise in pH
- Alkalosis-induced depression of central ventilatory drive
- Impairment of oxygen diffusion
- Ventilation-perfusion mismatching due to pulmonary leukostasis
- Loss of carbon dioxide via dialysate-induced hypoventilation

Hypoxemia during hemodialysis is now considered as a predictable effect of loss of carbon dioxide (CO_2) into the dialysis fluid. Removal of CO_2 into the dialysis fluid during hemodialysis leads to decrease in minute ventilation.[96,97] The diffusion of CO_2 into the dialysis fluid is substantially more with acetate buffer than with bicarbonate buffer.[98]

Due to the large cardiopulmonary reserve, the reduction in arterial PaO_2 has no significant effect in patients with normal cardiopulmonary function. In patients with compromised function, supplemental oxygen during hemodialysis should be given. Composition of dialysis membrane and the dialysate buffer should also be appropriately changed.

Vasculitides and Alveolar Hemorrhage Syndrome

The involvement of both lungs and kidneys in systemic vasculitides and granulomatoses commonly manifests with hemoptysis and renal failure.[99-101] Such a syndromic presentation may occasionally pose problems of differential diagnosis from primary renal disorders with pulmonary features.

OTHER SYSTEMIC DISEASES

Pulmonary manifestations are also common with rheumatological, and connective tissue disorders as well as with hematological and lymphatic diseases, either with primary or secondary involvement of the lungs. Similarly, diseases of brain, nerves, muscles and bones may also present with pulmonary complications. Readers are advised to refer to different chapters for their details.

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Pulmonary Manifestations in Cardiovascular and Neuromuscular Diseases

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CARDIOVASCULAR DISEASES

Embryological and anatomical relationship entails the heart and the lung in the thoracic cavity to complement the action of each other. Any deviation of this complementary action of pressure and volume or the gas exchange will have consequences on the others. Increase in pressure or volume in the pulmonary vasculature, as a consequence of ischemic, hypertensive or intrinsic left heart dysfunction induces abnormalities in the pulmonary volume and leads to disturbances in the gaseous exchange. Similarly, decreased pressure downstream curtails the force and endurance of the respiratory muscles, disposing them to mechanical disadvantage and ventilatory defects. On the other hand, an intrinsic defect in the parenchyma, airways or the vascular bed of the lungs produces right heart dysfunction that ultimately leads to altered geometry of the interventricular septum and compromised left heart function.

Cyclic physiological changes in the intracardiac hemodynamics induced by normal respiration is related to the variation in intrathoracic pressure, venous return, intrapericardial pressure and the interdependence of the cardiac chamber. Inspiration decreases intrathoracic and intrapericardial pressures leading to augmented filling and stroke volume of the right ventricle and a compensatory decrease in left ventricular stroke volume due to limited pericardial space. During expiration, these pressures increase and reciprocal changes ensues in two ventricles.

Heart Failure

Under normal condition, there is linear increase in the blood flow from apex to the base of the lung. Left heart failure and consequent increased left atrial pressure, as a result of various cardiac and extracardiac abnormalities causes shift of linear flow of blood to more uniformly distributed flow.[1] Modest increase in flow or pressures are accommodated and redistributed within the pulmonary venous circulation by capillary distension and recruitment without overt pulmonary edema. Additional safety mechanism that prevents edema formation is low permeability and active transport of alveolar epithelial cells, resorption into blood vessels and lymphatics and mediastinal and pleural drainage. A higher pulmonary filling, venous and capillary pressure promotes vascular distension and perivascular, peribronchiolar, interstitial and alveolar edema, leading to symptom complex of dyspnea, wheezing and exercise intolerance. This is shown in Table 163.1.[2-7]

Ventilatory Abnormalities

Alterations in the mechanical and gas-exchanging properties of the lungs, produced by left-sided heart failure of any cause are largely influenced by the water content of the lung. In general, Total Lung Capacity (TLC) and Functional Residual Capacities (FRC) are reduced,

TABLE 163.1: Mechanisms of dyspnea and exercise limitation in heart failure

- Decreased lung compliance[2]
- Bronchial hyper-responsiveness[3,4]
- Ventilation perfusion mismatch[5]
- Stimulation of lung stretch receptors[6]
- Respiratory muscle weakness[7]

whereas the residual volume may be normal or slightly increased.[8,9] The reduction in TLC is proportional to the severity of the heart disease. Influence of heart failure on resting dynamic pulmonary functions ranging from essentially normal values to primarily restrictive or obstructive defects to combined obstructive and restrictive defects with or without diffusion abnormalities are observed in various studies.[10-18] However, the majority of the studies are confounded by the changes due to normal aging, obesity and smoking. When changes in baseline pulmonary function influenced by stable chronic heart failure independent of these confounding factors were studied, only mild restrictive or normal values were observed.[8] Variable degrees of obstructive defects alone are more prevalent during periods of decompensation that improves with diuresis predominantly due to reduction in extravascular lung water and pulmonary and bronchial blood flow.[18-20] In stable patients, obstructive defects are predominantly related to adequacy of treatment, normal aging and smoking habits.[20]

These ventilatory abnormalities can be improved by the correction of the cardiac abnormalities, either through optimization of medical treatment or heart transplantation. Heart transplantation improves pulmonary function by 3 months and normal lung volumes and flows by one year following the surgery.[21,22]

The exact cause of restrictive defects in chronic heart failure remains elusive. Reduced lung compliance owing to cardiac size, augmented by increased interstitial fluid accumulation and general muscle weakness and wasting, likely accounts for the restrictive changes seen in heart failure. Additionally, parenchymal changes induced by increased levels of circulating cytokines, like tumor necrosis factor-α or pulmonary vascular remodeling due to chronic high left atrial pressures leads to altered lung compliance and consequent restrictive changes in the lung mechanics.

Diffusion Abnormalities

In heart failure, pulmonary diffusion impairment occur secondary to reduction in global perfusion of the lungs and a reduction in the conductance of the alveolar-capillary membrane.[15,18] Structural changes of the alveolar capillary membrane develop as the disease progresses, which leads to an impaired diffusion capacity. Decreased membrane conductance represents thickening of the alveolar-capillary barrier from the accumulation of fluid or fibrosis indirectly supported by the data from chronic heart failure patients, demonstrating reduced pulmonary microvascular permeability.[23] In the last decade, it has become increasingly evident that lung diffusion abnormalities not only strongly correlate with exercise performance and Congestive Heart Failure (CHF) severity, [24-26] but most importantly, with CHF prognosis as well.[27] In contrast to the ventilatory abnormalities, diffusion defects may not be fully reversible.[21,22,28]

Sleep Abnormalities

Another important pulmonary manifestation of heart failure is high prevalence of breathing abnormalities during sleep. Depending on the severity of heart failure, approximately 37 to 75% of patients will have Central Sleep Apnea (CSA) with periodic breathing or Cheyne-Stokes Respiration (CSR) and additional 10 to 25% of patients will have Obstructive Sleep Apnea (OSA).[29-31] The overlapping symptoms of heart failure and sleep apnea contributes to the underdiagnosis of sleep related breathing disorders in heart failure. However, presence of hypocapnia, atrial fibrillation, ventricular tachycardia, a low left ventricular ejection fraction, a high New York Heart Class (III and IV) and excess premature ventricular beats and couplets are clinical clues for the presence of sleep apnea in patients with heart failure. Ventilatory instability due to increased circulation time and increased loop gain in the metabolic control of ventilation is largely responsible for CSA, while predominantly upper airway collapse during sleep leads to OSA in heart failure.[32-34] Due to presence of CSA-CSR, CHF patients confers a worse prognosis, therapy with continuous positive pressure ventilation may ameliorate CSR-CSA and overall outcome by improving cardiac functions.

Neuromuscular Diseases

Pathological processes of the neuromuscular system can interfere with the function of the central nervous system, spinal cord, peripheral nerves, neuromuscular junction and muscles to produce respiratory manifestations. These disorders affect respiratory function, by weakening, singly or in combination, the muscles of inspiration particularly the diaphragm, muscles of expiration impairing cough and bulbar functions disrupting cough swallowing and speech. Consequently, aspiration associated with dysphonia is a common complication of neuromuscular disease.[35-37] Common final abnormality in these disorders is primarily ventilatory failure.

Assessment of Respiratory Muscle Function

Gas Exchange

Alveolar hypoventilation with a normal or elevated pH and a reduced arterial carbon dioxide (pCO_2), due to increased ventilatory drive is the initial manifestation of mild to moderate respiratory muscle weakness.[38] As the disease advances, further progression of muscle weakness leads to carbon dioxide retention. Other factors including altered control of breathing, compounded by blunted hypercapnic and hypoxic ventilatory drive, atelectasis and abnormal chest wall compliance may contribute for chronic hypercapnia seen in these patients.[9] Unless concomitant parenchymal or alveolar abnormality is present, arterial tension of oxygen (pO_2) and the alveolar-arterial oxygen tension gradient pO_2 (A–A) are normal.

Pulmonary Function Tests

Integrated function of respiratory muscle, nerves, airways and lung parenchyma can be assessed noninvasively by measuring TLC, Vital Capacity (VC) and Maximum Voluntary Ventilation (MVV). Alteration in the respiratory muscle and nerve limits the ability to lower intrathoracic pressure and reduces the ability to generate a full inspiration leading to restrictive defects. Furthermore, rapid and shallow breathing pattern due to neuromuscular weakness leads to increased dead space to tidal volume ratio that compromises their ventilatory function. [39] Characteristically, TLC and VC are reduced with normal or decreased FRC and when expiratory muscles are also severely involved Residual Volume (RV) is increased. [40-44] MVV is usually reduced similar or more than the VC. Due to sigmoid shape of the pressure volume relationship of the respiratory system, severe impairment of respiratory muscle strength (more than 50%) is required, before significant reduction in lung volumes is appreciated.[40] In contrast to the normal 10% drop in VC, when changing from upright to the supine position, VC may be reduced by more than 30% in the supine position in patients with bilateral diaphragmatic palsy. This positional variation is more sensitive indicator of respiratory muscle weakness than upright measurement of TLC and VC alone, however there is potential for false positive results in individuals without diaphragmatic palsy.[45]

In neuromuscular disorders reduction in FVC is proportional to the reduction in FEV_1, so that the ratio is preserved, unless concomitant obstructive processes are also present. This preserved ratio is largely because of above normal lung recoil and patent airways.

Respiratory Muscle Strength Assessment

Respiratory muscle weakness is the hallmark of neuromuscular disease that can be assessed by maximal static Inspiratory and Expiratory Pressures (PI max and PE max). PI max is measured at the airway opening during a maximal, static inspiratory effort (Muller maneuver) initiated at either FRC or RV, similarly PE max are measured at the airway opening during a maximal static expiratory effort (Valsalva maneuver). Generalized neuromuscular weakness reduces both PI max and PE max, however, these tests are totally dependent on effort and reproducibility of maximal pressures does not verify that maximal effort has been made.[46] Consequently, other factors like submaximal efforts or air leaks around the mouthpiece must be considered when low values are encountered. Alternatively, to reduce the variability, pressures during maximal sniff maneuvers measured at nose, esophagus or across the diaphragm can be performed. Maximal sniff maneuver is a more reliable means of assessing respiratory strength than the Muller maneuver in patients with inspiratory muscle weakness.[47-49]

Diaphragmatic Paralysis

The diaphragm is the most important muscle of ventilation, supplied by the phrenic nerve (C_3–C_5). It consists of noncontractile central tendon and contracting muscle fibers attached to the inner surface of the lower six ribs, costal cartilage anteriorly and to the upper three lumbar vertebral bodies posteriorly. In the supine breathing, the diaphragm alone is responsible for most of the inspiratory effort. Diaphragmatic paralysis may involve one leaflet (unilateral) or the whole diaphragm (bilateral). Causes of unilateral or bilateral diaphragmatic paralysis are more or less similar with different prevalence, as shown in Table 163.2.

TABLE 163.2: Etiologies of diaphragmatic paralysis

Neurological disorders	*Myopathic disorders*
Multiple sclerosis	Limb-girdle muscular dystrophy
Amyotrophic lateral sclerosis	Acid maltase deficiency
Spinal cord transection	Hypothyroidism or hyperthyroidism
Guillain-Barré syndrome	Systemic lupus erythematosus
Poliomyelitis	Mixed connective-tissue disease
Chronic inflammatory demyelinating polyneuropathy	Amyloidosis
Phrenic nerve lesions • Blunt trauma • Cardiac surgery	Malnutrition

TABLE 163.3: Difference between unilateral and bilateral

	Unilateral paralysis	*Bilateral paralysis*
Dyspnea	Absent or only on exertion	Always present
Orthopnea	Occasional	Unable to lie supine
Hypoxemia	Rare	Common
Hypercarbia	Rare	Common
FVC	Normal	Drop of > 30% from upright to supine
Chest X-ray	Eventeration of diaphragm	Bilateral small lungs due to atelectasis
Fluoroscopy	Sniff test positive	Absence of caudal displacement

Clinical Features

The degree of symptoms of diaphragmatic paralysis is variable, depending upon the underlying lesion (a uni or bilateral paralysis), concurrent lung or heart disorders and the degree of obesity as demonstrated in Table 163.3.[50,51] In unilateral disease, only shortness of breath upon undertaking of strenuous physical exertion or totally absence of symptoms may be present. Occasionally, a Hoover's sign (i.e. an uninhibited movement of the costal margin, away from the midline on the side of the injury) or unilateral abdominal paradox at the affected side is observed.

Bilateral paralysis occurs as part of severe generalized muscle weakness, but it may present as an isolated process, as the first manifestation of a more generalized neuromuscular syndrome with later involvement of other muscles. These patients often present with dyspnea on mild activity, especially during activity that requires expiratory muscle recruitment, like bending or lifting and sensing suffocation in the supine position.[52] A unique symptom is dyspnea with immersion in water due to decrease in VC of greater than 30%, as compared to less than 10% in normal individuals.[53] With disease progression dyspnea worsens and progressive hypercapnia and hypoxemia develop that are worse during sleep.

Diagnosis

i. *Clinical examination:* Under normal condition, expansion of the abdomen and rib cage occurs synchronously during inspiration, while in supine position there is greater expansion of the anterior abdominal wall during inspiration due to enhanced abdominal compliance. Diaphragmatic paralysis leads to the inward movement of the abdomen, as the rib cage expands during inspiration, a phenomenon known as paradoxical respiration.[54] These paradoxical motions can be detected noninvasively using magnetometry or respiratory inductance plethysmography.[55,56]

ii. *Pulmonary function:* For screening significant diaphragmatic impairment simpler test, like VC in upright and supine position may be used. In the supine position, due to reduced effectiveness of the intercostal muscle, secondary to expanded rib cage and abdominal contents encroaching upon the diaphragm, the VC decreases up to 10%. In bilateral diaphragmatic paralysis, characteristically the decreases in VC from erect to supine position is 30 to 55%.[57] Isolated diaphragmatic dysfunction may be suspected, if the predominant abnormality is a low PI max (lower than 60 cm H_2O) with relatively preserved PE max, however, a normal PI max due to the preserved strength of the accessory muscles may also be seen in these individuals.[58]

iii. *Maximal transdiaphragmatic pressure:* Contraction of the diaphragm lowers the intrathoracic pressure, while increases the intra-abdominal pressure. Pressure developed specifically by the diaphragm, can be measured as the difference between abdominal pressure, as assessed with a gastric catheter (Pga) and the pleural pressure, as assessed with an esophageal catheter (Pes). Transdiaphragmatic Pressure (Pdi) is then calculated as Pdi = Pga - Pes. The change in Pdi during normal tidal respiration and at TLC is typically 10 cm H_2O and above 30 cm H_2O, respectively and it can be increased to values greater than 150 cm H_2O during maximal inspiratory efforts (i.e. Muller maneuver).[59] Although Pdi specifically assesses diaphragmatic function, the requirement to place esophageal and gastric pressure transducers in patients with swallowing impairment and a complex procedure to generated maximum Pdi, obviates it as a useful maneuver.

iv. *Phrenic nerve stimulation:* The phrenic nerve is accessible transcutaneously for direct stimulation, either by electric or magnetic impulses as it traverses the neck.[60,61] In contrast to the electric impulse, which selectively stimulates phrenic nerve, magnetic impulses tends to stimulate cervical nerve roots as well that may activate rib cage muscles and give false positive results. Once stimulated both conduction time to assess the integrity of the phrenic nerve and Pdi to assess the mechanical output of the diaphragm can be measured. A conduction time of less than 9 ms and a twitch Pdi between is 25 and 35 cm H_2O is considered normal. Diaphragm mechanical output is measured as the magnitude of twitch Pdi.[62-64] Major disadvantage of phrenic nerve stimulation is the contraction history and dependence of twitch Pdi magnitude on the impedance of the abdomen and rib cage.

v. *Diaphragm imaging:* Chest radiography allows visualization of the elevated hemidiaphragms, but additional testing is required to exclude other pathologies. In addition, it also detects other pulmonary pathologies as a cause of respiratory symptoms. Fluoroscopy provides a real-time examination of diaphragm dome motion, best seen when both hemi diaphragms are visualized simultaneously in a lateral projection. A cephalad motion of diaphragm during inspiration is characteristic. Fluoroscopic sniff test, although sensitive and specific for unilateral diaphragm paralysis, is not sensitive for bilateral diaphragm paralysis. Kienback's sign is positive on fluoroscopy, if the affected diaphragm moves paradoxically upward with a vigorous sniff.[65,66] At least 2 cm of upward motion is considered abnormal.

Ultrasound with a 7 to 10 MHz transducer placed over the lower rib cage between the seventh and ninth intercostal spaces in the midaxillary line helps to visualize the diaphragm in the zone of apposition to the rib cage as well as the contraction of the diaphragm muscle itself. The diaphragm muscle in the zone of apposition is represented as a nonechogenic central structure bordered by two echogenic lines, the peritoneal and diaphragmatic pleurae.[67] Once visualized, diaphragm thickness (tdi) at end-expiration along with the change in tdi during inspiration can be measured. Changes in tdi during inspiration are proportional to diaphragm shortening in adults and infants, whereas tdi measured at end-expiration is proportional to diaphragm strength.[68-70] In patients with neuromuscular weakness, ultrasound to distinguishes between a functioning and a nonfunctioning diaphragm. With diaphragm paralysis, tdi is less than 2 mm and the diaphragm does not thicken during inspiration.[71]

Treatment

Most patients with diaphragm paralysis maintain adequate ventilation and gas exchange, by a compensatory increase in motor output to the intercostal muscles and increased output to the normal hemidiaphragm in patients with unilateral paralysis.[50,72]

In unilateral disease, main aim of treatment is exclusion of serious underlying intrathoracic pathology. Prognosis is good in patients with mild symptoms and routinely they don't need treatment.[50,51,73] In patients with disproportionate symptoms, surgical plication of the affected hemidiaphragm may provide excellent results.[74,75] Surgical plication causes improved lower lobe expansion and prevention of the paradoxical motion, leading to improved efficiency of remaining innervated respiratory muscles.

The treatment of bilateral diaphragmatic paralysis depends on the cause of the paralysis. In bilateral disease, in the absence of myopathy and preserved phrenic nerve, phrenic nerve pacing with radiofrequency signaling can be used.[76] Even in patients with nonfunctional phrenic nerve, if the intercostal nerve is functional and can be anastomosed, pacing can be done.[77] Once pacer is implanted, retraining the deconditioned diaphragm requires expertise and careful monitoring. Diaphragmatic pacing is limited by potential to fail abruptly, induction of diaphragm fatigue, upper airway obstruction and high cost, thus its use should be chosen considering all these factors.

In patients with nocturnal hypercapnia, some form of mechanical ventilatory support is required. Mechanical support can be provided by rocking bed, cuirass respirator, nasal Continuous Positive Airway Pressure (CPAP) or intermittent positive pressure ventilation by nasal mask and/or appliances.[78-81] With isolated diaphragm paralysis and no other neuromuscular impairment, Noninvasive Ventilation (NIV) is preferred to invasive mechanical ventilation.

Sleep Abnormalities in Neuromuscular Diseases

Sleep-associated breathing disorders in neuromuscular disease is fairly common, occurring in up to 42% of individuals.[82] Frequently nocturnal breathing abnormalities precede respiratory failure during wakefulness by months or even years.

In normal subjects, because of the withdrawal of the wakefulness drive to breathe, minute ventilation and oxyhemoglobin saturation (SaO_2) fall with the onset of sleep, whereas arterial carbon dioxide (CO_2) tension rises associated with reduction of number of protective reflex systems.[83] Physiologically, ventilation decreases by ±10% during sleep due to:[84,85]

1. Reduced wakefulness ventilatory drive stimulation at the respiratory centers
2. Reduced ventilatory response to chemical stimuli (hypercapnia and hypoxia)
3. Rapid Eye Movement (REM) sleep related muscle paralysis
4. Increased upper airway resistance due to reduced neural input to airway dilator muscles

In various neuromuscular diseases, distribution of respiratory muscle involvement dictates the nature of sleep associated breathing disorders. An obstructive defect is likely to predominate in patients with intact diaphragm, but upper airway or intercostal muscles are weak. In contrast, hypoventilation and gaseous exchange abnormalities will predominate in severe diaphragm dysfunction due to suppression of intercostal and accessory muscles in REM sleep.

Weakness of the pharyngeal muscle dilators, especially when the diaphragm is relatively spared causes generation of normal or increased negative intrathoracic pressure during inspiration that favors upper airway closure leading to obstructive events in these disorders. However, absent of chest wall movement due to severely weakened inspiratory muscles, these may be interpreted as central events despite continued inspiratory effort.[86] Additionally, pharyngeal neuropathy in neuromuscular disease may affect the normal stabilizing function of the pharyngeal muscles as well as the local reflex mechanisms that prevent upper airway collapse during inspiration.[87] Moreover, severe sleep apnea with hypoxemia has also been shown to induce axonal neuropathy.[88] In disorders characterized by significant bulbar involvement, such as Amyotrophic Lateral Sclerosis (ALS), weakness of the upper airway muscles has been thought to predispose to an increased incidence of obstructive sleep apnea.[89]

The most frequently reported discrete sleep breathing events in patients with respiratory muscle weakness are central hypopneas due to reduced tidal volume, which are more frequent and prolonged in REM sleep.[90,91] Inherent abnormalities of the ventilatory control may also be associated with neuromuscular diseases that reduce respiratory drive and ventilation via mechanisms unrelated to respiratory muscle weakness.

Screening sleep studies have been recommended in patients with neuromuscular disease, often guided by serial daytime respiratory function tests (typically spirometry plus/minus blood gases).[92] The gold standard for identifying breathing and other abnormal events during sleep is the Polysomnogram (PSG).

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Pulmonary Involvement in Tropical Diseases

S Jain, SK Jindal

INTRODUCTION

Tropical diseases encompass all those conditions that occur solely, or principally, in the tropics. In practice, the term is often taken to refer to infectious diseases that thrive in hot, humid climatic conditions. Many of these diseases involve the lungs directly or indirectly through various mechanisms. The vivid clinical features pose problems in the differential diagnosis of pulmonary diseases. This is especially so when such a condition, being uncommon, is not routinely recognized in a particular geographical region or a country. The involvement may also have adverse effects on the prognosis of the disease and in turn lead to increased mortality.

Theoretically, almost any tropical infection can involve the respiratory system (Table 164.1), but a few which are more common and important are included in this chapter. Many other important conditions have been discussed in other chapters.

TABLE 164.1: Tropical infections that commonly involve the respiratory system

- BACTERIAL – Pneumonias, Tuberculosis, Enteric Fever
- FUNGAL – Aspergillosis, other fungal pneumonias
- VIRAL - Hanta virus, Dengue, Influenza
- PARASITIC – PROTOZOAL- Malarial parasites, *E. histolytica*, *L. donovani*, *T. gondii*, Babesia
- HELMINTHIC – E. granulosus, Filariasis, Schistosomiasis, A. lumbricoides

MALARIA

Malaria is a very important cause of mortality in the developing countries. Apart from classical presentation of fever with chills and malaise, it may present with respiratory and other systemic manifestations. Important time may be lost in such cases in instituting antimalarials due to late diagnosis, leading to higher morbidity and mortality. Pulmonary involvement occurs in 3 to 10% cases, most commonly in malaria due to *Plasmodium falciparum*.[1] Different clinical forms of pulmonary complications have been described in malaria (Table 164.2). Three types of pulmonary involvements were known in malaria in the past: bronchitic, pneumonic and bronchopneumonic.[2] However, more definitive involvements are now recognizable.[3-7]

Acute Respiratory Distress Syndrome (ARDS)

Pulmonary edema is common in patients with hyperparasitemia, renal failure and pregnancy and is

TABLE 164.2: Important pulmonary complications of malaria

i. Pulmonary edema – noncardiogenic
   - Fluid overload – Iatrogenic
   - Acute respiratory distress syndrome

ii. Cardiac pulmonary edema (following malarial myocarditis)

iii. Pneumonias
   - Malarial
   - Postconvulsive aspiration
   - Nosocomial

iv. Acute asthma like presentation

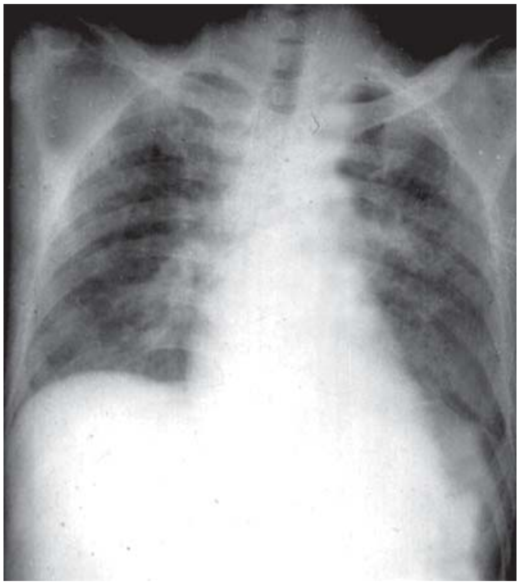

Fig. 164.1: Pulmonary edema of non-cardiogenic origin in a patient of malaria due *P. falciparum* infection

commonly associated with hypoglycemia and metabolic acidosis. It may develop suddenly after delivery, due to fluid overload. Pulmonary edema is the terminal event in many cases of fatal falciparum infection (Fig. 164.1). Cerebral edema is commonly present in these cases. Pulmonary edema was seen in 21% of patients of cerebral malaria of whom 40% fulfilled the ARDS criteria.[8] It was reported in 30% of intensive care unit patients admitted with severe malaria.[9] Incidence of pulmonary edema in malaria from India has been described in several studies in up to 20% of patients.[10-15] Pulmonary edema has been rarely described in patients with *Plasmodium ovale* and *Plasmodium vivax* infections.[16-20] The first indications of impending pulmonary edema include tachypnea and dyspnea, followed by hypoxemia and respiratory failure requiring intubation.

It can also develop in patients with normal capillary wedge pressures. Such cases may happen due to the increased permeability of pulmonary capillaries. It is generally produced by a disturbance in the pulmonary microcirculation. Sequestration of red cells, hypoalbuminemia, clogging of pulmonary microcirculation and disseminated intravascular coagulation with immune complex disease may also play their role in the pathogenesis. A central mechanism with hypothalamic dysfunction due to disturbed oxidative metabolism leading to pulmonary venular spasm has also been suggested.

The most severe form is acute pulmonary edema, which manifests with acute respiratory distress, is rapidly progressive and occurs in the absence of cardiac decompensation or fluid overload. It has been proposed that *P. vivax* infected erythrocytes may sequester within the pulmonary microvasculature and cause greater inflammatory response to a given parasite burden than with *P. falciparum*.[21] A longitudinal study in patients with uncomplicated (n=50) and severe falciparum malaria suggested persistent pulmonary vascular occlusion in both types of patients, likely from sequestration of red and white blood cells; severe malaria patients however, had persistent impairment of alveolar-capillary membrane dysfunction.[22] Refractory to the usual treatment of cardiogenic pulmonary edema, it has a high mortality with up to 50% of the patients succumbing to the complication. The mechanism of pulmonary edema is not clearly understood. It has a close resemblance to adult respiratory distress syndrome. Multiple mechanisms have been hypothesized. Over-hydration has been proposed as the cause in some cases of pulmonary edema. This, compounded by venous and lymphatic obstruction, leads to elevated capillary wedge pressure.

Other Manifestations

Acute asthma like picture has been also described.[7] Clinical features may develop rapidly, even after initial response to antimalarial treatment and clearance of parasitemia. The various pulmonary symptoms of malaria include cough (80%), dyspnea (40%), expectoration (32%), chest pain (18%) and hemoptysis (4%). The common signs are tachypnea, tachycardia and hypotension.[8] Chest radiographic abnormalities range from confluent nodules to basilar and/or diffuse bilateral pulmonary infiltrates. Benign forms have rarely been described in the literature. These cause minimal or no respiratory difficulty, and can present as pleural effusions, interstitial edema and lobar consolidation. They often go undiagnosed and unrecognized as part of the clinical and radiologic spectrum of acute malaria, and are probably more common than reported.

Postmortem studies of the lungs have grossly revealed congested, edematous lungs with frequent serosanguinous effusions. Typically, the effusions are transudative and negative on culture. Microscopic findings include large pigmented phagocytes in dilated septal capillaries, thickened alveolar septae, micro hemorrhages, hyaline membranes and diffuse alveolar edema.

Management

Treatment for respiratory complications need urgent attention. Fluid overload should be avoided at all costs,

TABLE 164.3: Recommendations for treatment of severe and complicated malaria (National Drug Policy on Malaria, 2008; Director of National Vector Borne Disease Control Programme, Delhi)

Parenteral artemisinin derivatives (for nonpregnant women) or quinine should be used irrespective of chloroquine resistance status of the area. However, the guidelines for specific antimalarial therapy as per the World Health Organization recommendation are given below:

- **Quinine salt** 20 mg/kg* body weight (bw) on admission (IV infusion or divided IM injection) followed by maintenance dose of 10 mg/kg bw 8 hourly; infusion rate should not exceed 5 mg salt/kg bw per hour.
  (*loading dose of Quinine salt, i.e. 20 mg/kg bw on admission may not be given if the patient has already received quinine or if the clinician feels inappropriate).
- **Artesunate:** 2.4 mg/kg bw IV or IM given on admission (time = 0), then at 12 h and 24 h, then once a day.
- **Artemether:** 3.2 mg/kg bw IM given on admission then 1.6 mg/kg bw per day.
- **Arteether:** 150 mg daily IM for 3 days in adults only (not recommended for children).

especially in pregnant women. The central venous pressure should be maintained between 0-5 cm of H_2O by regulating fluid intake and nursing the patient propped up at 45°. All intravenous fluids should be stopped immediately and diuretics may have to be administered. Initial management of pulmonary edema includes treatment with oxygen, back-rest and diuretics if there is evidence of fluid overload. Injectable furosemide (40 mg intravenously) increased to 200 mg in the absence of a desired response is generally used. Fluid volume can be further reduced by venesection and letting of 250 ml of blood initially. This blood or its packed cells can be retransfused once the problem settles down. The procedure can be repeated carefully if needed.

If the patient deteriorates with conservative treatment, mechanical ventilation is indicated. Treatment in such a condition, is provided as for any other patient of acute respiratory distress syndrome. Drugs like corticosteroids are not of any proven benefit in the management of these cases. Noninvasive ventilation used for the management of acute lung injury/ARDS associated with vivax malaria has been shown to be associated with good outcome.[23]

Antimalarial treatment in addition to the respiratory support is an important component of overall management. Detailed guidelines for treatment have been provided as per National Drug Policy on Malaria (2008) in India (Table 164.3).[24] Antibiotics, bronchodilators and other symptomatic treatments are required depending upon the presence of complications. Antimalaria drugs like mefloquine are occasionally associated with pulmonary complications such as pneumonitis.[25]

TYPHOID

Typhoid is a systemic febrile illness caused by Salmonella typhi. The estimated prevalence globally is around 21.6 million cases per year and 216,500 deaths worldwide in 2000.[26] The incidence in developing countries is 540 cases per 100,000 while in the developed countries it is reported in about 0.2 cases per 100,000 population.[27] It develops due to the consumption of contaminated food and water or contact with chronic infected carrier.

The involvement of lung in typhoid fever is not an uncommon entity (Table 164.4). The exact pathogenesis is not known. It was long back in 1885 when Artaud noticed typhoid like bacilli in lungs of patient with pulmonary apoplexy. Because of hematogenous spread of the organism, it has been long tried to isolate the organism from the lungs.[28] The endotoxin released from organism is considered responsible for the signs and symptoms of pulmonary disease. Predisposing factors for lung involvement include, but are not limited to immunocompromised host, alcoholism, sickle cell disease or preexisting pulmonary disease. Fever, toxaemia and abdominal pain are the most common manifestations of typhoid fever, while 10 to 15% of the patients with illness lasting more than two weeks develop systemic complications.

Pleuropulmonary complications are the most common extraintestinal manifestations.[29] The incidence

TABLE 164.4: Pulmonary complications of important tropical infections

Enteric fever
1. Typhoid bronchitis
2. Pneumonia and sepsis
3. Acute respiratory distress syndrome
4. Salmonella lung abscess—Rarely

Leptospirosis
1. Pulmonary hemorrhages
2. Acute respiratory distress
3. Leptospiral pneumonia

Dengue fever
1. Hemoptysis
2. Severe pulmonary hemorrhage

Amebiasis
1. Pulmonary amebiasis (Pneumonia, Empyema)
2. Hepatobronchial/ hepato-bronchopleural fistula

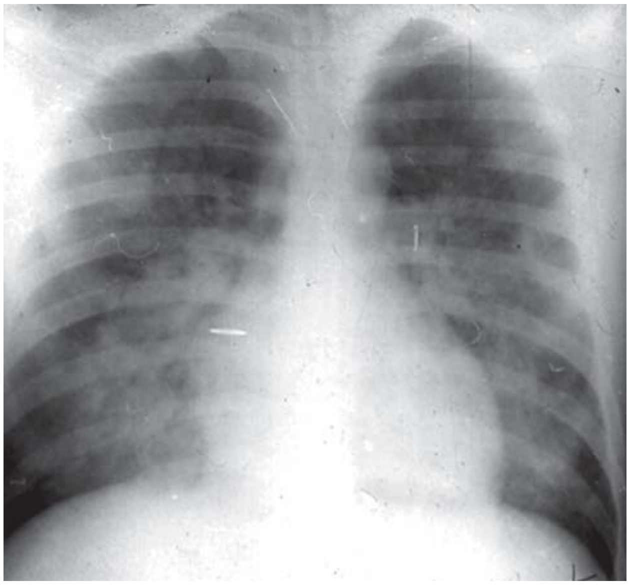

Fig. 164.2: Pulmonary edema with normal cardiac shadow in a patient of enteric fever presenting with acute respiratory distress

of pulmonary manifestations ranges from 1 to 7%. In one study of 65 cases of typhoid involving lungs, the incidence was found to be 6.2%. The chief symptoms and signs included cough (86%), crackles (64%), coryza (60%), chest pain (60%) and pleural effusion (5%). Pneumonia is uncommon (1%) but can occur in 50% of patients with empyema, bronchopleural fistula, lung abscess or effusion. It is one of the various life-threatening complications of typhoid fever. Bronchopneumonia is more common, although lobar pneumonia may also be seen rarely in these patients. In advanced disease, secondary bacterial pneumonia may occur due to aspiration or other organism. Reports of ARDS, occurring in typhoid fever has been also reported (Fig. 164.2).[30-32] In most patients, ARDS manifests in the early phase, i.e. first two weeks of illness.[32]

Nonspecific radiographic infiltrates are seen in one-fourth of the patients with pulmonary symptoms. It is rare to isolate salmonella from the sputum though blood culture may be positive in majority, which is the best test to diagnose salmonellosis. Occasionally, lung abscess caused by salmonella typhi, sometimes in a preexisting hydatid cyst has been reported.[33,34]

The treatment of typhoid involves the appropriate and timely use of antibiotics along with supportive respiratory care. Steroid use decreases the mortality from typhoid fever.[32] Outcome of ARDS is frequently fatal. Ventilatory and other supportive care are crucial to management.[30]

LEPTOSPIROSIS

Leptospirosis caused by Leptospira interrogans, is a reemerging zoonosis occurring as large outbreaks throughout the world.[35] This is especially so in the Asian countries with an enormous load of diseases with tropical pathogens.[36] The natural reservoirs are the mammals (rodents, cattle, dogs, horses, sheep) with humans getting incidentally infected after contact with contaminated animal urine. Risk factors include outdoor activities like walking barefoot, gardening and forest activities. Wet soil, refuse around the home, pets at home, and skin wounds may also help in promoting the spread of disease.

Leptospirosis can manifest with variable clinical picture ranging from mild subclinical illness to multi-organ failure (Table 164.4). The incidence of lung involvement in leptospirosis ranges from 20 to 70%, often goes as an unrecognized illness poses difficulties in management of complicating problems which sometimes are fatal.[37-40] Pulmonary involvement is often mild, but for the severe pulmonary hemorrhage that are sometimes described.[40-43] The pathophysiology of pulmonary hemorrhages is unclear and probably related to vascular injury and focal hemorrhages.[44] The incidence of pulmonary hemorrhage seems to increase in the recent reports.

The etiology of pulmonary hemorrhages is probably multifactorial.[37,39] It could possibly be sepsis related with disturbed platelet function.[37] Linear definition of immunoglobulin and complement on the alveolar surfaces may play a role in causing hemorrhages.[45] Two mechanisms related to damage have been proposed: one, toxin-mediated capillary vasculitis and second, the immune mediated damage by host. Leptospira are found in a lesser number than in the liver suggesting that the toxins generated by the liver circulate in the body and cause damage at a distant site. Leptospira can disseminate due to its ability to penetrate tissue without being inhibited by immune cells. Outer membrane protein of leptospira is the most important for toxin-mediated damage. Peptidogylcans activate vascular endothelial cells to increase their adhesiveness for neutrophils and may be involved in mediating local and systemic inflammation. Cytokines like Tumor Necrosis Factor-Alpha (TNF-α) may also play some role in causing damage. Immune-mediated damage depends on the antibody production against the Lipopolysaccharide (LPS) antigen of the cell wall. It influences the severity of the disease.

Respiratory symptoms could occur during both the anicteric and the icteric phases, include hemoptysis, chest pain, cough and dyspnea. Acute respiratory distress syndrome is a serious complication with high rates of mortality.[41,42,46] Severe pulmonary form of leptospirosis (SPFL) appears in four to six days of illness, is the most serious form with deaths (30 to 60%) occurring within 72 hours. Chest radiographs may show small nodular densities (57%), confluent consolidation (16%) or a ground glass appearance (27%).[47] High resolution computed tomography chest delineates the picture better. It may show ground glass opacities, pleural effusion or consolidation. Sometimes, chest manifestations occur pre-terminally and suddenly.[48] It is therefore, important to keep a strict vigil for the problems in patients with severe leptospirosis.

It often goes unnoticed because of the lack of clinical suspicion, varying clinical presentation and lack of adequate molecular diagnostic facilities.[38] Diagnostic tests like Dot test or Enzyme-Linked Immunosorbent Assay (ELISA) for leptospira immunoglobin M (IgM) antibody and Polymerase Chain Reaction (PCR) for 16s rRNA on blood and urine samples are used for confirmation. Pulmonary involvement and hemoptysis is shown as a strong predictor of mortality in patients with severe leptospirosis.[49]

The treatment of leptospirosis should be initiated early based on epidemiological and clinical features to shorten the illness, and because respiratory involvement needs urgent care. Besides the supportive care, plasma exchange with immunosuppression is shown to improve survival in the presence of pulmonary hemorrhage.[38,50] Activated protein C was shown to be helpful in sepsis attributed to dual infection with *P. falciparum* and leptospirosis.[51] Assisted ventilation should be started at the first sign of clinical suspicion of respiratory failure.

DENGUE

Dengue fever is a common tropical illness leading to high morbidity in the developing countries. It was identified as the most common cause of systemic febrile illness among travelers to the developing countries. It is an endemic illness especially in the countries of Africa, Southeast Asia and the Eastern Mediterranean. It presents with a wide range of manifestations ranging from mild illness to a severe shock-like state. It is caused by dengue virus, which is a Flavivirus, spread by the bite of Aedes mosquito.

There are four serotypes of dengue virus (DENV-1 to 4). Infection with one serotype leads to classic dengue fever with lifelong immunity to that serotype. Infection with second serotype leads to dengue hemorrhagic fever with severe manifestations.[52] There are only a few case reports of respiratory involvement in Dengue Hemorrhagic Fever (DHF). It may manifest with cough, sore throat or nasal congestion. Pneumonitis or pleural effusion may develop as reactive phenomena.[52,53] Hemoptysis has been reported to develop in 1.4% and pulmonary hemorrhages occur in a small number of cases. Pulmonary hemorrhages may present with mild hemoptysis and bilateral areas of consolidation on chest roentgenogram.[54-56] Sometimes, the hemorrhages are rather fatal.[57,58] Occassionally dengue can also present with ARDS like picture.[59]

The development of clinical manifestations is related to pulmonary capillary leak. Dengue virus causes endothelial cell dysfunction. The virus attaches to the endothelial surface, may serve as target for antibody binding and complement activation. Cytokines like TNF-α, IL-8, IFN-γ and free VEGF have been observed in patients with DHF. Besides this, abnormalities in the coagulation cascade, thrombocytopenia, platelet dysfunction, disseminated intravascular coagulation and vascular defects all play a role in the development of DHF.

Radiologically, pulmonary hemorrhages are seen as ground glass opacities. There may be pleural effusion, associated consolidation and diffuse infiltrates in the lung fields. Hemagglutination Inhibition (HI) assay remains the gold standard serologic test for dengue virus-specific antibodies. Immunoglobulin M assay for dengue virus is less sensitive and specific than HI assay and becomes positive only after 10 to 14 days of acute phase. The dengue viral Nonstructural Protein 1 (NS1) can be detected in plasma, especially during the first five to six days of illness, high levels early in infection were associated with DHF.

Treatment of DHF with pulmonary manifestations is primarily supportive. There is no specific therapy for DHF. Careful early intervention with appropriate intensive care can decrease the mortality to less than 1%.

AMEBIASIS

It is a caused by a protozoan *Entamoeba histolytica* that is endemic in the developing countries and responsible for high morbidity and mortality. Transmission occurs by the consumption of contaminated food and water or oro-anal contact. The infectious form is the cyst which after being ingested, excysts in the lumen of intestine, converts to trophozoite, attach to the wall of the intestine causing symptoms. As is well known, it causes gastrointestinal manifestations ranging from diarrhea to severe colitis with bloody diarrhea.[3] Extraintestinal manifestations occur mainly in the liver as abscess formation, which can spread to lung tissue. It can manifest as reactionary pleural effusion or the abscess may rupture into the lung parenchyma causing respiratory distress, empyema and lung abscess development.[60-62] Hematogenous spread to the lung may also occur. There may be sputum production ranging from mild to copious. Rarely, superior vena cava syndrome due to pulmonary amebiasis is reported.[63] If hepatobronchial fistula develops, sputum may be purulent with an anchovy sauce appearance. There is no eosinophilia and jaundice is uncommon.

The diagnosis of amebiasis rests on detection of trophozoites or cysts in the stool. It is not a very sensitive or specific test for extraintestinal manifestations. Antigen detection in the stool or pus is more reliable for *Entamoeba histolytica*. Most patients develop antibodies against *E. histolytica,* which can be detected in the serum. Immunoglobulin M antibody detection is a useful test for acute infection. Immunoglobulin G antibodies may be detected years after active infection, its presence does not indicate active disease. Metronidazole or tinidazole are highly effective for intestinal or extraintestinal manifestations. To prevent recurrence, luminal agents like iodoquinol are effective. Mild pleural effusion does not require treatment. Drainage along with anti-amoebic antibiotics is necessary to manage a lung abscess or empyema to prevent complications.

Pulmonary involvement can occur in several other tropical infections either in isolation or along with other system manifestations. Several such syndromic manifestations are region specific described in different parts of the world. Readers are advised to refer to different chapters of this book or other specific texts for details on conditions of interest.

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165

Pregnancy and Pulmonary Diseases

Lakhbir K Dhaliwal, Preeti Verma

Hormonal changes in pregnancy cause significant alterations in pulmonary physiology, which are important to understand for the interpretation of diseased state. A number of pulmonary disorders are encountered during pregnancy.

PULMONARY PHYSIOLOGICAL CHANGES DURING PREGNANCY

Changes in upper respiratory tract include hyperemia, mucosal edema, hypersecretion and increased mucosal friability. These are attributed to the presence of tissue edema, capillary congestion and hyperplasia of mucous glands, due to the estrogen effect. The enlarged uterus pushes the diaphragm upwards by as much as 4 cm, the anteroposterior and transverse diameter of thorax increases. Diaphragmatic function remains normal. Lung volumes and lung capacities are significantly altered during the pregnancy (Table 165.1).[1]

TABLE 165.1: Lung function changes during pregnancy

- Vital capacity and inspiratory capacity - increase by 20% in late pregnancy.
- Expiratory reserve volume - decreases from 1,300 ml to approximately 1,100 ml.
- Tidal volume - increases by approximately 40%.
- Respiratory rate remains constant.
- Minute ventilation - increases by about 30 to 40%.
- Arterial pO_2 increases from 100 to 105 mm Hg.
- Carbon dioxide production increases by approximately 30%, but because of an increase in the diffusion capacity and the alveolar hyperventilation, the pCO_2 decreases from 40 to 32 mm Hg.
- Residual volume decreases by approximately 20% (from 1,500 ml to approximately 1,200 ml).

The enlarged uterus and the increased abdominal pressure cause chest wall compliance to reduce by a third. Thus the functional residual capacity (the sum of expiratory reserve and residual volume) decreases by 10 to 20%. Pregnancy does not appear to change the lung compliance, but chest wall and total respiratory compliance are reduced at term. Basal oxygen consumption increases incrementally by 20 to 40 ml/min in the second half of pregnancy. There is physiological hyperventilation that results in increased kidney bicarbonate excretion. Serum levels of bicarbonate decrease to approximately 15 to 20 mEq/L, which leads to slightly alkalotic pH at 7.45.

Dyspnea During Pregnancy

Dyspnea is commonly seen in around 60% of women during pregnancy. It is physiological, occurs early in pregnancy and does not interfere with daily activities. The increased progesterone level leading to hyperventilation is thought to be the most important mechanism. This physiologic dyspnea should be differentiated from breathlessness caused by disorders complicating pregnancy. The patient should be carefully evaluated. The presence of other symptoms and signs of cardiopulmonary disease indicate a possible pathologic nature of dyspnea, which needs careful evaluation.[2]

Asthma in Pregnancy

Asthma affects between 3% and 12% of pregnant women worldwide. The prevalence among the pregnant women seems to rise. It is a well recognized fact that women with asthma are at risk for poor pregnancy outcomes.[3]

Pathophysiology

The pathophysiology of asthma is complex. It has a major hereditary component. Airway inflammation, intermittent airflow obstruction and bronchial hyperresponsiveness are the major factors. The presence of airway edema and mucus secretion also contributes to airflow obstruction and bronchial reactivity.

The presence of airway hyperresponsiveness or bronchial hyperreactivity in asthma is an exaggerated response to numerous exogenous and endogenous stimuli. The stimulus can be caused by different allergens, viral infections, aspirin, cold air and exercise. Clinical course of asthma ranges from mild wheezing to severe bronchoconstriction. Asthma may be clinically classified according to the frequency of symptoms, Forced Expiration Volume in one second (FEV_1) and peak expiratory flow rate.[4]

Effect of Pregnancy on Asthma

The effects of pregnancy on asthma are variable; 23% improve and 30% become worse during pregnancy, intrapartum exacerbation is seen in 20% of patients.[5] Maternal morbidity seen with asthma is around 2.3% in mild, 19.3% in moderate and 26.9% in severe asthma, requiring hospitalization during pregnancy for asthma exacerbations.[6] In one of the large prospective studies, approximately each one-third patients improved, remained unchanged, or clearly worsened.[7] If asthma is going to worsen, it will usually do so between 24 and 36 weeks of gestation. Symptoms are likely to be less troublesome in the peripartum period. In most women, asthma severity returns to the prepregnant state within three months of delivery, but in rare cases it may be worse than before the pregnancy.[8,9]

Effect of Asthma on Pregnancy

In the recent years, pregnancy outcome in asthmatic women has improved. Clinical features are the same as in the non-pregnant state. Earlier studies on the effects of asthma on pregnancy reported inconsistent findings with regard to perinatal mortality, pre-eclampsia, preterm birth, hemorrhage and low birth-weight.[10-12] However, in a recent study, it is concluded that severe disease affects the pregnancy outcome.[13] There is increased risk of pre-eclampsia, preterm labor, placental abruption, preterm rupture of membranes, low birth-weight infants and perinatal mortality.[13,14] Asthma medication and poor asthma control leading to hypoxia, have been hypothesized to explain these observations.[15]

In a recent European study, the risks of obstetrical complications were not higher in asthmatic pregnant women than in non-asthmatics except for depression, miscarriage and cesarean delivery.[16] There are some data to support a correlation with poor asthma control indicated by increased hospitalization for exacerbations and decreased FEV_1 values directly proportional to low birth-weight and ponderal index and inversely to gestational hypertension and preterm delivery.[5,15,17] Most of the literature available till date shows that patients with more severe asthma may have the greatest risk for complications during pregnancy, whereas better controlled asthma is associated with decreased risks.[5,15,18-21] In status asthmaticus, muscle fatigue with respiratory arrest, pneumothorax, pneumomediastinum, acute cor pulmonale and cardiac arrhythmias can occur, which can often be life threatening.

The fetus, dependent for its oxygen supply on maternal arterial oxygen content, exists in a precarious state of oxygenation. Compensatory mechanisms of the fetus to combat potentially adverse conditions of oxygenation include a hemoglobin level of atleast 16 g/dl and a P_{50} of 22 mm Hg. With reasonable control of asthma, perinatal outcomes are generally good. Poorly controlled asthma or severe asthma attacks further threaten the fetus because of increased maternal hypoxemia and diminution of uterine artery blood flow, secondary to hypocapnic vasoconstriction and an alkaline induced leftward shift of oxyhemoglobin dissociation curve. These fetuses have increased the incidence of intrauterine growth retardation, low birth-weight, prematurity and neonatal hypoxia.[5,15,19]

The possible teratogenic and adverse effects of drugs in asthma are important concerns. However, there is enough evidence that the commonly used drugs cause no harm to fetus.[22-24]

Management of Chronic Asthma

The management of asthma during pregnancy should be aggressive, with the aim of eliminating symptoms, restoring and maintaining normal lung function. Cooperation between the respiratory physician and obstetrician is important throughout pregnancy for women with severe asthma. The guidelines by the Working Group on Asthma and Pregnancy recommend a multipronged approach to management (Table 165.2).[4]

TABLE 165.2: Components of asthma management during pregnancy

- Patient education
- Avoidance or control of environmental precipitating factors
- Objective assessment of pulmonary function and fetal well-being
- Pharmacological therapy to provide baseline control and treat exacerbations

Objective Measures for Assessment and Monitoring

Subjective measures of lung function by the patient and physician provide an insensitive and inaccurate assessment of airway hyperresponsiveness, airway inflammation and asthma severity. The FEV_1 following a maximal inspiration is the single best measure of pulmonary function. However, repeated measurement of FEV_1 is generally impractical. The Peak Expiratory Flow (PEF) correlates well with the FEV_1 and has the advantages that it can be measured reliably with inexpensive, disposable, portable peak flow meters. Patient self-monitoring of PEF provides valuable insight to the course of asthma throughout the day, assesses circadian variation in pulmonary function and helps to detect early signs of deterioration so that timely therapy can be instituted. The FEV_1 ideally is >80% of predicted. For PEF, predicted values range from 380 to 550 L/min.[25]

Asthma Pharmacotherapy

The goal of asthma therapy is multiphasic: (1) to relieve bronchospasm, (2) to protect the airways from irritant stimuli, (3) to prevent the pulmonary and inflammatory response to an allergen exposure, and (4) to resolve the inflammatory process in the airways, leading to improved pulmonary function with reduced airway hyperresponsiveness. Although it is assumed that asthma medications are as effective in pregnant as in non-pregnant patients, differences in maternal physiology and pharmacokinetics may affect the absorption, distribution, metabolism and clearance of medications during pregnancy. Endocrinologic and immunologic changes during pregnancy include elevations in free plasma cortisol, possible tissue refractoriness to cortisol and changes in cellular immunity.[26,27]

Inhaled β_2-Agonists

Beta$_2$-agonists are currently recommended for use with all the degrees of asthma during pregnancy.[28,29] The commonly used inhaled β_2-agonists are salbutamol (albuterol), terbutaline, fenoterol and long-acting agents like salmeterol and formoterol. Salbutamol is preferred because of the availability of more human data on safety. It has the advantage of a rapid onset of effect in the relief of acute bronchospasm through smooth muscle relaxation. Side effects include tremors, tachycardia and palpitations, associated with an increased risk of death with chronic use.[30,31] β_2-agonists appear to be safe, based on a review of six published studies with 1,599 women with asthma who took β_2-agonists during pregnancy.[28] Additionally, in a large prospective trial, they were not associated with adverse pregnancy outcomes.[32]

Inhaled Corticosteroids

They are the mainstay of treatment in moderate to severe asthma and appear to have a good safety profile in pregnancy.[28] The use of inhaled corticosteroids among non-pregnant asthmatics has been associated with a marked reduction in fatal and near-fatal asthma. Inhaled corticosteroids produce clinically important improvements in bronchial hyperresponsiveness that appear to be dose related.[33] The National Asthma Education and Prevention Working Group reviewed 10 studies, including 6,113 patients who took inhaled corticosteroids during pregnancy for asthma. Based on these studies, there was no evidence of any increase in congenital malformations or adverse perinatal outcomes with inhaled corticosteroid use.[28] Data are available describing budesonide use during pregnancy than with other inhaled corticosteroids. Budesonide is considered as a preferred medication, but if a woman is well-controlled by a different inhaled corticosteroid before pregnancy, it seems reasonable to continue that medication during pregnancy. All inhaled corticosteroids are currently labeled Food and Drug Administration (FDA) pregnancy class C, except budesonide, which is class B.

Theophylline

Theophylline is a methylxanthine with various anti-inflammatory actions that may potentiate the efficacy of inhaled corticosteroids.[34,35] New dosing guidelines have recommended that serum theophylline concentrations be maintained at 5 to 12 mcg/ml during pregnancy.[28] Symptoms of adverse theophylline effects, including insomnia, heartburn, palpitations and nausea, may be difficult to differentiate from typical pregnancy symptoms. High doses have been observed to cause jitteriness, tachycardia and vomiting in mothers and neonates.[36,37]

The main advantage of theophylline is the long duration of action, which is especially helpful in the management of nocturnal asthma.[38] Theophylline may be employed as an alternate treatment when β_2-agonists and inhaled anti-inflammatory agents do not adequately control symptoms. Indicated only for chronic therapy, it is not effective for the treatment of acute exacerbations during pregnancy.[39] In a recent randomized controlled trial, there were no differences in asthma exacerbations or perinatal outcomes in a cohort receiving theophylline compared with the cohort receiving inhaled beclomethasone. However, the theophylline cohort had significantly more side effects and instances discontinuation of study medication.[20]

Leukotriene Moderators

Treatment with leukotriene receptor antagonist montelukast has been shown to significantly improve pulmonary function as measured by FEV_1. The leukotriene receptor antagonists, zafirlukast and montelukast are both pregnancy category β drugs.[31] There are minimal data regarding the efficacy or safety of these agents during human pregnancy.

Oral (Systemic) Corticosteroids

The National Asthma Education and Prevention Working Group reviewed eight human studies, including one report of two meta-analyses.[28] Most of the subjects in these studies did not take oral corticosteroids for asthma. The Panel concluded that findings from the current evidence review were conflicting. Oral corticosteroid use during the first trimester of pregnancy was associated with a three-fold increased risk for isolated cleft lip with or without cleft palate, with a background incidence of about 0.1%; the excess risk attributable to oral steroids would be 0.25 to 0.3%.[40]

Because of the definite risks of severe uncontrolled asthma both to the mother and the fetus, the Working Group recommends the use of oral corticosteroids when indicated for the long-term management of severe asthma or for severe exacerbations during pregnancy.

Cromolyn and Nedocromil

Cromolyn and nedocromil, both inhibit mast cell degranulation. Cromolyn, which is virtually devoid of significant side effects, blocks both the early- and late-phase pulmonary response to allergen challenge, as well as prevents the development of airway hyper-responsiveness.[49] Both are ineffective for acute asthma. They are less effective than inhaled corticosteroids in reducing the objective and subjective manifestations of asthma. Cromolyn appears to be safe during pregnancy.[32]

Antenatal Management

Patients with moderate and severe asthma should be considered at risk for pregnancy complications. Adverse outcomes can increase by the underestimation of asthma severity and under treatment of asthma exacerbations. The first prenatal visit should include a detailed medical history with attention to medical conditions that could complicate the management of asthma. The patient should be questioned about the presence and severity of symptoms, episodes of nocturnal asthma, the number of the days of work missed due to asthma exacerbations, history of acute asthma emergency care visits and smoking history. The type and amount of asthma medications, including the number of puffs of β_2-agonists used each day should be recorded.

Gravidas with moderate or severe asthma should have scheduling of prenatal visits based on clinical judgement. In addition to routine care, monthly or more frequent evaluations of asthma history and pulmonary function (FEV_1 or PEF) are recommended. Those with mild and well-controlled asthma may receive routine prenatal care. Patients should be instructed on proper dosing and administration of asthma medication. The least number of medications needed to control asthma symptoms should be used.

Moderate and severe asthmatics should have additional fetal surveillance in the form of ultrasound examinations and antenatal fetal surveillance. Because asthma has been associated with intrauterine growth restriction and preterm birth, it is necessary to accurately establish pregnancy dating. Ultrasound examinations are also needed to evaluate fetal viability, anatomy, amniotic fluid volume, placental location and interval fetal growth. The intensity of antenatal fetal surveillance should be based upon the severity of asthma.

Management of Acute Asthma

The treatment of acute asthma is same as in non-pregnant state. The principal goal should be the prevention of hypoxia. Continuous fetal monitoring should be initiated if gestation has advanced to the point of potential fetal viability. First line of therapy is β-agonists, such as terbutaline, salbutamol, isoetharine, epinephrine, isoproterenol or metaproterenol, which are given subcutaneously, orally, or in inhaled forms. Salbutamol (2.5 to 5 mg every 20 minutes for three doses, then 2.5 to 10 mg every 1 to 4 hours as needed, or 10 to 15 mg/hour continuously) should be delivered by nebulizer, driven with oxygen.[28] Occasionally nebulized treatment is not effective when terbutaline, 0.25 mg can be administered subcutaneously every 15 minutes for three doses. The patient should be assessed for the general level of activity, color, pulse rate, use of accessory muscles and airflow obstruction determined by auscultation and FEV_1 or PEF before and after each bronchodilator treatment. Measurement of oxygenation through pulse oximeter or arterial blood gases is essential. Arterial blood gases should be obtained if oxygen saturation remains less than 95%; chest radiographs are not commonly needed. Assessment to treatment is assessed as good, incomplete or poor (Table 165.3).

TABLE 165.3: Assessment of response to initial treatment of acute asthma

Good Response

- FEV_1 or PEF >70%
- Response sustained 60 minutes after last treatment
- No distress
- Physical examination: normal
- Reassuring fetal status
- Discharge home

Incomplete Response

- FEV_1 or PEF 50% but <70%
- Mild or moderate symptoms
- Continue fetal assessment until patient stabilized
- Monitor FEV_1 or PEF, O_2 saturation, pulse
- Continue inhaled salbutmol and oxygen
- Inhaled ipratropium bromide
- Systemic (oral or intravenous) corticosteroid
- Individualize decision for hospitalization

Poor Response

- FEV_1 or PEF <50%
- P_{CO_2} >42 mm Hg
- Physical examination: severe symptoms, drowsiness, confusion
- Admit to hospital intensive care
- Continue fetal assessment

Status Asthmaticus and Respiratory Failure

Severe asthma of any kind not responding after 30 to 60 minutes of intensive therapy is termed as status asthmaticus. Early intubation and mechanical ventilation may be needed. Management in intensive care has resulted in good outcome.[42]

Labor and Delivery Management

Asthma medications should not be discontinued during labor and delivery. The patient should be kept hydrated and receive adequate analgesia in order to decrease the risk of bronchospasm. If systemic corticosteroids have been used in the previous four weeks, then intravenous corticosteroids, hydrocortisone 100 mg q 8 hours should be administered during labor and for the 24-hour period following delivery to prevent adrenal crisis.[28]

It is rarely necessary to perform a cesarean delivery for an acute asthma exacerbation. Usually, maternal and fetal compromise will respond to aggressive medical management. Oxytocin and prostaglandin (PG) E_2 or E_1 can be used for cervical ripening and induction. Postpartum hemorrhage is treated with oxytocin and prostaglandin E2. Carboprost (15-methyl PGF_2-alpha) and methylergonovine can cause bronchospasm, so are contraindicated. Magnesium sulfate, which is a bronchodilator, is a safe choice for treating preterm labor. Indomethacin can induce bronchospasm in the aspirin-sensitive patient. There are no reports of the use of calcium channel blockers for tocolysis among women with asthma.

Lumbar epidural anesthesia has the benefit of reducing oxygen consumption and minute ventilation during labor.[43] Fentanyl may be a better analgesic than meperidine. Meperidine which causes histamine release is occasionally associated with the onset of bronchospasm during labor. Conduction analgesia is preferred since tracheal intubation can trigger bronchospasm.

Breastfeeding

Breast milk may contain very small amounts of the drugs used to treat asthma, but, in general, these are not known to be harmful to the infant. Prednisone, theophylline, antihistamines, beclomethasone, β_2-agonists and cromolyn are not considered as contraindications for breast feeding. However, among sensitive individuals, theophylline may cause toxic effects in the neonate, including vomiting, feeding difficulties, jitteriness and cardiac arrhythmias.

Pneumonia in Pregnancy

Pneumonia is the sixth leading cause of death overall and the number one cause of death from an infectious disease. Over 5 million cases occur annually, with more than 1 million persons requiring hospitalization.[44,45] Although associated with far less mortality, women of reproductive age are susceptible to pneumonia from a bacterial, viral or fungal source. Pregnant women do not get pneumonia more often than non-pregnant women, but can result in greater morbidity and mortality because of the physiologic alterations of pregnancy. These include a decrease in pulmonary functional residual capacity, as well as alterations in cell-mediated immunity. Thus, pregnant patients require a higher level of surveillance and intervention.

Currently, pneumonia has been classified into several types:[46] (1) Community-acquired pneumonia, commonly seen in young and pregnant women; (2) Healthcare–Associated Pneumonia (HCAP) resembles hospital acquired pneumonia; (3) Other types of pneumonia are nursing home acquired pneumonia and ventilator associated pneumonia. The hospitalization rate for community-acquired pneumonia in pregnant women was 1.51 per 1,000 pregnancies.[47] Several recent articles have reported an incidence of 1 per 660 deliveries.[47,48]

Hypoxemia and acidosis due to severe pneumonia are poorly tolerated by fetus and frequently stimulate preterm labor. Any pregnant women suspected of having pneumonia should undergo chest radiography.

Bacterial Pneumonia

Incidence and causes: Pregnancy causes no change in the course of pneumonia. Organisms found to cause bacterial pneumonia include *Streptococcus pneumoniae, Haemophilus influenzae, Chlamydia pneumoniae, Mycoplasma pneumoniae and Legionella pneumophila. Streptococcus pneumoniae* is the most commonly identified bacterial cause. Though in some studies causative organism could be identified in only 27% of cases, others identified the organism in 75% of patients.[49,50] Even with extensive diagnostic testing, the etiology may not be identified in 50% or more of cases.[51] A Gram's stain and culture of sputum can be helpful in focusing therapy, but its use is controversial. Bacterial cultures of sputum have poor sensitivity and specificity.[51] Risk factors for pneumonia include asthma and other chronic respiratory diseases, Human Immuno Deficiency Virus/Acquired Immuno Deficiency Syndrome (HIV/AIDS), smoking and drug use.[52]

Diagnosis: Signs and symptoms of bacterial pneumonia in pregnancy are same as in non-pregnant individuals: Cough (90%), sputum production (66%), dyspnea (66%) and pleuritic chest pain (50%).[53] In patients who have the findings of fever, crackles and abnormal breath sounds and in whom pneumonia is suspected, a chest radiograph should be performed. The chest radiograph will confirm pneumonia, rule out other diagnoses, suggest a possible etiology and aid in determining the severity of illness. Multilobar pneumonia is considered a more severe process than single lobar involvement (Table 165.4).[51]

TABLE 165.4: Criteria for severe community acquired pneumonia

- Respiratory rate $\geq$30/min
- $PaO_2/FiO_2 \leq 250$
- Multilobular infiltrates
- Confusion/disorientation
- Uremia
- Leucopenia – WBC <4,000/µl
- Thrombocytopenia – platelets <1,00,000/µl
- Hypothermia – temperature <36°C
- Hypotension requiring aggressive fluid resuscitation

Management: Generally, all pregnant women who have pneumonia are hospitalized for observation and initial therapy. Work-up should include a complete blood count, electrolytes, assessment of oxygenation and blood cultures; however, blood cultures have been found to be positive only 7 to 15% of the time.[52] Intravenous antibiotic therapy should be empirically started. Erythromycin is an acceptable initial choice for treatment, because it is considered safe in pregnancy. Treatment success rates up to 99% have been reported.[48] If gram-negative organisms or drug-resistant S pneumonia is suspected, a β-lactam, such as ceftriaxone or ampicillin should be added.

For women with severe disease, the American Thoracic Society guidelines call for: 1) fluoroquinolone – levofloxacin, moxifloxacin or gemifloxacin, 2) a β-lactam plus a macrolide. Most patients will have a clinical response within three days. Therapy should not be changed in the first 72 hours unless there is a marked clinical deterioration. Radiographic abnormality will take up to six weeks to resolve. Upto 20% of patients develop pleural effusion. Therapy is recommended for minimum of five days. [51]

Pregnancy outcome with pneumonia: Many different complications of bacterial pneumonia have been reported. Meningitis, arthritis, endocarditis, empyema and pericarditis have all been reported. Severe cases of pneumonia can be complicated by sepsis, heart failure, renal failure and Acute Respiratory Distress Syndrome (ARDS), requiring intensive care treatment.

Obstetric complications include fetal distress secondary to poor oxygenation and preterm birth. Women, who have pneumonia, are significantly more likely to deliver before 34 weeks.[54] Preterm birth has been reported to be more common when the woman who has pneumonia, has some underlying comorbid condition.[55] Anemia has also been reported in several studies of pneumonia during pregnancy.[48,52,54,56] Birth-weights of infants born to women having antepartum pneumonia have been found to be significantly less than the controls.[48,52]

Prevention: Pneumococcal vaccine is 60 to 70% protective. The vaccine is not recommended for otherwise healthy pregnant women. It is recommended for immunocompromised patients like those with HIV infection, diabetes, cardiac or renal disease and asplenia, such as sickle cell disease.[57]

Influenza

Influenza is a significant cause of morbidity and mortality from febrile respiratory illness worldwide. Influenza in pregnant women has historically been associated with a higher rate of morbidity and mortality.

High-risk groups include children aged 6 to 23 months; people aged 65 or older; residents of long-term care facilities, adults and children who have chronic illnesses, asthma, diabetes, immunosuppression and pregnant women. This risk is higher in pregnancy, if they have an underlying medical condition, are of advanced age or are exposed in the third trimester. In one study, women in the third trimester were three to four times more likely than postpartum women, to be hospitalized for an acute cardiopulmonary illness during influenza season.[58] Asthma in pregnant women increased the rate of hospitalizations for a respiratory illness during influenza season by 10-fold.[59]

Clinical presentation: The virus is spread from person to person via aerosolized droplets. Particles are created when a person coughs, sneezes or speaks. These particles are filtered in the recipient's nose and pharynx and then reach the alveoli.[60] The clinical presentation of influenza does not appear to be altered by pregnancy. The incubation period for influenza is one to four days, with an average of two days.[61] Patients are generally infectious the day before the onset of symptoms and for five days thereafter, however, young children and immunocompromised adults can shed virus for much longer periods of time.

Symptoms of influenza include cough, fever, malaise, rhinitis, myalgias, headache, chills and sore throat. Nausea and vomiting, otitis and conjunctival burning are less common symptoms. Signs of influenza include the presence of fever, tachycardia, facial flushing, clear nasal discharge and cervical adenopathy. Fever in adults generally lasts for three days, with resolution of symptoms normally within one week; however, the cough and malaise may persist for longer than two weeks.

Diagnosis: Influenza is usually diagnosed in the presence of clinical features during the influenza season. Rapid testing by either immunofluorescence or immunoassay has the advantage of providing same-day diagnosis; however, it does not have the same sensitivity as that of culture. Nasal samples provide a higher level of sensitivity than do throat samples when performing rapid testing. Patients who have a clinical picture are highly suggestive of influenza, but with a negative rapid test should still be cultured, because false negatives do occur.[60] Viral culture is necessary to subtype influenza, as well as for drug sensitivities.

Management: Supportive treatment with antipyretics and bed rest is recommended for uncomplicated cases. The antiviral agents' adamantanes, M2 ion-channel inhibitors, amantadine and rimantadine have activity only against influenza A. Given for chemoprophylaxis, they are 70 to 90% effective in preventing influenza. They also can be given within the first 48 hours of symptoms to reduce the symptom duration. The Center for Disease Control and Prevention in 2006 recommended against their use due to rapid resistance of influenza strain H3N2 to these drugs.[62]

The neuraminidase inhibitors are effective in the treatment of influenza A and B. Oseltamivir, given orally 75 mg twice daily, is approved for both treatment and chemoprophylaxis. It is reported to be 70 to 90% effective in preventing influenza.[63] The most commonly reported side effects are nausea and vomiting. Zanamivir is an inhaled medication approved only for treatment. It should be noted that there have been several reports of bronchospasm in patients of asthma after this drug.[64] Both shorten the duration of symptoms by, on an average, one day. There are limited data on their safety in pregnancy. All four are US FDA category C drugs and therefore should be used only when the benefits outweigh the risks.

Prevention/vaccination: The primary method of influenza prevention is vaccination. Vaccination is most effective when performed in October or November, although non-vaccinated patients should not be denied vaccination later in the season. The recommendation of the Advisory Committee on Immunization Practices (ACIP) is that all women who will be pregnant during the influenza season shall receive the vaccine. Vaccination can be performed safely in any trimester of pregnancy.[64] Breastfeeding is not a contraindication to vaccination. Of the two different vaccines available, the inactivated vaccine is used for pregnant women, as well as for all other high-risk groups.

Effects on pregnancy: Pneumonia, either viral or superimposed bacterial, is a well-recognized complication of influenza. Superimposed bacterial pneumonia typically occurs 2 to 14 days after the symptoms of influenza have resolved. Local consolidation is seen on chest radiograph with superimposed bacterial pneumonia. Myopathy is another complication that has been associated with influenza. Patients may develop rhabdomyolysis and myoglobinuria. In adults, myopathy is more commonly found with influenza A. Carditis has also been reported. Finally, encephalopathy is a rare complication of influenza. The virus has been isolated from Cerebrospinal Fluid (CSF) and brain tissue at autopsy.

Fetal effects: There is a paucity of prospective data on the effects of intrapartum, laboratory confirmed influenza on fetal outcome. There are no significant differences between women who had serum-confirmed influenza and controls, in the incidence of congenital malformations.[65] In the study of the influenza epidemics of 1957 to 1960, there was no increased incidence of fetal death or malformations in pregnant women who had influenza.[66] According to some studies, influenza has been associated with limb reduction and neural tube defects, including anencephaly.[67-69] Other investigators have not found an association between influenza and anencephaly. Some studies have noted an increased incidence of schizophrenia in people who were born two to three months after an influenza epidemic, implying that maternal exposure to influenza in the second trimester, when fetal neurons are migrating, is a risk factor.[70,71] There have also been reports of an increased incidence of cleft lip.[72]

Varicella Pneumonia

Varicella is a Deoxyribonucleic Acid (DNA) virus that affects 0.7 per 1,000 pregnancies.[73] Pneumonia is the most common complication in adults, occurring in 10% of cases.[74] The mortality rate in the era of antiviral therapy is approximately 14%. Risk factors for varicella pneumonia include smoking and the presence of 100 or more skin lesions.[75] Pulmonary symptoms cough, hemoptysis, dyspnea, tachypnea and pleuritic chest pain infiltrates begin 2 to 5 days after the onset of rash and fever. Treatment is with intravenous acyclovir, although its value has not been proven in rigorous scientific studies.[76]

Congenital varicella syndrome occurs in 1 to 2% of cases of maternal varicella, depending on gestational age.[76,77] In a study conducted by the Maternal Fetal Medicine Units Network, the rate of congenital varicella was 0.4% in 347 pregnant women who had varicella.[78] Congenital varicella is characterized by limb hypoplasia, chorioretinitis, cutaneous scars and cortical atrophy.[79,80] Varicella pneumonia has been also associated with preterm labor.[79] Varicella-zoster immunoglobulin given within 96 hours of exposure to varicella can attenuate or prevent infection in susceptible individuals. It is not contraindicated in pregnancy. The varicella vaccine, however, is contraindicated in pregnancy because it is a live-attenuated vaccine.[81]

Severe Acute Respiratory Syndrome

Severe Acute Respiratory Syndrome (SARS) is caused by a novel coronavirus. Since 2002, this atypical pneumonia has affected over 8,000 people and resulted in more than 800 deaths worldwide.[82] Transmission is by respiratory droplets or close personal contact. The virus can live in urine and stool for 1 to 2 days. Symptoms are the same in pregnant as in non-pregnant women. Various symptoms include fever, chills, rigors, malaise and myalgias.[83]

Complications of SARS pneumonia include respiratory failure, superimposed bacterial infections and Disseminated Intravascular Coagulation (DIC). The largest case series of pregnant women who had SARS reported high rates of morbidity and mortality.[84] The case fatality rate was 25%. A large portion of the cases was complicated by first-trimester spontaneous abortions, preterm births and intrauterine growth restriction; however, there have been no cases of vertical transmission reported. Treatment includes broad-spectrum antibiotics to cover superimposed bacterial infections, high dose steroids and possibly ribavirin. Ribavirin has been shown to have teratogenic effects in animals; its use in pregnancy has not been established.

Fungal Pneumonia

Fungal pneumonias with *Aspergillus, Candida* and *Cryptococcus* are seen in those women who are immunocompromised or hospitalized.[85] Management of these opportunistic fungal infections during pregnancy is same as in non-pregnant women. These are generally serious, life-threatening conditions. With the physiologic suppression of cell-mediated immunity in pregnancy, endemic fungal pneumonias can be seen in otherwise healthy women. There have only been a handful of cases of pneumonia secondary to histoplasmosis.[86] Of 19 cases of blastomycosis in pregnancy, 78% had pulmonary involvement; all recovered or were at least reported as having a "good response."[87]

The 2007 American Thoracic Society Guidelines recommend the use of itraconazole in disseminated fungal infections.[88] However, this may be embryotoxic in large doses, so avoided in early trimester. Regardless of the type of pneumonia, it is important to be aggressive with monitoring and treatment for the sake of the mother and the fetus. Broad-spectrum empiric antibiotics should be started before the identification of the etiologic agent, antibiotic therapy should be tailored to specific organisms. Given that the majority of pregnant women are young and healthy, intense, early treatment is likely to result in a good outcome.

With the increasing number of pregnant women infected with HIV, *Pneumocystis jiroveci* pneumonia (PJP), previously known as *Pneumocystis carinii* is a common complication. Among pregnant women, this is a leading cause of AIDS-related death in the United States.[89] Symptoms include dry cough, dyspnea and tachypnea. A diffuse infiltrate is seen on chest radiograph.

In a report of 22 cases of PCP in pregnancy, the mortality rate was extremely high at 50%, while 59% required mechanical ventilation.[90] These numbers may be inflated since none of the patients had received antiretroviral therapy, all were diagnosed with HIV when diagnosed with PJP. Treatment is given with trimethoprim-sulfamethoxazole or pentamidine. HIV-infected patients who have a $CD4^+$ T-lymphocyte count of less than 200/mL, a history of oropharyngeal candidiasis, or an AIDS-defining illness should receive prophylaxis.[91] The preferred regimen is trimethoprim-sulfamethoxazole, one double-strength tablet per day. Prophylaxis is 90 to 95% effective.

Tuberculosis and Pregnancy

Considering the high prevalence of Tuberculosis (TB) in India, a large number of pregnant women can be expected to suffer from TB, but exact data about the proportion of pregnant women with tuberculosis are unavailable. The clinical and laboratory diagnosis and treatment during pregnancy, safety of anti-tuberculosis therapy and excretion of these drugs in breast feed are concerns of the physicians giving care to these pregnant women. The diagnosis and management of tuberculosis in pregnancy is of utmost importance, especially since the untreated disease poses much greater risk to both the mother and the fetus.

Clinical Presentation

About half to two-thirds of pregnant women with tuberculosis remain asymptomatic.[92] The clinical presentation of tuberculosis in the pregnant women is similar to that in the non-pregnant patients (Table 165.5). Non-specific symptoms like lethargy, alteration in bowel habit, or failure to gain weight are commonly interpreted as usual symptoms of pregnancy, hence the cause of delay in the diagnosis.[93]

TABLE 165.5: Symptoms of tuberculosis in pregnancy

Common	*Less common*
Cough, sputum	Lethargy, malaise
Weakness, weight loss	Abdominal distension
Fever, sweating	Irritability, headache
Hemoptysis	Skin lesions, lymph nodes
Fatigue, tiredness	Alteration in bowel habit

During pregnancy, pulmonary tuberculosis is more common than extrapulmonary tuberculosis. Only 5 to 10% of pregnant women have extrapulmonary disease most commonly of lymph nodes, pleura, genitourinary tract, bones, joints, meninges and peritoneum.[92-95] Extrapulmonary tuberculosis is now seen more often because of HIV coinfection.

Effect of Pregnancy on Tuberculosis

Effect of pregnancy on tuberculosis was a matter of controversy since the days of Hippocrates.[96] Raised diaphragm during pregnancy was believed to cause atelectasis of basal lung regions.[97] In early 20th century, it was believed that pregnancy has deleterious effects on tuberculosis and induction of abortion was recommended.[94,98] Now, it is believed that TB gets flared up by the stress of pregnancy, especially if associated with poor nutritional and immunodeficient states, or coexistent diseases. There is also an increased risk of development of postpartal TB during lactation, due to the loss of protective antibodies in mother.[99] However, all this is still controversial and more studies are needed to support these hypothesis.

Effect of Tuberculosis on Pregnancy (Table 165.6)

The pulmonary and extrapulmonary forms of tuberculosis affect pregnancy in the same way as in non-pregnant state (Table 165.7).[100-104] With the advent of chemotherapy, most studies have demonstrated that TB does not increase complications of pregnancy and labor.[94]

TABLE 165.6: Effects of tuberculosis on pregnancy

- Spontaneous abortions
- Intrauterine death
- Premature labor
- Small for gestational age neonates
- Low birth-weight
- Increased perinatal mortality

Diagnosis

It is important to identify pregnant women with tuberculosis since an early diagnosis and treatment will result in better maternal and neonatal outcomes. A careful history is mandatory in high-risk cases in the antenatal period. History of exposure to tuberculosis and the similarities of symptoms between tuberculosis and pregnancy should be kept in mind.

Chest radiograph: In the past, chest X-ray was advocated to detect tuberculosis. In view of the risk of radiation

TABLE 165.7: Studies showing effect of tuberculosis on pregnancy

	Study	*Year*	*Outcome*
1.	Selikoff et al[100]	1965	Seven spontaneous abortions, nine antepartum and intrapartum fetal deaths
2.	Schaeffer et al[101]	1975	No increased risk of prematurity
3.	Jana et al[102]	1994	Two fold increase in prematurity, small for gestational age and low birth-weight neonates, 6-fold increase in perinatal deaths
4.	Maurya and Sapre[103]	1996	Four spontaneous abortions, two premature delivery, one intrauterine death
5.	Kothari et al[104]	2006	Two abortions, two preterm deliveries

exposure, the routine use of chest radiograph is not justified. If tuberculin skin test is greater than 10 mm of induration, a chest radiograph should be obtained in asymptomatic patient with proper abdominal shielding preferably after first trimester.

Tuberculin skin test: In India where about half of the population is tuberculin positive, the routine use of the test remains questionable. Tuberculin test is deemed a safe and useful method for screening tuberculosis infection in pregnancy (Table 165.8).

TABLE 165.8: Indications of tuberculin skin test during pregnancy

- Symptoms and signs of tuberculosis
- Pregnant women with diabetes or HIV
- Women employed in hospitals, old age homes
- Prisoners
- Low socioeconomic status

In women who are HIV positive, there may be diminished or negative tuberculin reaction, therefore an area of 5 mm or greater induration in an HIV-positive patient is considered positive.[105]

Microbiological methods: Essential laboratory methods for detection or verification of infection include microscopy, culture, nucleic acid amplification assays and drug susceptibility testing. Demonstration of Mycobacterium tuberculosis by Ziehl-Neelsen staining or culture in sputum or material obtained confirms the diagnosis. Bronchoscopy may be required if patient is unable to produce sputum.

Treatment of Tuberculosis in Pregnant Women

Treatment with Anti-Tuberculosis Treatment (ATT) should be initiated without delay when TB is diagnosed in pregnant women. The decision to treat tuberculosis in pregnancy must keep into account the potential benefits and risks to mother and fetus. It is widely considered that the benefits of treating tuberculosis in pregnancy outweigh any risk of treatment. The indications for treatment of active tuberculosis in pregnant women are the same as for non-pregnant women. None of the first line ATT, isoniazid, rifampicin, streptomycin and ethambutol (Table 165.9) was found to be teratogenic, except streptomycin which caused ototoxicity in fetus.

TABLE 165.9: First line anti-TB drugs used in pregnancy

Anti-TB drug	*Mode of action*	*Recommended dose (mg/kg)*
Isoniazid (H)	bactericidal	5 (4–6)
Rifampicin (R)	bactericidal	10 (8–12)
Ethambutol (E)	bacteriostatic	15 (15–20)
Pyrazinamide (Z)	bactericidal	25 (20–30)

The same regimens are recommended for use in pregnancy as for the non-pregnant state with the exception of streptomycin. Pyrazinamide should preferably be avoided in pregnancy. Currently, an intermittent regimen (thrice weekly on alternate days) under the Directly Obeserved Treatment Short-Course (DOTS) strategy of Revised National Tuberculosis Control Program (RNTCP) is increasingly used worldwide for the pregnant women having tuberculosis.[106] In a retrospective analysis of 12,367 TB patients who were put on DOTS, there were 16 pregnant women suffering from either pulmonary or extrapulmonary form of disease, of whom 25% had become pregnant while receiving ATT; all the 16 completed their treatment without any adverse pregnancy outcome.[107]

Treatment of Tuberculosis in Lactating Women

The safety of breastfeeding, if mother is on ATT, is a very important issue. There is general consensus that although small concentrations of anti-tuberculosis drugs are excreted in breast milk, treatment for tuberculosis is not a contraindication to breastfeeding. Under RNTCP, breastfeeding of neonates is recommended regardless of the mother's tuberculosis status.

Care of newborn:

- If the mother is sputum-positive or on ATT, the infant needs evaluation for active tuberculosis with chest

radiograph and examination of gastric aspirate or sputum for Acid Fast Bacilli (AFB).
- If there is no evidence of active tuberculosis, the infant should receive INH prophylaxis for three months or until after the mother's sputum becomes negative and the baby is tuberculin negative.
- Bacillus of Calmette and Guerin (BCG) vaccination may be postponed or done with INH-resistant BCG vaccine.
- If the infant is tuberculin positive, the INH prophylaxis should be given for a total period of six months after ruling out active tuberculosis.
- If the mother is suffering from Multi Drug-Resistant Tubercle Bacilli (MDR–TB), then INH prophylaxis has no role, hence should not be given. In such cases, the infant should receive BCG vaccination, which has been shown to have a protective effect.[108-110]
- BCG is contraindicated in HIV-positive children.

If tuberculosis is diagnosed and treated appropriately and early, the prognosis for both mother and child is excellent.

Contraception: Rifampicin accelerates the metabolism of oral contraceptives and other drugs resulting in sub-therapeutic serum levels.[94] So, the reliability of oral contraceptive is decreased in women taking ATT.[111] All other contraceptive measures can be considered in postpartum women taking anti-tuberculosis treatment.

Pulmonary Embolism

Peripartum hemorrhage (PE) is the leading cause of maternal mortality in the developing world, whereas it is Venous Thromboembolism (VTE) in the developed nations.[112] The incidence of VTE in pregnant women, derived from retrospective cohort studies, is estimated as 5–12 events per 10,000 pregnancies antenatally (from conception to delivery), seven to ten times higher than the incidence in age-matched controls. The risk is similar in all three trimesters.[114]

Signs and symptoms of Pulmonary Embolism (PE) are not diagnostic because dyspnea and tachypnea are common in pregnancy. In non-pregnant patients, tachypnea, dyspnea, chest pain (pleuritic), apprehension and crackles are present in atleast 50% of patients. Chest radiographs are abnormal in 80% or more of patients. Electrocardiogram findings are abnormal, but nonspecific in 70% of patients with PE. Arterial oxygen tension is low in the majority of patients with PE.[115]

Objective Diagnostic Testing

As with VTE, PE requires objective diagnostic testing to confidently confirm or exclude the diagnosis. This is particularly true in pregnancy. The diagnosis of VTE or PE necessitates: (1) prolonged therapy (2) prophylaxis during future pregnancies, and (3) avoidance of oral contraceptive pills.

The first objective diagnostic test should be compression ultrasonography. Perfusion scanning alone is recommended initially, the ventilation scan is added when perfusion defects are noted. Pulmonary angiography is necessary if lung scan findings are of low probability or are indeterminate and the clinical suspicion remains high. Several studies show no increased risk of teratogenicity in patients undergoing radiological procedures in the diagnosis of maternal venous thromboembolic disease. A complete and adequate evaluation to document the presence or absence of PE requires a dose of less than 0.005 gray of the radioisotope.[116]

Management

Patients, whether pregnant or not, in whom PE is strongly considered should be treated immediately with intravenous unfractionated heparin unless a high risk or contraindication is present for the use of any anticoagulant. Extensive clinical experience and cohort studies establish heparin as the safest anticoagulant to use during pregnancy, because it does not cross the placenta. The initial loading dose of 5,000–10,000 units is followed with an infusion of 18 U/kg. The patient's activated partial thromboplastin time should be monitored and kept in the therapeutic range of 1.5–2 times the baseline value.

Low Molecular Weight Heparin (LMWH) is the treatment of choice for PE in pregnant (and non-pregnant) patients. LMWH is atleast as effective and safe as Unfractioned Heparin (UFH) in non-pregnant women for the treatment of acute VTE.[117,118] Although only a relatively modest amount of data have been gathered, low molecular weight heparin, which does not cross the placenta, can be given once a day and does not require monitoring. Low molecular weight heparin has not been shown to increase the risk of bleeding with surgical procedures, including with the cesarean delivery.[119]

Warfarin should be avoided throughout pregnancy. It can result in embryopathy characterized by mental retardation, optic atrophy, cleft lip, cleft palate and cataracts in addition to hemorrhage. The teratogenic effects are particularly common during the first trimester. Warfarin crosses the placenta; it can cause fetal and neonatal hemorrhage and placental abruption.[120]

Patients who sustain a VTE or PE antepartum should receive anticoagulation therapy with heparin throughout the pregnancy. After delivery, warfarin should be started; the heparin can be discontinued once an adequate International Normalized Ratio is achieved. Warfarin should be continued for atleast six weeks postpartum or until atleast three months of anticoagulant therapy have been completed.

Complications of Treatment

Osteopenia has been reported with unfractionated heparin administered for more than six months. No information is available about the beneficial effects of concomitant multivitamins, calcium or vitamin D supplementation. The problem of osteopenia and osteoporosis might be less with low molecular weight heparin, but providing optimum calcium and vitamin D supplementation is reasonable for all patients receiving long-term heparin administration during pregnancy.

Prophylaxis

In women with history of VTE during pregnancy, the recurrence rate in a subsequent pregnancy has been estimated as 4 to 15%. Women with a known hypercoagulable state are also at increased risk of VTE during pregnancy and should receive prophylaxis. Effective prophylaxis has been demonstrated with unfractionated heparin administered twice daily with an average daily dose of 16,400 IU/d or 225 IU/kg of body weight per 24 hours. The amount of heparin required for adequate prophylaxis might increase through the second and third trimester. Therefore, heparin should be adjusted to mid interval plasma heparin levels of 0.05–0.25 U/mL measured as factor Xa activity. Low molecular weight heparin is most appropriate for prophylaxis because it requires a single daily dose, does not require laboratory monitoring and may be associated with a lower risk of osteoporosis and bleeding.

Sarcoidosis

A large number of restrictive, Interstitial Lung Diseases (ILD) affect women, including in the child-bearing age. Of them, sarcoidosis is particularly important and frequently recognized in India.[121] Sarcoidosis, is a multisystem granulomatous inflammatory disease, commonly seen in female.[122] Clinical presentation may vary in different individuals, more than half of the patients have dyspnea and dry cough with or without constitutional symptoms and around 10 to 20% of patients are asymptomatic at the time of diagnosis.[120]

There is no evidence that sarcoidosis affects fertility. Although the reproductive organs may be pathologically involved, there is no evidence to support any link between the disease and decreased fertility in women. Many investigators have evaluated the effect of pregnancy on the course of sarcoidosis.[123] Sarcoidosis generally does not prevent successful pregnancy and delivery, the endogenous estrogen in pregnancy may even have a slightly beneficial immunomodulatory effect. In most cases, the course of sarcoidosis is unaffected by pregnancy, there is improvement in a few cases and worsening of symptoms in very few cases.[124]

Pregnancy may represent a significant stress in patients with severe, pre-existing physiologic derangements caused by sarcoidosis. Individuals with a normal chest radiograph before pregnancy generally remain stable during pregnancy and in the postpartum period. The presence of parenchymal lesions on chest radiograph, advanced radiographic stage and extrapulmonary disease have been suggested as prognostic markers for progression of disease during pregnancy.[125]

Indications for treatment in pregnant patients are same as in non-pregnant patients, including patients with progressive pulmonary disease and vital organ involvement.[123,126] Anticipatory observation for difficulties with early augmentation or initiation of therapy is warranted throughout the pregnancy. If symptoms secondary to sarcoidosis develop or increase and require corticosteroid therapy, the patient should be monitored carefully for glucose intolerance and infectious complications. Management of labor and delivery should be directed by obstetric indications, with general goals directed to minimize pain and decrease oxygen consumption.[127]

Good maternal and fetal outcomes are possible in women with restrictive lung disease in general and with sarcoidosis in particular. The management of pregnancy, labor and delivery are not altered by the presence of sarcoidosis. After delivery, all patients with sarcoidosis should be evaluated routinely for a possible relapse of disease.

Cystic Fibrosis

Cystic Fibrosis (CF) is an autosomal disorder arising from a defect on chromosome 7 in the region coding for the CF transmembrane regulator protein. Disordered production or function of this protein results in abnormal chloride transport and sodium and water movement across glands in many organ systems. The resulting desiccated, tenacious secretions lead to loss of function and eventual organ damage. The clinical picture is dominated by early bacterial colonization of the airways and chronic airway infection, leading to bronchiectasis and obstructive pulmonary disease. The decline in lung function is inevitable and eventual respiratory failure causes death in more than 90% of patients with CF.[128]

Better understanding of the pathophysiology of CF and aggressive treatment with antibiotics, mucolytics and airway clearance techniques and attention to nutritional parameters resulted in dramatically prolonged survival. The median survival increased from less than 1 year in the 1940s to an estimated 40 years in 2002.

Infertility

It is commonly believed that women with CF have fertility problems secondary to multiple causes, including malnutrition-induced delayed menarche and ovulation, cervical plugs caused by thickened secretions, and frequent vulvovaginal infections.[128] A Scandinavian study showed that 75% of women with CF succeeded in becoming pregnant.[129] Pregnancy is possible in patients with CF; even patients who are underweight or require transplantation, can conceive.

Pregnancy and Cystic Fibrosis

Early reports of pregnancy in patients with CF were discouraging, but attested to the safety of pregnancy in women with good lung function.[130-132] Pregnant women with severe pulmonary dysfunction had shorter gestation periods and increased perinatal mortality rates than did pregnant women with preserved lung function.[131]

Other investigators also concluded that pregnancy had little impact on patients with mild disease, but resulted in poor outcome for those with advanced disease, leading some researchers to suggest that pregnancy can be terminated in women with CF in whom the forced vital capacity or forced expiratory volume in 1 second (FEV_1) is 50 or 60% of predicted or less, respectively.[132,133] However, there are a number of reports of women with CF and severely diminished spirometry who gave birth without complications.[133] Other factors that may affect long-term survival are nutritional status, the existence of diabetes mellitus, the presence of Burkholderia cepacia and frequent infectious exacerbations. The Cystic Fibrosis Foundation (CFF) National Patient Registry database Information from the registry showed no difference in the rate of hospital admissions, use of home intravenous antibiotics, use of supplemental oxygen and supplemental feedings in the year after pregnancy.[134] Most investigators agree that pulmonary hypertension, a late complicating event, is likely an indication for counseling against pregnancy or for therapeutic abortion.[128-130]

Management

Preconception genetic counseling of both future parents should be offered. Women with cor pulmonale and pulmonary hypertension should be counseled against pregnancy. Women can be advised that there is little evidence that the child will be affected by the mother's CF or by medication used to treat exacerbation through the course of pregnancy. Women who choose to become pregnant should have close surveillance for the development of superimposed infection, diabetes and heart failure. The ability of the mother to carry a pregnancy to term seems to relate to lung function before pregnancy. They should be monitored closely with pulmonary function tests. When the FEV_1 is generally at least 70%, pregnancy is tolerated well. β-adrenergic bronchodilators for bronchoconstriction, inhaled recombinant human deoxyribonuclease to reduce sputum viscosity are used in managing these patients. Pancreatic insufficiency is treated with the replacement of oral pancreatic enzyme. Appropriate dietary counseling is also given to these patients. Pulmonary infections are treated with appropriate antibiotics and threshold for hospitalization is low. For labor and delivery, epidural analgesia is recommended.

Pregnancy-Specific Problems

Besides the lung diseases which complicate pregnancy, there are several pregnancy specific problems (Table 165.10), which may frequently pose problems of diagnosis and treatment.

TABLE 165.10: Some important pregnancy-specific pulmonary problems

- Amniotic fluid embolism
- Tocolytic pulmonary edema
- Pre-eclampsia and pulmonary edema
- Peripartum cardiomyopathy
- Gestation

Amniotic Fluid Embolism[135]

Amniotic fluid embolism is a rare (1 case per 8,000–80,000 births), but potentially catastrophic complication, with a mortality rate of 10 to 80%. This usually occurs with labor and delivery, but can be associated with uterine manipulation, uterine trauma and the early postpartum period. Amniotic fluid containing particulate cellular elements enters the vascular circulation through endocervical veins or uterine tears, obstructs the pulmonary vessels and causes vascular spasms, resulting in pulmonary hypertension. Acute left ventricular failure might occur, probably due to humoral events mediated by cytokines.

Clinical presentation usually involves a sudden onset of severe dyspnea, hypoxemia and cardiovascular collapse. Hemorrhage caused by disseminated intravascular coagulation and fetal distress are other less common presentations. The diagnosis of amniotic fluid embolism is usually based on the typical clinical picture. Fetal squamous cells in a wedged pulmonary capillary aspirate have been used to confirm the diagnosis, but are not specific. The differential diagnoses include septic shock, pulmonary thromboembolism, ruptured placentae, tension pneumothorax and myocardial ischemia.

Treatment involves routine resuscitative and supportive measures with prompt attention to adequate oxygenation, ventilation and inotropic support. No specific therapy has been shown to be effective, although corticosteroids have been suggested. The survivors may develop complications of disseminated intravascular coagulation, ARDS, or both.

Tocolytic Pulmonary Edema[136]

β-adrenergic agonists, particularly ritodrine and terbutaline, are used to inhibit uterine contractions and preterm labor. These might cause pulmonary edema during pregnancy. The frequency varies from 0.3 to 9%. Mechanisms include prolonged exposure to catecholamines (which causes myocardial dysfunction), increased capillary permeability and a large volume of intravenous fluid that may have been administered in response to maternal tachycardia. Glucocorticoids administered in preterm labor can also contribute to fluid retention. The clinical presentation is that of acute respiratory distress with the features of pulmonary edema. The diagnosis is generally made in an appropriate clinical situation. The differential diagnoses include cardiogenic pulmonary edema, amniotic fluid embolism and aspiration pneumonia β-agonist therapy must be discontinued; pulmonary edema usually resolves rapidly. The additional treatment which includes diuresis is mostly supportive.

Pre-eclampsia and Pulmonary Edema[137]

Pulmonary edema may rarely occur in association with preeclampsia (approximately 3%). Patients with preeclampsia are usually volume depleted, pulmonary edema most commonly occurs in the early postpartum period, often associated with aggressive fluid replacement. Reduced albumin concentration and myocardial dysfunction contribute to edema formation. The presentation is of an acute respiratory distress in a patient with preeclampsia. The standard approach is to restrict fluids, administer supplemental oxygen and diuresis. Invasive monitoring might be useful if inotropic vasodilator therapy becomes necessary.

Peri-partum Cardiomyopathy

Cardiogenic pulmonary edema is an important consideration in the differential diagnosis of acute respiratory failure in pregnancy. Cardiac failure can occur in the absence of preexisting heart disease as a result of hypertensive disease of pregnancy and peripartum cardiomyopathy. This idiopathic condition presents during the last month of pregnancy or during the postpartum period and is associated with significant mortality. During labor and early postpartum, tachycardia and increased cardiac output can precipitate pulmonary edema.

Gestational Trophoblastic Disease

Pulmonary hypertension and pulmonary edema can complicate benign hydatidiform pregnancy due to trophoblastic PE. This commonly occurs during the evacuation of the uterus, the incidence of pulmonary complications is higher in later gestations. Molar pregnancy can also be associated with the development of choriocarcinoma, which commonly produces multiple discrete pulmonary metastases and occasional pleural effusions.

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166

Rare Lung Diseases

Sanjeev Mehta, PS Shankar

PART I: PULMONARY ALVEOLAR PHOSPHOLIPOPROTEINOSIS

Sanjeev Mehta

INTRODUCTION

Pulmonary Alveolar Proteinosis (PAP) is a rare, idiopathic and diffuse lung disease, characterized by the accumulation of large amounts of surfactant within the alveolar spaces. The name pulmonary alveolar proteinosis, as it is commonly known, is actually a misnomer, since only 2% of the intra-alveolar content is protein, the rest is mostly dipalmitoyl lecithin. Hence, pulmonary alveolar phospholipoproteinosis is more appropriate term for this condition.

Initially, described by Rosen et al. in 1958, PAP is characterized by pulmonary infiltrates with varying degrees of hypoxemia.[1] The disease is rare, with an estimated prevalence of only 0.37 per 100,000 people and an incidence rate of one in two million people. Male:female ratio is 3:1. 72% patients have a history of smoking and that may account for some of the male predominance. Over 80% of cases, occur in the third or fourth decade of life, with a median age of diagnosis of 39 years.[2]

Etiology and Pathophysiology

Pulmonary Alveolar Proteinosis is likely a common phenotypic response to a number of biochemical or molecular abnormalities, resulting in altered surfactant homeostasis, i.e. excessive production and/or reduced clearance of surfactant, by defective function of the alveolar macrophage and the growth factor necessary for its maturation, the Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF). There is recent evidence to suggest a strong association of autoantibodies to GM-CSF or GM-CSF receptor gene mutations, which has implicated GM-CSF, signalling abnormalities in the pathogenesis of PAP. Thus, deficiency in GM-CSF activity may be responsible for PAP and opens the possibility of its treatment with GM-CSF augmentation therapy.

Clinical Classification

Multiple clinical forms of PAP have been described based on presumed etiology.[3,4] Most cases are idiopathic or primary PAP. These are likely caused by mutations in the genes encoding surfactant protein B or C or the C chain of the receptor for GM-CSF. While, the exact etiology is unknown, most patients are smokers. Secondary pulmonary alveolar proteinosis develops in association with conditions involving functional impairment or reduced numbers of alveolar macrophages. These are being increasingly recognized and PAP like pathology is noted in several conditions, as mentioned in Table 166.1.

Pathology

Under light microscopy, the alveoli and terminal bronchioles are filled with an eosinophilic, granular lipoproteinaceous material that stains deep pink with Periodic Acid Schiff (PAS) stain. This fluid consists of phospholipids and surfactant proteins A, B, C, and D and tubular myelin, membranous vesicles and structures that on electron microscopy are recognized, as lamellar bodies. These lamellar bodies are phospholipids that are

TABLE 166.1: Causes of secondary pulmonary alveolar proteinosis

- Subjects exposed to volcanic ash, aluminum dust, titanium, chlorambucil and busulfan
- Conditions, where alveolar macrophage function may be altered or suppressed
  - Immunodeficiency states
  - Hematological malignancies, e.g. myeloid leukemias, neutropenia and lymphomas
  - Fanconi’s anemia
  - IgG monoclonal gammopathy
  - Silico-proteinosis (in sandblasters)
  - Atypical mycobacterioses
  - Pneumocystis carinii pneumonia
  - Mycoses
- Pulmonary diseases associated with/aggravated by smoking:
  - Chronic Obstructive Pulmonary Disease (COPD)
  - Interstitial Pulmonary Fibrosis (IPF)
  - Carcinoma
  - Calcification of pleural plaques in asbestosis
  - pulmonary eosinophilic granuloma
  - Alveolar hemorrhage in Goodpasture syndrome

identical to inclusions found in normal type II pneumocytes. The cellular component of PAP in the Bronchoalveolar Lavage (BAL) fluid consists predominantly of enlarged, foamy macrophages, which contain numerous complex phospholipoprotein inclusions. The alveolar architecture is well-preserved in “primary” form of PAP, this is shown in Figure 166.1. In secondary PAP, septal thickening, edema and lymphocytic and neutrophilic infiltration can be seen, as illustrated in Figure 166.2.

Symptoms and Signs

1. PAP has been noted in young and middle aged individuals
2. Males are often more affected than females
3. It involves the lungs alone
4. Clinically, nearly one-third are asymptomatic or minimally symptomatic.[3,4] Most patients with acquired PAP, present with progressive exertional dyspnea of insidious onset and cough. Less frequently fever, chest pain or hemoptysis occurs, especially if secondary infection is present.
5. In some patients, PAP may begin with an initial febrile episode, followed later by progressive dyspnea, productive cough, low grade fever, chest pain and loss of weight. Cough is minimally productive with gelatinous white “chunky” expectoration. Hemoptysis is rare.

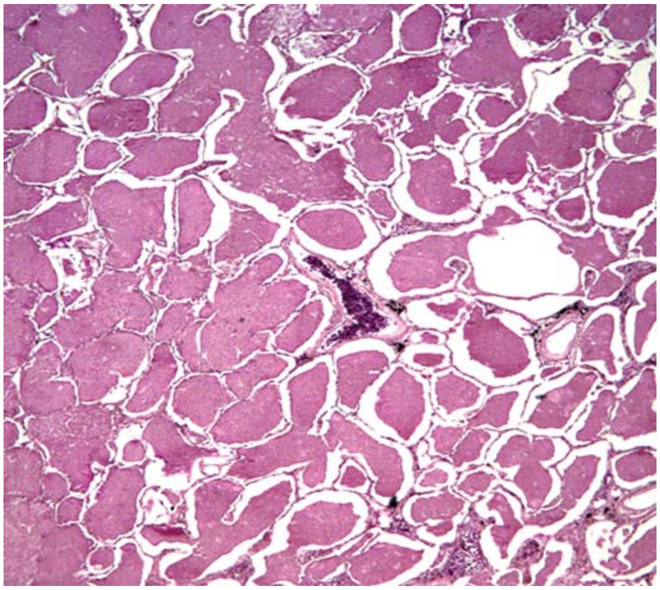

Fig. 166.1: Alveolar eosinophilic material filling the alveolar lumina with preserved architecture in primary alveolar proteinosis

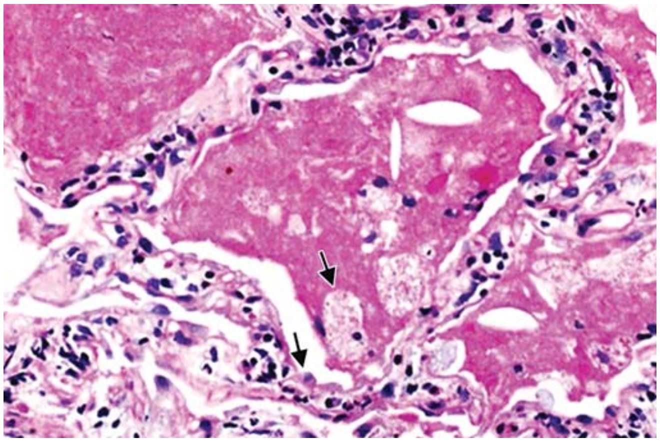

Fig. 166.2: Secondary PAP: Septal thickening, edema and inflammatory infiltration of alveoli

6. Physical examination may be unremarkable, but crackles are present in about 50%, cyanosis in 25% and clubbing in a smaller number of patients.

Radiology

The extent of radiographic abnormalities is often disproportionate, to the severity of the symptoms and physical findings. The chest X-ray shown in Figure 166.3, usually reveals bilateral air space infiltrates with an ill-defined acinar nodules, ground glass opacification or confluent pattern, greater in the lower two-thirds of the lungs. It may be asymmetric in 20%. The “classic” perihilar

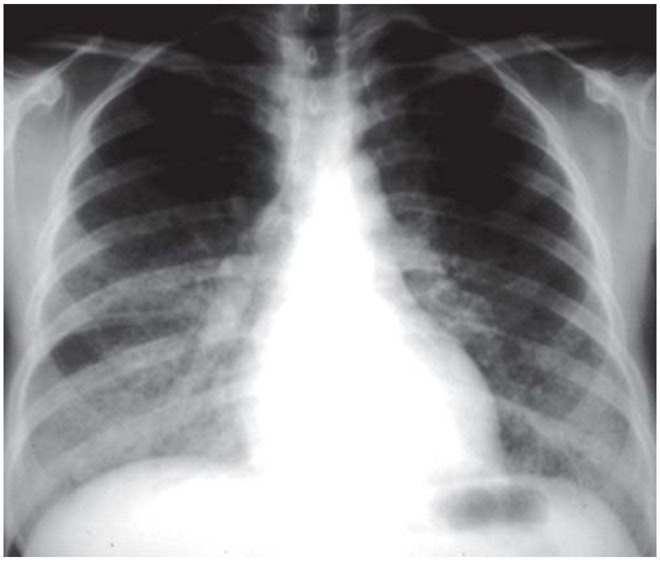

Fig. 166.3: Chest roentgenograph of PAP-bilateral air space infiltrates, acinar nodules and ground-glass opacification

"bat wing" or "reverse pulmonary edema" pattern is seen in about 50% cases. Air bronchograms are not a predominant feature of this disease. As the disease progresses, the alveolar infiltrates become denser. High Resolution Computed Tomography (HRCT) scan of the chest, shown in Figures 166.4A and B reflects the alveolar filling process, as patchy airspace consolidation (ground glass opacity) with thickened interlobular septae, which are predominantly perihilar, with relative sparing of the peripheral lung. Accentuation of the interlobular septa is usually caused by presence of the proteinaceous material in the septal interstitium. There is a sharp transition between the normal and the abnormal lung. It is described as "crazy paving" an appearance that is characteristic, but not entirely specific for PAP. In chronic cases, interstitial infiltration (early fibrosis) can be seen.

Laboratory Tests

Routine laboratory tests are usually unremarkable. There may be mild leukocytosis. Elevated serum Lactate Dehydrogenase (LDH) may be a useful marker. Elevated serum levels of carcinoembryonic antigen, cytokeratin 19, mucin KL-6 and surfactant proteins A, B and D have been reported, but of unclear value.

Pulmonary function tests usually reveal a restrictive ventilatory defect, with reduced lung volumes and a disproportionate reduction in Diffusing Capacity of Carbon Monoxide (DLCO). Hypoxemia caused by ventilation-perfusion inequality and intrapulmonary shunting is common, resulting in a widened alveolar-arteriolar diffusion gradient. Open lung biopsy has been the gold standard for diagnosis, but bronchoscopic lung biopsy may suffice. Bronchoalveolar lavage is also helpful. Aspiration of opaque milky or sandy or light-brown fluid from an affected segment is characteristic. BAL material stains pink with PAS, but negative with alcan blue, which allows the differentiation of the phospholipoprotein aggregates from mucins. Assay using monoclonal antibodies to SF-A has shown Surfactant Protien-A (SP-A) concentrations are 400 times higher in patients with PAP than in controls. It appears to be useful for diagnosis of PAP, especially where lung biopsy is contraindicated. Serum lactic acid dehydrogenase may be elevated.

Treatment

Therapy is essentially supportive. About 30% patients may improve spontaneously, especially those with a $PaO_2 \geq 70$ mm Hg) or P Alveolar-arterial (A-a) $O_2 \leq 40$ mm Hg. Steroids have not shown to be beneficial.

Treatment of the underlying cause should be undertaken, wherever possible. Aggressive attempts should be made at cessation of smoking.

Whole lung lavage, using normal saline, one lung at a time is the mainstay of therapy.[5,6] The usual reported benefit is for 15 months. Patients with severe and or recurrent disease require repeated lavages at intervals of several weeks to months. When whole lung lavage can not be performed, segmental or lobar lavage, using flexible bronchoscope can be attempted. Whole lung lavage is not having any effect on the pathogenetic mechanisms and is often associated with many complications. Subcutaneous and inhaled administration of GM-CSF has been reported to be effective, but this strategy, while promising, remains experimental. Aerosolized trypsin has been used to treat PAP, but the results are not consistent. Treatment of infection and supportive care, such as the use of oxygen should be administered as appropriate. Lung transplantation is rarely indicated for an advanced disease.

Progress and Complications

Progressive respiratory failure occurs from disease persistence. Interstitial fibrosis develops in chronic cases. Infection with unusual organisms, such as *Nocardia* species, *Aspergillus* species, *Mycobacteria*, *Pneumocystis*, *Cryptococcus* neoformans and other organisms are known to occur.

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PART II: PULMONARY CALCIFICATION AND OSSIFICATION SYNDROMES

Sanjeev Mehta

Pulmonary calcification is commonly seen on the chest X-ray and is usually an incidental finding. It may be metastatic, benign or malignant or dystrophic in origin. The list of causes is rather exhaustive.[1] Frequency-wise, the dystrophic causes of infectious etiology are more common, as shown in the Table 166.2.

The condition depends on abnormalities in serum calcium and phosphate concentration, alkaline phosphatase activity and local physicochemical conditions, such as pH. It is most common after about 10 years of hemodialysis.

Pathophysiology

Metastatic calcification is usually seen at an elevated calcium-phosphate product of 70 mg^2/dl^2 (normal <40). When it occurs at normal or even at low serum calcium, it may be attributed to azotemia (previous or current), elevated parathyroid hormone levels and/or exogenous vitamin D administration.

Calcium salts get precipitated in an alkaline environment. Blood pH in the lung is more alkalotic than in other organs because of the CO_2 removal. The upper lobe predilection of some pulmonary calcific disorders, may occur due to a higher blood pH (approximately 7.51) and lower $PaCO_2$ (approximately 30 mm Hg) at the apex due to the higher ventilation-perfusion ($\dot{V}/\dot{Q}$) ratio (about 3.3 vs 0.63 respectively). Hypercalcemia and alkalosis most likely act synergistically to predispose to ectopic calcification, when other risk factors are present.

Dystrophic calcification occurs with normal serum calcium levels in the injured or the abnormal tissues. It is typically seen in granulomas and in lymphadenopathy associated with fungal diseases, tuberculosis and sarcoidosis. It has also been described in amyloidosis and after inhalation exposures in coal workers pneumoconiosis and silicosis. Injury results in caseation, necrosis or fibrosis. The calcification is most likely due to the production of 1, 25 vitamin D in the macrophages within the granulomas and increased intestinal absorption of calcium and phosphate, which provides an additive or synergistic factor that promotes calcification in these tissue.

Sarcoidosis related calcification could be dystrophic or metastatic, secondary to hypercalcemia or both. It may sometimes mimic pulmonary alveolar microlithiasis with a calcified micronodular pattern. Pulmonary Vascular Calcification (PVC) is dystrophic due to shear stress. Pulmonary Alveolar Microlithiasis (PAM) is a unique idiopathic calcific disorder with distinct histologic and

TABLE 166.2: Causes of pulmonary calcification

- Dystrophic calcification
  - Tuberculosis
  - Sarcoidosis
  - Histoplasmosis and other fungal infections
  - Post-varicella pneumonia
  - Smallpox handler's lung
  - Parasitic infections: Paragonomiasis
  - Amyloidosis
  - Silicosis
  - Coal worker's pneumoconiosis
  - Pulmonary vascular calcification
  - Idiopathic: Pulmonary alveolar microlithiasis
- Metastatic
  - Chronic renal insufficiency on hemodialysis
  - Primary hyperparathyroidism
  - Hypervitaminosis D
  - Excess exogenous administration of calcium and vitamin D (milk-alkali syndrome)
  - Osteopetrosis
  - Osteitis deformans (Paget's disease)
  - Malignant causes
    - Parathyroid carcinoma
    - Multiple myeloma
    - Lymphoma/leukaemia
    - Choriocarcinoma

radiographic features that do not fit into either metastatic or dystrophic calcification.[2,3]

Pulmonary ossification is more complex and needs factors, such as angiogenesis, chronic venous congestion, lung fibrosis and/or the influence of various growth factors. It can be idiopathic in origin or result from a variety of underlying pulmonary, cardiac, or extracardiopulmonary disorders, these are illustrated in Table 166.3. Pulmonary metastatic malignant lesions can become calcified or ossified.

TABLE 166.3: Causes of pulmonary ossification

- Pre-existing pulmonary disorder
  - Tuberculosis
  - Sarcoidosis
  - Pulmonary amyloidosis
  - Idiopathic pulmonary fibrosis
  - Metastatic breast cancer
  - Histoplasmosis
  - Chronic busulfan therapy
  - Pulmonary metastases of osteogenic sarcoma
  - Metastatic melanoma
- Other systemic causes
  - Primary and secondary hyperparathyroidism
  - Hypervitaminosis D
  - Mitral stenosis
  - Chronic left ventricular failure
  - Pyloric stenosis with alkalosis
  - Idiopathic hypertrophic subaortic stenosis
- Idiopathic pulmonary ossification

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PART III: PULMONARY ALVEOLAR MICROLITHIASIS

PS Shankar

INTRODUCTION

Pulmonary alveolar microlithiasis is a rare disorder, characterized by the intra-alveolar deposition of a large number of minute calcific concretions, uniformly throughout both the lungs. Harbitz first noted in 1918, the occurrence of extensive calcification of the lungs as a pulmonary disease.[1] The condition was labelled as pulmonary alveolar microlithiasis by Pahr in 1933.[2] The cases are sporadically reported from different parts of the world including from India.[3-8]

Etiopathology

The etiology is undetermined. A local alteration in the cells of alveolar septa appears to predispose to the occurrence of calcification. There is no abnormality of calcium metabolism. The cases have been reported in age group 30 to 50 years. Females are affected more than males. There is a familial incidence with a tendency to appear in siblings.[5] A family of pulmonary alveolar microlithiasis was reported from India, where three sisters of the five siblings had the disease.[4]

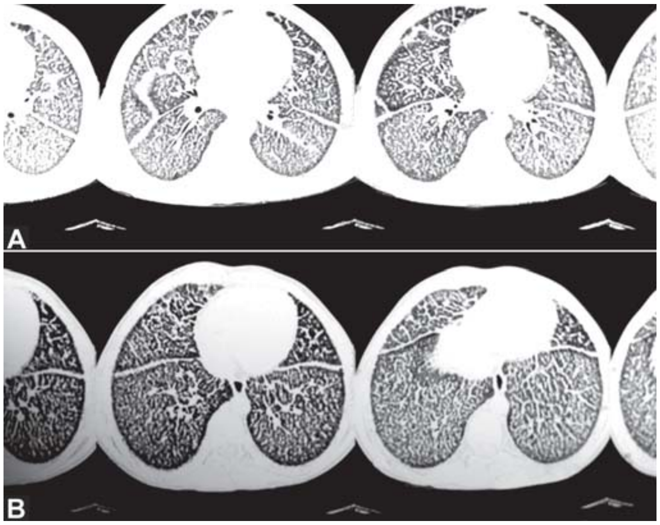
The lungs are solid containing sand-like grains (colcospherite) that are distributed diffusely, more so at the bases, a saw may be required to cut the lung.[5] Under microscope, they appear as "onion-skin" bodies in the alveoli and are densely calcified. There can be emphysematous blebs at the apices or along anterior margins of the lungs. Pulmonary interstitium is not involved. Such calcification is not encountered in other organs.

Clinical Features

Although the condition presents as abnormal chest radiograph from an asymptomatic patient, the advanced cases can present with cough, dyspnea and respiratory failure. Hemoptysis may occasionally occur[6] and very rarely calcified bodies may be coughed. There can be occurrence of recurrent pneumothoraces.[7] Physical examination of the chest often does not reveal any abnormality, even in the presence of markedly abnormal chest radiograph. In advanced stages, the disease may show the presence of inspiratory crackles and ultimately, the signs of cor pulmonale.

Investigations

The chest radiograph gives widespread snow-storm appearance from minute calcified mottled shadows. They may be so profuse, as to make the lung diffusely white, especially in mid and lower lung zones obscuring the cardiac borders, as shown in Figure 166.4A. Pleural calcification gives pencilthin sharp dense white lines along



Figs 166.4A and B: Chest roentgenograph and CT scan in pulmonary alveolar microlithiasis: Shows bilateral, diffuse distinct micro nodular, sand like mottling of lungs giving the appearance of a white lung (*Courtesy:* Dr Sanjeev Mehta)

the costal surfaces and over the hemidiaphragm. Presence of bullae may be considered to be a feature of advanced stage of disease.[4] The radiological appearance of stenosis, talc granulomatosis and calcified military histoplasmosis may simulate microlithiasis, but the lesions in those conditions are larger and have different distribution.[5]

The lungs appear like sack of sand containing innumerable homogeneous intra-alveolar deposit of calcium containing bodies. Lung biopsy reveals alveolar spaces containing aminated calcific microliths, with fibrosis and thickening of the alveolar walls.[9] Transbronchial lung biopsy is helpful to confirm histological diagnosis.[10] The spherules exhibit a concentric lamellar appearance (onion-skin bodies) implying their growth, by the addition of successive layers and contain calcium and phosphorus. Computed Tomography (CT) demonstrates extensive microcalcific deposits in the posterior and inferior subpleural spaces and along bronchovascular bundles, interstitial fibrosis and bronchiectasis. Calcified nodules larger than 1 mm (up to 5 mm) are visible on high resolution CT scans, as shown in Figure 166.4B. Thin-walled subpleural cysts, indicative of early fibrosis can be seen on HRCT images.[11] Scintigraphy shows intense uptake of radiotracer technetium 99 m by calcified spherules.[12,13]

Pulmonary function studies do not show any abnormality despite extensive radiographic changes. In the later stages of disease, there is a restrictive pattern of lung volumes due to alveolar filling and a reduction in diffusing capacity.[14] Exponential analysis of lung static pressure-volume obtained by whole body plethysmography, shows decreased lung compliance, normal shape curve and reduced extrapolated lung volume at infinite distending pressures.[15]

Treatment

There is no specific treatment. The disease is slowly progressive leading ultimately to development of chronic cor pulmonale, respiratory or cardiac failure. Nasal continuous positive-airway pressure ventilation has been tried to improve oxygenation in patients with respiratory failure.[16] Bilateral sequential lung transplantation may be other alternative.[17]

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Section

22

PERSPECTIVES IN PULMONARY AND CRITICAL CARE MEDICINE

SK Jindal

167

Ethics in Respiratory Care

Basil Varkey

> *"Ethics is an inherent and inseparable part of clinical medicine."*
>
> —Singer P, Pellegrino ED, Seigler M[1]

In all physician-patient interactions there is a moral component; some interactions (e.g. withdrawal of ventilator in an ICU) pose an obvious and dramatic ethical consideration while others (e.g. decisions on aggressive treatments in end stage diseases in office settings) are less obvious. Patient care decisions involve more than selecting a treatment or intervention on a scientific basis; the physician's ethical obligation to benefit the patient and to avoid or minimize harm and the values and preferences of the patient and family members are all very much in play. Competence in ethics has been shown to improve the quality of care in certain areas[2,3] and is a requisite to provide competent patient care.

SCOPE OF ETHICS

Several factors (abuses of human subjects in research, experimentation in concentration camps in World War II, advances in medicine and medical technology and societal changes) contributed to the rapid evolution of bioethics from one concerned about professional conduct and codes to its present status with an extensive scope that includes research, public health, organizational and clinical (also referred to as medical) ethics. However, because of common and familiar usage the term medical ethics or ethics, rather than the more precise term bioethics, is used in this chapter.

Current Status of Knowledge and Skills

Knowledge and skills and attitudes about ethics of practicing physicians and resident physicians are variable and often less than satisfactory. Although the obligation to respect patient preferences on care at the end of life is accepted in the United States (US), a seminal nationwide study found significant deficiencies in physician performance.[4] Another study found that physicians often failed to disclose medical errors although disclosure is an ethical duty.[3] Other studies have documented deficiencies in knowledge and skills in resident physicians.[5,6] These and similar studies along with an increased recognition of the importance of ethics in all medical professional activities and especially in medical practice have spurred educational efforts at all levels.

Ethics Education

Ethics has been included as a formal required part of curriculum for medical students in the US. The Accreditation Council for Graduate Medical Education Outcome Project has introduced a program for training and evaluation of resident physicians in six core competencies and ethical principles are a key part in the definitions of three of them: professionalism, interpersonal and communication skills and patient care. Continuing education programs are offered and in some cases required by several states; physician organizations, locally and nationally offer ethics courses. The goals of ethics education are applicable for learners at any level (Table 167.1).[7] Core behavioral skills in ethics include obtaining informed consent, assessing decision-making

TABLE 167.1: Goals for Ethics Education*
Awareness and appreciation of ethical dimension in patient care.
Understanding of core ethical principles and values of the medical profession.
Knowledge of commonly encountered ethical issues in general and specific to one's specialty.
Demonstrated competence in "core bioethics behavioral skills".
Competency in using a method for analyzing and resolving ethical problems.
Appreciation of cultural diversity and its impact on bioethics.
Willingness and ability to teach bioethics to students and trainees in clinical settings.

Reference 7 with permission.

capacity, discussing resuscitation status and use of life-sustaining treatments, advanced care planning, breaking bad news and effective communication.[7] Ethics education has been shown to improve learner awareness, attitudes, confidence, knowledge and in moral reasoning.[8,9]

The preceding discussion on the assessment of physician knowledge, skills and attitude and on education interventions, it is hoped, will provide an impetus for physicians in academia and practice in India and other developing countries to conduct similar studies with the support of their organizations and perhaps with private or governmental grant. A most desirable goal would be to introduce ethics at the undergraduate medical student level and to continue it through postgraduate training and practice.

Ethics and Morality

Ethics is a generic term covering different ways of examining the moral life. Normative ethics attempts to answer the question "Which general moral norms for the guidance and evaluation of conduct should we accept and why?"[10] Some moral norms about right conduct are common to human kind–transcends cultures, regions, religions and other group identities—and constitute common morality; examples of which include—not to kill or harm or cause suffering to others, not to steal, not to punish the innocent, to be truthful, to obey law, to nurture the young and dependent to help the suffering and rescue those in danger. Particular morality norms bind groups special because of their culture, religion, profession, etc. and include responsibilities, ideals, professional standards, etc., and the explication or adjudication in some cases may need experts or religious authorities.

Professional moralities that include moral codes and standards of practice are one form of particular morality. Physicians have specialized knowledge and training and a commitment to provide services to patients. The standards and rules of their organizations attempt to keep them competent and trustworthy so that they can fulfill their obligations to their patients. These obligations based on the accepted role of a physician then form in a basic level, the ethics of the profession. Physicians organizations have also codified their standards to reduce the vagueness of professional morality based on "the accepted role of a physician". Codes, although well-intentioned, may simplify moral requirements and may lead physicians to mistakenly consider that they are fulfilling the moral norms by complying with the codes. Critics have observed that these codes have inconsistently appealed to general ethical standards or to a source of moral authority and "has often appeared to protect the profession's interests more than to offer a broad and impartial moral viewpoint or to address issues of importance to patients and society".[11]

THE FOUR-PRINCIPLE APPROACH TO MEDICAL ETHICS (PRINCIPLISM)

Common morality, described earlier, is the base from which the 4 principles of biomedical ethics evolved. They are: (1) Respect for autonomy, (2) Nonmaleficence, (3) Beneficence and (4) Justice. The principles of respect for autonomy and justice evolved later than the other two. A notable book on medical ethics by Percival[12] written more than two centuries ago did not feature patient autonomy and justice but he did underscore the patient's best medical interest as the proper goal of medicine. In modern times Beauchamp and Childress' book on Principles of Biomedical Ethics is considered a classic for their erudite and insightful exposition of the four principles of bioethics[10] without disregarding alternative approaches.[13,14]

Respect for Autonomy

The philosophical underpinning for autonomy, as interpreted by philosophers Immanuel Kant and John Stuart Mill, and accepted as an ethical principle, is that all persons have intrinsic worth and therefore should have the power to make rational decisions and moral choices and each should be allowed to exercise his or her capacity for self-determination.

Autonomy, as is true for all four principles, needs to be weighed against competing moral principles and in some instances may be overridden; an obvious example would be if the liberty for autonomous action causes harm to another person or persons. The principle of autonomy does not extend to persons who lack the capacity (competence) to act autonomously; examples include infants and children and incompetence due to developmental, mental or physical disorder. A rigid distinction between incapacity (assessed by health professionals) and incompetence (determined by court of law) is not of practical use as a clinician's determination of a patient's lack of decision-making capacity has the same practical consequences as a legal determination of incompetence.[15]

Detractors of the principle of autonomy question the focus on the individual and propose a broader concept of relational autonomy that is a product of social relationships and complex determinants, such as gender, ethnicity and culture.[16] The differences in attitudes to disclosure of terminal illness and to decision-making at the end of life in elderly subjects of different ethnic make ups was reported in a study from California. Korean Americans and Mexican Americans were less likely than African Americans to believe that patients should be told of a terminal prognosis and less likely to believe that the family should make decisions about life support.[17]

These views, on careful consideration, do not negate the principle of patient autonomy if one appreciates that autonomous choice is a right of a patient and the patient may choose a family member or members to make decisions for him/her. Physicians have a professional obligation to ensure that their patients have the right to choose and inherently the right to accept or decline information.

Respecting the principle of autonomy also obliges the physician to disclose medical information and treatment options that are necessary for the patient to exercise self-determination. The proper understanding of the principle of autonomy supports other moral rules, such as informed consent, truth-telling and confidentiality.

Informed Consent

In order for a consent for a medical or surgical procedure or intervention or for research to meet the requirements of an informed consent, the patient or subject: (1) Must be competent to understand and decide, (2) Receives a full disclosure, (3) Comprehends the disclosure, (4) Acts voluntarily and (5) Consents to the proposed action.

The validity and applicability of these requirements, that emanated from western culture, universally to all countries have been questioned; instead it has been suggested that informed consent requirements be adapted to accommodate the cultural mores of countries.[18] In a spirited and vigorous defense of the afore listed five requirements of informed consent, Angell wrote "There must be a core of human rights that we would wish to see honored universally, despite variations in their superficial aspects—" and "The forces of local custom or local law cannot justify abuses of certain fundamental rights, and the right of self-determination on which the doctrine of informed consent is based, is one of them". She went on to pose a question whether apartheid simply represents a South African custom that is morally neutral or does it offend universal standards of justice?[19] In the matter of informed consent, the writer of this chapter is an universalist.

Since competence is the first of the requirements for informed consent, one should know how to detect incompetence. Standards (used singly or in combination) that are generally accepted for determining incompetence are based on the patient's inability to state a preference or choice, inability to understand one's situation and its consequences and inability to reason through a consequential life decision.[20]

Incompetent (nonautonomous) patients and previously competent (autonomous) but presently incompetent patients would need a surrogate decision-maker. In a nonautonomous patient either a substituted judgment standard (what would the patient wish in this circumstance not what the surrogate's wish) or a best interest standard (highest net benefit to the patient by weighing risks and benefits) can be used by the surrogate. In a previously autonomous, but presently incompetent patient the previously expressed preferences (prior autonomous judgments) should be respected even in the absence of a written formal advance directive.[21]

Truth-telling

Truth-telling, besides being a common virtue, is an obligation for the physician as it respects patient autonomy, honors the implicit contract with the patient and promotes trust. Conveying bad news, such as diagnosis of cancer and prognosis, is not an easy task. Specific instructional tools, such as standardized patient cases, observed role play and feedback are increasingly used to improve communication skills of medical students and resident physicians.

In the United States, there has been a marked shift in physicians' attitude toward full disclosure. In 1961, 88% of physicians surveyed indicated their preference to avoid disclosing a diagnosis;[22] in 1979, however, 98% of surveyed physicians were in the favor of disclosure.[23] Surveys in the United States show that patients with cancer and other diseases wish to have fully informed. While full disclosure to the patient is considered a norm in the United States, disclosure is highly variable in other countries.[24]

Cultural differences, traditional role of physician authority, and conflicts between ethical principles (discussed later) account for this difference.[25] A pattern that is not uncommonly followed, in nonwestern countries is to disclose the information to the family and not to the patient. This violates patient autonomy unless the patient chooses this option and authorizes the physician to do so. The likely reasons for the resistance of physicians to convey bad news are concern that it may cause anxiety and loss of hope, uncertainty of about the outcome, belief that the patient would not be able to understand the information and may not want to know. An autonomous patient has a right to choose not to know, but the physician must know about this choice. Providing full information, with tact and sensitivity, to patients who want to know should be the standard. The sad consequences of not telling the truth regarding a cancer include depriving the patient of an opportunity for completion of important life-tasks: writing a history for ones children, putting financial affairs in order, reconciling with estranged family members, attaining spiritual order by reflection, prayer and religious sacraments.[26,27]

Confidentiality

Physicians are obligated not to disclose confidential information given by the patient to another party without the patients' authorization. An obvious exception (with implied patient authorization) is the sharing necessary of medical information for the care of the patient from the primary physician to consultants and other health care teams. In the present day, modern hospitals with multiple points of tests and consultants and the use of electronic medical records there has been an erosion of confidentiality. However, individual physicians must exercise discipline in not discussing patient specifics with their family members or in social gatherings.[28]

There are some noteworthy exceptions to patient confidentiality. These are legally required in the reporting of gunshot wounds and venereal diseases and exceptional situations that may cause major harm to another; examples are partner notification in HIV disease and relative notification of certain genetic risks.

Nonmaleficence

Nonmaleficence is the obligation of a physician not to harm the patient. This simply stated principle supports several moral rules — do not kill, do not cause pain or suffering, do not incapacitate, do not cause offense and do not deprive others of the goods of life. The practical application of nonmaleficence is to have the physician is weigh the burdens against benefits of all treatments, to eschew those that are inappropriately burdensome and to choose the best course of action for the patient. This is particularly important and pertinent in difficult end-of-life care decisions on withholding and withdrawing life-sustaining treatment, medically administered nutrition and hydration and in the doctrine of double effect in pain and other symptom control.

Beneficence

The principle of beneficence is the obligation of physician to act for the benefit of the patient and supports a number of moral rules — to protect and defend the right of others, prevent harm, remove conditions that will cause harm, help persons with disabilities and rescue persons in danger. Note in distinction to nonmaleficence the language is one of positive requirements. The principle calls for not just avoiding harm but to benefit patients and to promote their welfare. Rather than the idealized view of physicians' beneficence as based on altruism and philanthropy, an argument can be made that it is based on reciprocity for the debt to society (education, in some instances subsidized by state governments, and privileges) and to their patients (for learning from them in practice and research).

Justice

Distributive justice is by one definition fair, equitable and appropriate distribution determined by justified norms that structure the terms of social cooperation.[29] The following principles of distributive justice, to each person, have been proposed: an equal share, according to the need, effort, contribution, merit and free-market exchanges. It is easy to see the difficulty in choosing, balancing and refining these principles to form a coherent and workable solution to distribute medical resources. This large health care policy discussion is beyond the scope of this chapter.

However, issues of justice are encountered daily in hospital practice and office practice. A few examples: allotting scarce equipment (e.g. ventilator), giving expensive drugs when the budget is tight, dealing with uninsured patients, providing a benefit not covered by insurance and even in allotting time for outpatient visits (on what basis: equal time for every patient or based on need or complexity or based on social status). Difficult as it may be and in spite of the many constraining forces, physicians must accept the requirement of fairness contained in this principle.[30]

Conflicts between Principles

Each one of the principles is to be taken as a *prima facie* obligation that must be fulfilled unless it conflicts, in a specific instance, with another principle. When faced with such a conflict, the physician has to determine the actual obligation to the patient by examining the respective weights of the competing *prima facie* obligations based on the content and context. Consider an example of a conflict that has an easy resolution: a patient in shock treated with urgent fluid-resuscitation and the placement of an indwelling intravenous catheter caused pain and swelling. Here the principle of beneficence overrides that of nonmaleficence. Many of the conflicts that physicians face, however, are much more complex and difficult. Consider a competent patient's refusal of a potentially life-saving intervention (mechanical ventilation) or request for a potentially life-ending action (withdrawing mechanical ventilation). Nowhere in the arena of ethical decision-making is conflict as pronounced as when the principles of respect for autonomy and beneficence collide.

Beneficence has enjoyed a historical role in the traditional practice of medicine. However, giving it primacy over patient autonomy is *paternalism** that makes a physician-patient relationship analogous to that of a father to a child. A father may refuse a child's wishes, may influence a child by a variety of ways – nondisclosure, manipulation, deception, coercion, etc., consistent with his thinking of what is the best for the child. Paternalism can be further divided into soft and hard.

In soft paternalism the physician acts on grounds of beneficence (and at times nonmaleficence) when the patient is nonautonomous or substantially nonautonomous (examples are cognitive dysfunction due to severe illness, depression, drug addiction).[31] Soft paternalism is complicated because of the difficulty in determining whether the patient was nonautonomous at the time of decision- making, but is ethically defensible as long as the action is in concordance with what the physician believes to be the patient's values. Hard paternalism is action by a physician, intended to benefit a patient, but contrary to the voluntary decision of an autonomous patient who is fully informed and competent. In contrast to soft paternalism, hard paternalism is ethically indefensible with very rare exceptions.

On the other end of the scale is consumerism, a rare and extreme form of patient autonomy that holds the view that the physician's role is limited to providing all the medical information and the available choices for interventions and treatments while the fully informed autonomous patient selects from the available choices. In this model, because of the limited role a physician cannot use his/her knowledge and skills to benefit the patient and therefore, partaking in this model of care is a form of patient abandonment.

Faced with the contrasting paradigms of beneficence and respect for autonomy and the need to reconcile these to find a common ground, Pellegrino and Thomasma, argue that beneficence can be inclusive of patient autonomy as" the best interests of the patients are intimately linked with their preferences" from which "are derived our primary duties to them".[32]

Several models to analyze and resolve ethical problems have been proposed. One model uses a systematic four points approach as follows: (1) Medical (identifying medical problems, treatment options, goals of care), (2) Patient (finding and clarifying patient preferences on treatment options and goals of care), (3) Quality-of-life (QOL) (effects of medical problems, interventions and treatments on patient's QOL with awareness of individual biases on what constitutes an acceptable QOL), (4) Context (many factors that include family, cultural, spiritual, religious, economic and legal). Using this model the physician can identify the principles that are in conflict, ascertain by weighing and balancing what should prevail and when in doubt turn to ethics literature and expert opinion.[7]

ETHICS IN END-OF-LIFE (EOL) CARE

Having laid the ground work on ethical principles as they apply to clinical practice in the preceding discussions, this segment will focus on aspects of particular, some of exclusive importance to pulmonary and critical care physicians. A substantial number of patients die with unrelieved symptoms that are poorly recognized and

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**Although paternalism is a term well-entrenched in bioethics literature a more appropriate term for modern times would be the gender-inclusive term parentalism.*

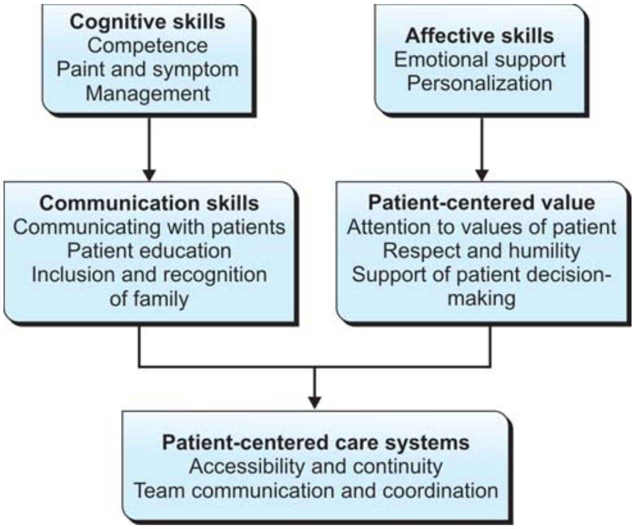

Cognitive skills
Competence
Paint and symptom
Management
Affective skills
Emotional support
Personalization
Communication skills
Communicating with patients
Patient education
Inclusion and recognition
of family
Patient-centered value
Attention to values of patient
Respect and humility
Support of patient decision-
making
Patient-centered care systems
Accessibility and continuity
Team communication and coordination

Fig. 167.1: Domains of physician's skills needed to provide high-quality EOL care (based on analysis of focus group transcripts)[34]

poorly treated, physicians are often unaware of patients' wishes regarding EOL care and interventions often are not consistent with patients' preferences.[4,33] End-of-Life care demands a diverse set of physician skills (Fig. 167.1),[34] professionalism and ethics and ethically competent care is linked with quality of care.[2] Dealing with EOL issues, more than any other patient/family and physician interactions, has the potential to compromise decision-making that is influenced by the physician's personal and cultural values and religious and spiritual beliefs.[35,36]

(See Appendix 1 (Chapter 168): End-of-Life Care—Religious beliefs and practices in India)

Pulmonary and critical care physicians provide care in various milieus (outpatient, inpatient hospital, ICU) for patients with cancer and chronic life-limiting diseases, such as Chronic Obstructive Pulmonary Disease (COPD) and pulmonary fibrotic diseases. In the latter group, prognostication is difficult and therefore, it is hard to decide when to initiate advanced care planning and EOL care. The quality of EOL care in chronic lung disease is poor,[37,38] and patients with COPD are more likely to die in the intensive care unit (ICU) than patients with cancer, while on mechanical ventilation and with dyspnea.[39] In the United States approximately 20% of all deaths occur in the ICU and a substantial number of them involve a decision to withhold or withdraw life-supporting therapy.[40]

Communication and Decision-Making in EOL Care

The initial communication step for a physician is to inquire as to the patient's preference regarding decision making- self or a designated family member or members. The patient or designated family member(s) may also defer some of the responsibility, especially for a difficult decision (e.g. do not resuscitate order) to the physician.[41] In such a case, the physician is obligated to provide periodic updates and to affirm that there has been no change in the delegated responsibility. As many critically ill patients in the ICU are not able to fully participate in discussions on their own EOL care their family members often play a key role in EOL decisions. Hence, the physician should be sensitive to the stresses and burdens of the family, help them understand the clinical status and prognosis, elicit from them the patient's values, and in partnership with them develop goals of care and treatment plan that are based on the patient's prognosis, values and preferences.[42]

Sorrily, in one European study, only one half of the ICU's involved patients and family in decision making and wide variations in practice were noted between countries.[43] Even when guidelines are in place the practice patterns may vary greatly.[44] There is a dearth of information on EOL decision-making process in the ICUs from the most populous countries—India and China.

Seriously ill patients and their families identify communication skills as one of the most important skills for physicians,[45] and communication successes and failures generate more gratitude and complaints than any other aspect of EOL care.[46] Several components of communication are shown to improve quality of EOL and these along with a useful mnemonic for family conferences[47] are shown in Table 167.2.

Medical Futility and Conflicts

The concept of medical futility is controversial and the term is fraught with ambiguity. Futility can be used to cover various situations of predicted improbable outcomes, improbable success and unacceptable benefit-burden ratios.[48] Typically, the term is used in a situation in which dying patients have reached a point at which further treatment provides no physiologic benefit or is hopeless and becomes optional. "Clinically nonbeneficial interventions" has been proposed as an alternative term for futility.[49]

Invoking medical futility as the reason to withhold or withdraw life-sustaining treatments against the wishes of a patient or surrogate decision maker is ethically very problematic. Such conflicts can be substantially reduced with timely and structured communications that builds trust between physician and the patient and family. To incorporate the provision to avoid interventions of no

TABLE 167.2: *Communication Components associated with Improved Quality of Care or Family Ratings of Satisfaction with Communication

Identify a private place for communication with family members

Increased proportion of time listening to family rather than talking

Identify commonly missed opportunities:
- Listen and respond to family members
- Acknowledge and address family emotions
- Explore and focus on patient values and treatment preferences
- Explain surrogate decision-making to family
- Affirm non-abandonment to patient and family

Provide support for decisions made by family

Use of VALUE mnemonic during family conferences
V = Value statements made by family members
A = Acknowledge emotions
L = Listen to family members
U = Understand who the patient is a person
E = Elicit questions from the family

Provide consistent communication from team members

**Reference 47 with permission.*

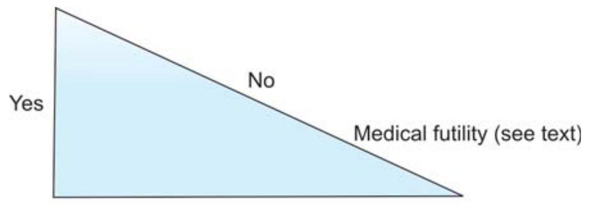
benefit (medical futility) in to a frame work of EOL decision making is essential, provided 'benefit' is defined with reference to the patient's preferences and values. An approach to such a framework is outlined in Figure 167.2.[50] The American Medical Association recommends that when a patient or surrogate decision maker insists on a therapy that the physician believes is futile, a communication and negotiation process should be started to reconcile these differences, and the treatment should be provided until the differences are reconciled.[51]

Discussion with patient/family

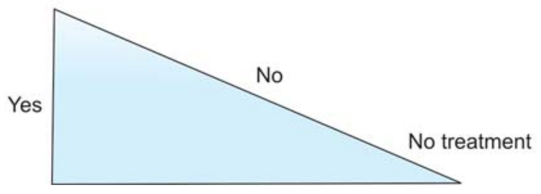
1. Elicit and understand patient's values and preferences for treatments and outcomes.
2. Formulate patient's wishes into appropriate goals of treatment and care.

Treatment decision

3. Determine whether treatment can achieve at least one reasonable treatment goal.



4. Determine whether the patient wants the treatment.



Treat and periodically reassess

Fig. 167.2: A framework for discussing goals and treatment[50]

Withholding or Withdrawing Life-Sustaining Measures

Most of the deaths in the ICU and acute care wards occur after a decision to withdraw life-sustaining treatments.[40,52,53] Some physicians are uncomfortable in withdrawing treatment that is already in place but feel justified in withholding (not started) treatment. This distinction, from an ethical standpoint is unclear and irrelevant and morally untenable.[54] Assigning a preference and priority to withholding over withdrawal can lead to under-treatment (not using it to avoid the decision to withdraw later) of some patients who may possibly benefit from it, and over-treatment (continuation of treatment that is no longer beneficial) in others.

Pulmonologists, intensivists and other physicians practicing in ICUs should understand the goals of withdrawing life sustaining treatments, and to remove all treatments no longer desired or indicated while ensuring patient comfort. Discussion with families should include explanation of the process, assurance that a palliative approach to alleviate all symptoms and to provide comfort will be provided, the expected length of survival (range and if uncertain state so) and learning of specific patient and family preferences (especially religious and cultural) prior to death.[55,56] Documentation should include the rationale for withdrawal of life-sustaining treatments, plans on how the procedure will be done and how complications, if any, will be handled.

Modalities such as vasopressors, antibiotics, nutrition can be discontinued without a taper. As abrupt mechanical ventilation withdrawal may cause discomfort from dyspnea and secretions a protocol for ventilator withdrawal[57] and a protocol for analgesia and sedation[58] should be followed. There is no set upper limit for the sedative and analgesic drugs used in this setting as symptom control is the overriding objective (see the following section under Doctrine of Double Effect). Moreover, higher dose of opioids and benzodiazepines used in the context of withdrawal of ventilator has not been shown to decrease the time from withdrawal to death.[59]

The reasons for the use of increased sedation and analgesia and monitoring of symptoms and treatments used from withdrawal of life sustaining-treatment until death should be documented. Prior to the withdrawal the family should be given time to say good bye to the patient and after withdrawal and control of symptoms the family should be allowed to be with the patient.

Doctrine of Double Effect (DDE)

This doctrine makes a distinction between intended effect and unintended but foreseen effect of a single act that has double effects— one good and one harmful. Under the DDE, if the action satisfies four elements it is morally permissible.[60] The four elements are: (1) The nature of the act, (2) The intention of the doer, (3) The distinction between means and effects, and the proportionality between the good effect and the bad effect (the bad effect is permissible only if the intended good effect in proportionality more than the bad effect). The classic clinical situation in which DDE comes into play is in severe symptom (e.g.: pain, dyspnea) management in EOL. In this context, the physician's obligation and intention to relieve the suffering of the patient by appropriate drugs such as opioids, overrides the foreseen but unintended harmful effects or outcome.

Meeting the Needs of the Family

In acute care settings, especially in ICUs, the needs of family members of the patent are largely unmet.[61] The modern ICU is not designed to be family-friendly. Family members are often excluded from the bedside.[62,63] Supportive and compassionate care to the family from physicians and other health care providers fall short due to factors that include- lack of role-models, deficiencies in attitude and skills, competing demands for time and constraints placed by hospital or by the physical layout of the ICU.

To meet the basic and minimum requirements of the family, any ICU anywhere in the world, should provide- a designated place/room (with chairs and toilet facility) for family members to rest, periodic updates on the patient's condition and access to the patient. Policies regarding visitation restrictions, that are generally more stringent in ICUs the developing world, should be reexamined. Issues that need to be addressed include: Are some of the restrictive policies more for the convenience of the health care providers than for patient benefit? Are risks of infections (not influenza, coryza and other viral infections) transmitted from the family to the patient proven and quantitated? Do these risks outweigh the positive benefits to the patient to have a loving family member at the bedside?

Culturally Sensitive Care

Culture is commonly defined as the customary beliefs, social forms and material traits of a racial, religious or social group and has a clear influence on the group's values, perspectives and decision-making. Recognition of culture-based differences that may exist between physician and patient is a critical step in providing culturally sensitive care[64] and skillfully managing these differences improves patient and family satisfaction and may also lead to a better outcome.[65]

However, this critical step of recognition of culture-based differences should be based on communication and the expressed opinions of the patient and not on assumptions based on religion, caste, race, socioeconomic status, gender or age. Cultural differences are also present, as expected, between countries and as a consequence some practices of medical ethics of the western world are either not accepted or resisted in other parts of the world; examples are the moral and legal equivalence of withholding and withdrawing life-sustaining treatment (previously discussed) and the definition of brain death.[66,67]

Resistance to some of the basic principles of ethics, such as patient autonomy—in nonwestern cultures is not unexpected. In countries with ancient civilizations, rooted beliefs and traditions, such as in India, the practice of paternalism by physicians emanated from beneficence. However, in the present times, a critical examination of paternalistic practice is needed for reasons that include technological and economic progress of the country, improved educational and socioeconomic status of the populace, globalization and societal movement towards emphasis on an individual than to a group. This needed examination can be accomplished only by research that includes well-structured surveys on demographics, patient preferences on who the decision-maker is, informed consent, truth-telling, confidentiality, EOL decisions and surveys of physicians on these same topics as well as their demographics, education in ethics and perceived barriers to practice based on ethical principles.

One major component of culturally sensitive care is respecting and accommodating the religious beliefs of the patient and family.[68-70] This is particularly important in EOL care when death is imminent. Prayers and rituals provide solace to the patient and family. Policies in ICUs and wards should be flexible within reason to honor rituals and prayers specific to the dying person's religion. At times, a simple provision for a ritual (e.g. sipping Ganges water) may be all that is needed to fulfill the last wish of a dying patient.[71]

A NEW COVENANT AND A CONCEPTUAL MODEL FOR PATIENT CARE

A New Covenant

The Hippocratic oath, attributed (authorship is questionable) to Hippocrates (460–370 BC), expressed physicians' obligations to patients of beneficence (to help the sick) and nonmaleficence (never to use it to injure or harm them). In more recent times, it has come under critical review for "sexism, secrecy, self-aggrandizement and sorcery".[72] Moreover, ethical issues of truthfulness, distribution of health care resources, safeguard of research subjects are not addressed and thus the Hippocratic oath, that enjoyed a long run of continuity until the 20th century, is inadequate and outdated.

Robin and McCauley[72] proposed a new oath relevant to modern times with 16 elements. Although I agree with all the elements, I have selected a few that are consonant with the theme of this chapter, and underscore some of the points I have made, and together they form an appropriate new covenant for physicians. These are:

1. I will remain a student all my professional life, attempting to learn not only from formal medical sources but from my patients as well.
2. I will attempt to function as a teacher for my patients so that I can care for them more effectively and can apply the lessons they provide to the care of other patients.
3. Knowing my own inadequacies and those of medicine generally, I will strive to cure when possible but to comfort always.
4. I will do unto patients and their families only what I would want to be done unto me or my family. I will not experiment on patients unless the patients give truly informed consent. I will strive to instruct patients fully so their informed consent is possible.
5. I will be honest with my patients in all medical matters. When this honesty reveals bad news, I will deliver it with understanding and sympathy and tact.
6. I will provide my patients with acceptable alternatives for various forms of diagnosis and medical and surgical treatment, explaining the risks and benefits as best I know them.
7. I will allow my patients to make the ultimate decision about their own care. In circumstances where my patients are incapable of making decisions, I will accept the decision of family members or loved ones, encouraging them to decide as they believe the patient would have decided.

A Conceptual Model for Patient Care

Drawing upon a life-time experience as a physician and teacher of physicians, I present a conceptual model of patient care in Figure 167.3. This model requires a physician to be both competent and virtuous and integrates elements in the text. Morality, both common and particular, and ethical principles have already received due attention in this chapter. The focal virtues expected of a physician (also applicable to other health care professionals) are depicted in the figure.

Compassion, a prelude to caring, combines an active regard for another's welfare with an imaginative awareness and emotional response of sympathy, tenderness and discomfort at another's misfortune or suffering.[73] Compassion presupposes sympathy and is expressed in acts of beneficence as in relieving pain and suffering.

Discernment is the ability to make fitting judgments and reach decisions without being unduly influenced by extraneous conditions and while keeping personal emotions in check. A discerning physician will thus recognize even in the face of conflicting options when comfort is paramount and provide the right type of consolation and care to the patient. Discernment is a particularly valuable virtue in situations where principles of ethics collide.

Trustworthiness leads to a good climate of trust between people, when trust is taken to be acceptance of being to some degree and some respects, in another's power.[74] Trustworthiness is an essential virtue as patients, at a time when they are most vulnerable and needy, place themselves in the hands of their physicians.

Integrity involves the coherent integration of one's emotions, knowledge and aspirations while being faithful to one's moral values and defending them when necessary. A person is deficient in integrity if he or she lacks firmly held moral convictions or fails to act on the one's convictions. Physicians will need to practice with both professional integrity and personal integrity. In the former, adherence to not only professional standards that are codified but also adherence to moral and ethical principles that may not be codified (examples are prescribing drugs that are not effective, placing monetary gain over patient's welfare, inappropriate relationships with patient, treatments without informed consent) are called for. A physician's personal integrity based on religious and moral convictions may face a challenge in

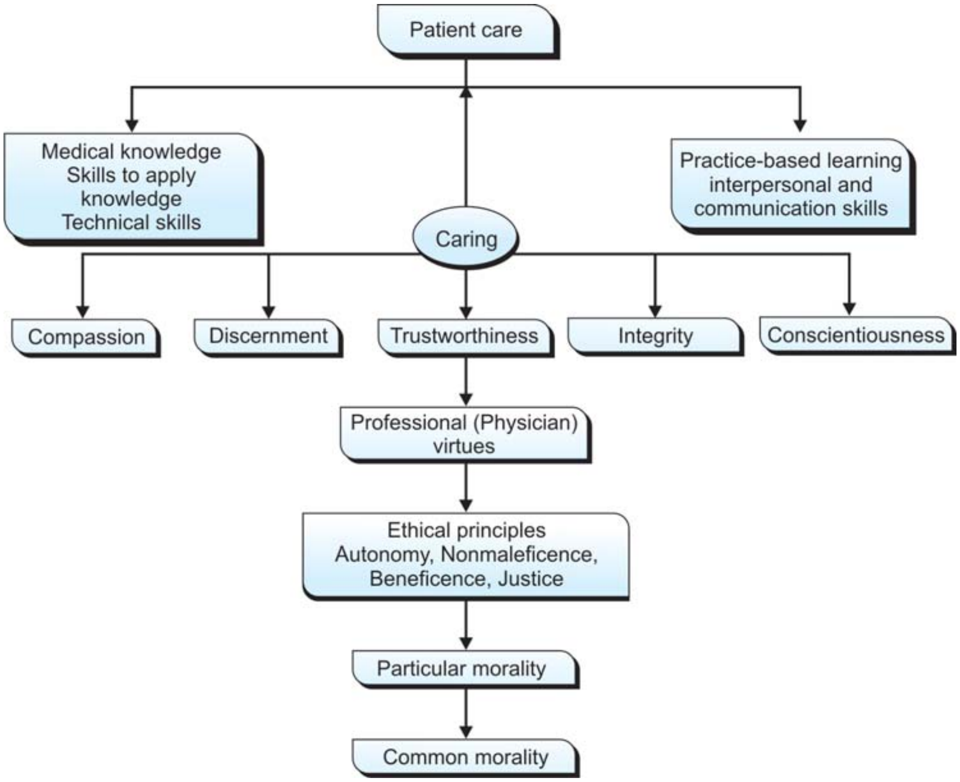

Patient care
Medical knowledge
Skills to apply knowledge
Technical skills
Practice-based learning interpersonal and communication skills
Caring
Compassion
Discernment
Trustworthiness
Integrity
Conscientiousness
Professional (Physician) virtues
Ethical principles
Autonomy, Nonmaleficence, Beneficence, Justice
Particular morality
Common morality

Fig. 167.3: A conceptual model of patient care by a physician that integrates morality, ethical principles, virtues and competencies

some clinical situations (examples are abortions, removal of life-sustaining treatments); in such situations the physician, in defense of one's moral convictions, can refuse to participate in action that compromises his or her integrity. However, these situations can be avoided or at least reduced by anticipating these problems; if facing such a situation is unavoidable, any adverse impact on the patient must be prevented by using institutional resources (policies, consultation, ethics committee) and delegation of care to another physician.

Conscientiousness is the virtue that motivates a person to do what is right, after diligently determining what is right. Conscience is not a special moral faculty and does not confer a self-justifying moral authority; rather it is an internal checking mechanism requiring critical reflection on good versus bad, right versus wrong and obligatory acts versus prohibited acts.

The virtues of compassion, discernment, trustworthiness, integrity and conscientiousness are the necessary building blocks for the fundamental virtue of caring. Caring is the defining virtue for all health care professionals and there is no greater duty for a physician than patient care. Francis Peabody, in 1927, in the last sentence of his memorable article used this simple yet profound definition " the secret of the care of the patient is in caring for the patient".[75]

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End-of-Life Care

Jeba S Jenifer, SK Jindal

End-of-life (EOL) care is an interdisciplinary clinical domain, which most physicians find stressful and challenging. Subtly, medical science has implied that death always reflects poorly on the skills of the health care providers, a failure on their part to save life. Death should not be viewed as a failure of medical care, but rather an inevitable natural course. Most certainly, all health care professionals should be able to provide good quality, compassionate and effective palliative care for their patients.

The American College of Chest Physicians supports the position that good quality palliative and EOL care should become an integral part of cardiopulmonary medicine.[1] The World Health Organization (WHO) defines palliative care as *"the active total care of patients whose disease is not responsive to curative treatment. It is the approach that improves the quality of life (QOL) of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"*.[2] QOL can be defined by its inverse relationship to the difference between an individual's expectations and his perception of the given situation, the smaller the gap the better QOL (Fig. 168.1).[3]

There is no clear consensus definition for EOL. Unfortunately EOL care is considered synonymous with palliative care. EOL care is a subset of palliative care, providing support and care more towards the terminal phase. Many principles and aspects of palliative care are applicable earlier in the course of an illness, in conjunction with disease modifying therapy and supportive care (Fig. 168.2). It is also important that palliative care continues to provide bereavement support. Importantly, the EOL is heavily dependent on cultural, social and religious beliefs and practices.

(See Appendix 1: EOL Care—Religious Beliefs and Practices in India).

PROGNOSTICATION

Identifying the EOL phase is a challenge and requires the clinical skill of prognostication. The transition into this phase may be very acute or subtle, depending on the disease and varies for malignant and non-malignant diseases (Fig. 168.3).

The illness trajectory in cancer is often a predictable decline until death, whereas in chronic respiratory diseases, such as Chronic Obstructive Pulmonary Disease (COPD), the clinical course is usually a slow deterioration, punctuated by dramatic exacerbations, that often ends in unexpected death. Arguably, the greatest challenge to provision of EOL care in COPD is the unpredictable disease trajectory, as compared to that of cancer. Moreover, in cancer, often there is maintenance of good functional status until a short period, with a predictable decline in the last weeks or months of life.[4] However, it is important to understand that death may occur prematurely without recognition, when good EOL care is impossible.

BARRIERS

The most important barrier that precludes provision of good EOL care is the difficulty in prognosticating and the chance of unexpected death. Sometimes, there is a prejudice amongst doctors and patients that COPD as well as lung cancer is usually self-inflicted diseases due to smoking and that they do not deserve measures to improve QOL.

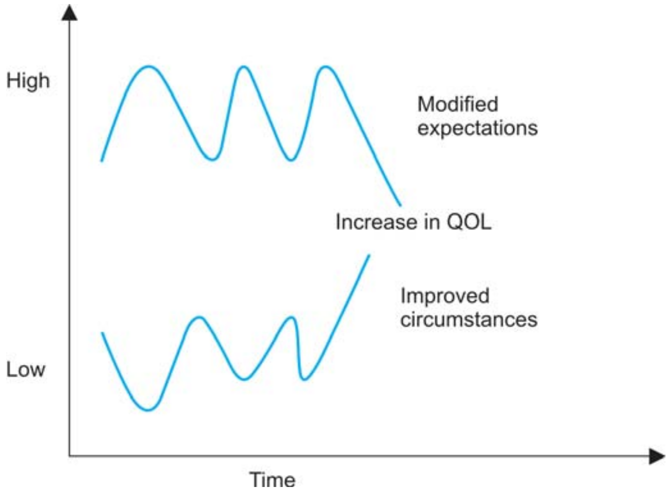

Fig. 168.1: Quality of life

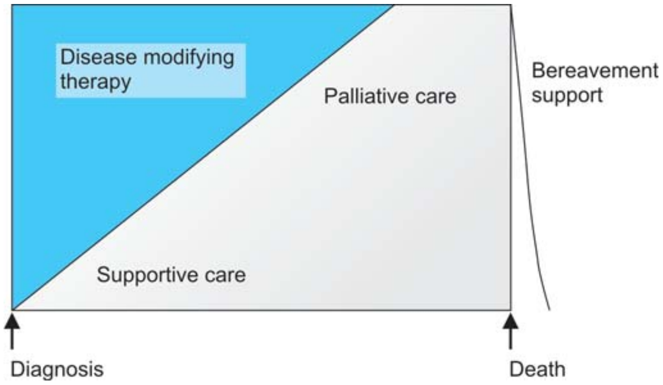

Fig. 168.2: Relationship between disease modifying therapy, supportive and palliative care

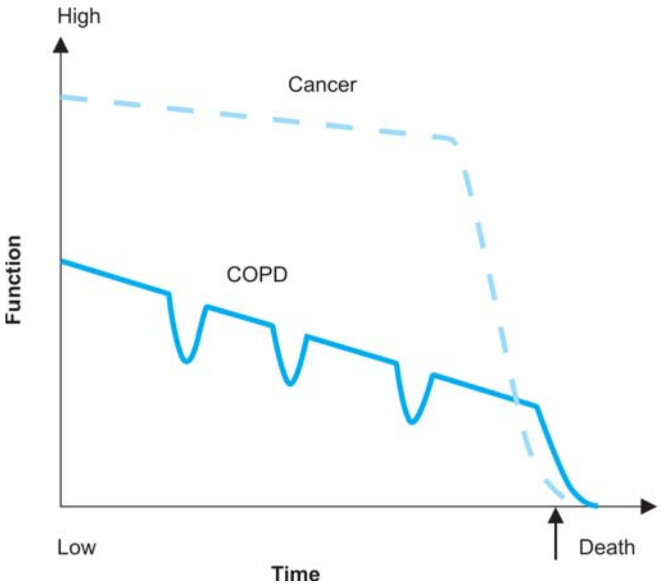

Fig. 168.3: Difference in illness trajectory in malignancy and COPD

Patients with chronic lung diseases at the EOL have physical and psychosocial needs at least as severe as patients with lung cancer.[5] Despite these needs, it has been reported that none of the end-stage COPD patients were offered or received input from palliative care specialists, while 30% of the lung cancer patients had received such care and 56% were aware of these services.[6] It is common for patients with COPD to have had a primary care visit or been admitted in ICU in the last 6 months of life and to have spent a significant time in their last six months in hospital.[7,8]

Breathlessness, fatigue and anxiety are more common in COPD than in advanced cancer, heart disease or renal disease,[9] but they are less likely to receive medication for symptom control, as compared with lung cancer patients.[8] This occurs despite the fact that most COPD patients prefer treatment focused on symptom control rather than on prolonging life and COPD patients are equally as likely as lung cancer patients to prefer not to receive cardiopulmonary resuscitation.[10] Although the reasons for this discrepancy are not entirely clear, it could be due to poor or infrequent patient-physician communication about EOL care and treatment preferences.[11]

Despite the existing barriers and difficulties, it is crucial for the health care team to identify the EOL phase and adopt a sensitive and structured approach of care.

COMPONENTS OF EOL CARE

Providing care at the EOL is not simply continuing all that was done before. EOL care focuses on symptom management, preservation of QOL, active communication with patients and carers and support of the physical, psychosocial and spiritual well-being.[12] It ensures that the supportive and palliative care needs of the patient and family are identified and met throughout the last phase of life and through bereavement.[13] There is ample evidence, mostly from cancer patients, that delivery of palliative care is associated with reduction in pain and other symptoms, improvements in QOL with enhanced family and patient satisfaction.[14-18] Inputs from hospital-based palliative care services are also associated with significantly lower likelihood of admission to ICU and lower inpatient costs.[19] Unrelieved symptoms and unmet needs can result in bitter memories and would be difficult to forget for relatives.

COMMON SYMPTOMS IN EOL

One of the essential components in EOL care is achieving maximal symptom control. Pain, breathlessness and fatigue are present in more than 50% of patients with end-stage respiratory disease.[9] Anxiety and depression are more common among COPD patients than among patients with lung cancer, 90% versus 52%, respectively.[6] Coexisting depression may play a significant role in EOL decisions and treatment preferences for life-sustaining therapies.[20] Patients with COPD and other lung diseases also have reduced health related QOL, with physical, emotional and social functioning significantly affected.[21-24]

Pain

The prevalence of pain among lung cancer patients attending the outpatient services and those using palliative care services is 27 and 76%, respectively. The pain may relate to cancer (73%) or to treatment (11%); nociceptive in nature in the majority, although 30% can have neuropathic pain.[25] Pain is often ignored and remains an uncontrolled symptom, as many physicians focus on ordering an array of investigations and making diagnosis and fail to prescribe analgesics at the appropriate dose and frequency. Although pain is a physical symptom, various aspects relating to pain should be addressed, to ensure "total pain" relief (Fig. 168.4).

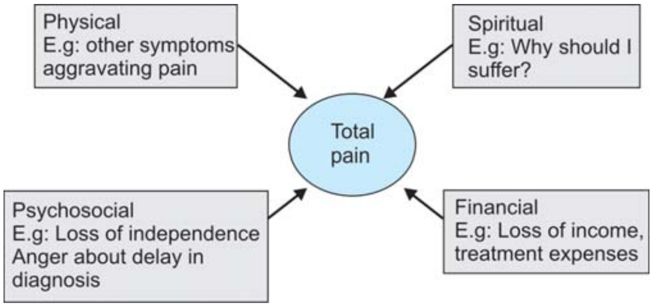
Physical
E.g: other symptoms aggravating pain
Spiritual
E.g: Why should I suffer?
Total pain
Psychosocial
E.g: Loss of independence
Anger about delay in diagnosis
Financial
E.g: Loss of income, treatment expenses

Fig. 168.4: Concept of total pain

Comprehensive pain evaluation, routine assessment, appropriate analgesic prescription and titration until adequate pain relief, are requisites for optimal pain management.[26] Inadequate treatment of pain is often because of poor pain assessment and discrepancy between patient and physician's assessment.[27] Joint Commission on Accreditation of Healthcare Organizations Standards require that all inpatient and outpatient health care facilities should systematically assess and document pain.[28]

The WHO cancer unit has developed simple analgesic prescribing guidelines, which constitute the gold standard in cancer pain management and an effective method to ensure rational titration of analgesia.[29] It is encouraging to know that by correctly following WHO analgesic ladder, pain can be controlled in nearly 90% of cancer patients.[30] Patients and families can be assured that pain can be relieved safely and effectively in the majority. The WHO analgesic ladder can be used for the treatment of pain in advanced chronic lung diseases.

The WHO analgesic ladder recommends the use of analgesics for all patients with pain on a regular basis, orally, in the right dose and frequency with analgesics given appropriately for breakthrough pain. Whenever possible, the oral route is preferred as it is convenient, non-invasive and cost-effective. The choice of analgesia should be based on the pain severity in a step-wise fashion and not on the stage of disease (Table 168.1).[31] To prevent side effects of opioids, prophylactic antiemetics and laxatives should be prescribed. This would enhance patient compliance. In mild, moderate and severe pain, Steps 1, 2 and 3 should be used, respectively. In Step 1 a non-opioid [Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or paracetamol] should be used. Step 2 includes a non-opioid and a weak opioid and Step 3 a strong opioid and non-opioid. NSAIDs should be avoided in patients with significant upper intestinal tract bleeding, renal failure, platelet dysfunction and those on anticoagulants.[32]

Opioids should be used at a reduced dose in the elderly and at a reduced frequency in those with renal/hepatic failure. Adjuvant analgesics which produce analgesic effect in some painful conditions, can be combined with any of the steps, especially for control of neuropathic pain (e.g. corticosteroids, tricyclic antidepressants, anticonvulsants). Palliative radiation therapy should be considered in patients with advanced lung cancer for pain relief.

An audit on pain assessment and analgesics prescription for cancer patients in a respiratory ward at a tertiary hospital in South India, revealed that educational interventions (teaching, provision of pocket guidelines and use of posters) improved analgesic prescription patterns.[31]

Dyspnea

Dyspnea is a distressing and frightening symptom to both the patient and the carers. The incidence of dyspnea among advanced cancer patients during the last six weeks of life is as high as 70%.[33] It significantly affects the physical, emotional and social well-being and results in poor QOL.[34] It is an important prognostic factor and predicts poor survival in cancer patients.[35,36] As a refractory symptom, it is associated with a five time increased probability of sedation at EOL.[37]

The three treatment categories in a patient with dyspnea include the correction of the correctable, use of

TABLE 168.1: Guidelines for pain management

WHO analgesic ladder with sample prescriptions

Step 3 (severe pain)
Tab Meloxicam 15 mg od
Tab Morphine 5 mg q4h and prn**
(titrated upwards if needed)
Tab Metoclopramide 10 mg tid
Tab Bisacodyl 10 mg hsod

*Non-opioid + strong opioid + / - adjuvant**

Step 2 (moderate pain)
Cap Proxyvon 1 q6h or q8h and prn (max 8 per day)
(**or** Tab Tramadol 50–100 mg q6h or q8h)
Tab Meloxicam 15 mg od
Tab Bisacodyl 5 mg hsod
Tab Metoclopramide 10 mg prn

*Non-opioid + weak opioid + / - adjuvant**

Step 1 (mild pain)
Tab Meloxicam 15 mg od
(**or** Tab Paracetamol 1 gram qid)
Cap Proxyvon 1 prn.

*Non-opioid + / - adjuvant**

Proxyvon is a combination of Dextropropoxyphene 65 mg and Paracetamol 325 mg.
* In patients with neuropathic pain, spinal cord compression, bone pain use of adjuvants/appropriate referral for expert opinion should be considered.
Analgesics should be given at the right dose, at the right time (round the clock at the right frequency), by the right route (oral).

Oral morphine prescribing guidelines
(For more information - http://www.jpalliativecare.com/documents/oralmorphine.doc)
Morphine should be given with a non-opioid.
Start with 5 mg q4h (unless patient is already on opioids **)
For break through pain, give an extra dose (same as the 4 hourly dose) up to 1–2 hourly
Do not omit the next regular dose, if a prn dose has been given.

Always……
Prescribe a stimulant laxative prophylactically
(e.g. Tab Bisacodyl 10 mg at night. Do not use bulk laxatives such as Naturolax.)
Prescribe an antiemetic prophylactically for the first few days.

****Morphine when patient is on opioids:**
If a patient is already taking > 4 capsules of Proxyvon, the starting dose would be at least morphine 5–10 mg q4h.

Increasing morphine dosage:
If pain is not controlled or > 2 prn doses are needed per day,
increase by approximately 50% of the starting dose
OR
Recalculate q4h dose based on total used in previous 24 hours.
If the oral route is no longer practical → Give **half** the dose by subcutaneous injection (10 mg per oral = 5 mg subcutaneous)

If pain is nonresponsive
- Check compliance
- Is the patient taking drugs prn only?
- Have you got the cause right?
- Does the opioid dose need to be increased?
- Is there a neuropathic element?
- Are psychosocial aspects being neglected?
- Will treatment of side effects permit more of analgesics?
- Will an alternate route of administration help?

Contd...

Contd...

Adverse effects

- Sedation can be common at the start of treatment, but resolves within few days.
- When starting the patient on opioids, use Tab Metoclopramide 10 mg q8h × 3 days.
- If patient is constipated on opioids even with bisacodyl 10 mg hsod,
  - consider bisacodyl 10 mg tid, along with a softener (e.g: cremaffin 15–30 ml tid)
  - If problem persists, intervene early with rectal measures
  - rectal examination to rule out impaction
  - bisacodyl suppository
  - high glycerine enema
  - digital rectal evacuation.

non-pharmacological interventions and use of drugs to palliate dyspnea (Fig. 168.5). Dyspnea could be related to the disease, the treatment or to other comorbidities. In advanced cancer patients, the cause of dyspnea is often multifactorial.[38] It is important to identify and treat the common reversible conditions in malignant and non-malignant respiratory diseases (Table 168.2). A cochrane review on the role of non-pharmacological interventions for breathlessness in advanced malignant and non-malignant diseases showed that neuro-electrical muscle stimulation, chest wall vibration, walking aids and breathing training are beneficial.[39] Other non-pharmacological measures can also be tried (Table 168.3). A respiratory physiotherapist should be part of the team offering EOL care, particularly for advice on non-pharmacological treatment.

Symptomatic treatment is indicated when there is no clear underlying correctable cause, the disease specific treatment is ineffective, difficult to tolerate or not consistent with patient preference. In advanced respiratory disease due to interstitial lung disease or COPD, palliative drugs are indicated when standard treatments including pulmonary rehabilitation, bronchodilators, antibiotics, corticosteroids, Long-term Oxygen Therapy (LTOT) or non-invasive ventilation have failed to relieve dyspnea or are not feasible on a long-term basis. There is strong research evidence from trials and from Cochrane review, for the use of oral and parenteral opioids to treat dyspnea in both malignant and non-malignant respiratory diseases. Nebulised morphine is not effective.[40, 41] Morphine can be used to reduce the sensation of dyspnea and relieve distressing tachypnea (Table 168.4). The side effects of morphine need to be addressed prophylactically. Morphine when used judiciously, with careful titration does not produce respiratory depression (i.e. does not increase CO_2 retention).[42,43] During the terminal phase of life, dyspnea and anxiety can worsen, with an increasing chance of delirium, this should be managed as per laid down principles and guidelines (Table 168.5).

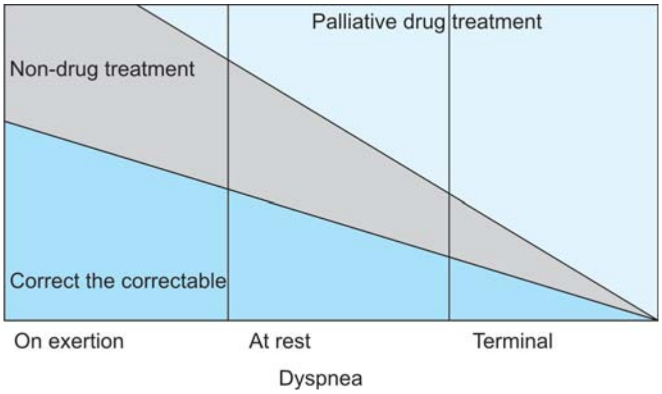

Fig. 168.5: Treatment of dyspnea

TABLE 168.2: Correctable causes of dyspnea in EOL

Typically in advanced cancer	*Typically in advanced respiratory disease*
Pleural/pericardial effusion	Pneumothorax
Superior vena cava obstruction	Pneumonia
Pneumonia	Pulmonary embolism
Pulmonary embolism	Anemia
Anemia	Cardiac failure
Cardiac failure	

TABLE 168.3: Non-pharmacological treatment for palliation of dyspnea

Explanation—symptom, acknowledge and address anxiety
Education—handling sudden episode of dyspnea/panic, activity pacing.
General measures—keep window open, use fan, loose clothing around neck.
Breathing techniques
Chest physiotherapy
Relaxation therapy
Pulmonary rehabilitation

Anxiety often coexists with and significantly affects the intensity of dyspnea, resulting in a vicious cycle.[44] Benzodiazepines are considered useful where there is significant anxiety or panic attacks that worsen dyspnea.[45] Combination of benzodiazepine with opioid is often found better than using either of them alone.[46] Benzodiazepines probably help through anxiolytic and sedative effect and possibly muscle relaxation. Care should be taken with diazepam, as it can accumulate due to its long half-life. Lorazepam (1–2 mg) is shorter acting and when given sublingually, provides immediate relief, hence especially useful during panic attacks. The cochrane review recommends the use of benzodiazepines as a second or third-line treatment within an individual therapeutic trial, when opioids and non-pharmacological measures have failed to control dyspnea.[47]

Most COPD patients receive regular bronchodilators. In cancer patients, bronchodilators are useful for the associated bronchospasm. Bronchospasm is found in more than half of dyspneic cancer patients.[38,48] A combination of inhaled short acting beta-2 agonists and anticholinergics are helpful.

Use of oxygen is not routinely indicated in advanced cancer. A Cochrane review clearly failed to demonstrate any benefit with inhaled oxygen in patients with end-stage malignancy.[49] Blowing cool air over the face with a fan is useful. A trial of oxygen can be considered if the patient remains breathless, even with drugs to palliate dyspnea (including morphine) and with persistent hypoxia. Oxygen should be given at 2 liters/ min via nasal prongs.[50] The patient should be reassessed after 24 hours and oxygen should be stopped if symptomatic response is not satisfactory.

In COPD patients with hypoxia, LTOT involving continuous oxygen use for more than 15 hours/day, is well established to enhance QOL, reduce sensation of dyspnea and improve survival.[51-53] If the patient does not satisfy the criteria for LTOT, giving oxygen only for palliation of dyspnea does not appear to have any benefit. Despite this lack of evidence of benefit, most breathless patients approaching EOL are commenced on oxygen. This practice should be strongly discouraged.

Before initiation of oxygen, the pros and cons should be tightly weighed on an individual basis. Patients can become psychologically dependent and may become anxious whenever oxygen is stopped. The oxygen equipment limits mobility and the mask impairs communication. Oxygen inhalation causes dryness of nasal mucosa. Risk of combustibility and added cost are the other negative factors in oxygen use. So if oxygen is used outside the indications for LTOT in COPD patients or on a trial basis in cancer patients, it should be used on an N-of-1 randomised controlled trial.[54,55]

TABLE 168.4: Guideline on the use of morphine for palliation of dyspnea

In patients who are opioid naive
(Patients who have not been on dextropropoxyphene (Proxyvon), tramadol, codeine, morphine, fentanyl)
- For mild dyspnea, prn doses of immediate-release oral morphine 2.5 mg will suffice
- In others, start with immediate release oral morphine 2.5 mg q4h and as required
- After 24 hours, if little or no improvement, increase to 5 mg q4h and as required
- Assess further response and titrate with 30–50% dose increments
- Relatively small doses should suffice 2.5–10 mg q4h

For patients already on round the clock regular morphine
Increase morphine dose based on the severity of dyspnea:
- Moderate dyspnea, give morphine at a dose equivalent to 50–100% of the q4h analgesic dose
- Severe dyspnea , give morphine at a dose ≥ 100% of the q4h analgesic dose
- Reassess and titrate with 30–50% dose increments.

Extreme dyspnea and distress
- Give morphine 2.5 mg subcutaneous (SC) followed by midazolam 2.5 mg SC (If the patient is not improving seek advice from specialist palliative care physician).

TABLE 168.5: Management guidelines for severe terminal dyspnea

- Convert oral to SC morphine (use half the oral dose)
- Increase the dose by 30–50% if the dyspnea was previously uncontrolled (round to the nearest 5 or 10 mg). Consider adding midazolam 10 mg as a continuous SC infusion over 24 hours
- In addition give haloperidol 2.5 mg at night OR along with the morphine and midazolam continuous SC infusion over 24 hours
- Extra prn doses of midazolam 2.5 mg SC with morphine 5 mg SC may be needed
- When reviewing after 24 hours the dose of morphine and midazolam may need to be revised in the light of the extra doses given
- Patients who are very old, very debilitated or who have severe renal or hepatic failure need dose reduction
- Other medications should be reviewed on a daily basis and simplified
- Explain to family that the intent is to reduce distress associated with breathlessness.

Cough

Cough is a normal but complex physiological mechanism that protects the airways and lungs by removing mucus and foreign matter from the larynx, trachea and bronchi; it has both voluntary and involuntary control. Pathological cough is common in those with cardiothoracic disorders and can be quite distressing. It is present in more than half the patients with chronic lung disease or lung cancer.

Cough can be classified as productive, with or without the patient being able to cough effectively and non-productive. Several causes of cough may coexist in one patient.[56] Management of cough depends on the type and cause of cough, the patient's performance status and prognosis. One should aim to reverse the cause of cough, whenever possible. Non-pharmacological measures like physiotherapy, teaching the patient to cough effectively and steam inhalation may be helpful. Simultaneously appropriate drugs to produce sympton relief should be prescribed. The choice of drugs would primarily depend on whether it is productive or non-productive cough, to aid or suppress expectoration respectively. Protussives include, nebulized saline, compound benzoin tincture, menthol, guaifenesin, carbocisteine. Anti-tussives include simple tinctur (demuscent) and opicid (codeine/morphine) and opioid derivatives like dextramethorphan. [57]

Hemoptysis

Massive hemoptysis in advanced lung cancer and chronic lung disease is rare, but can be very frightening and visually traumatic. The cause of hemoptysis in malignant or non-malignant situations is not always established. Management depends on the cause and prognosis. If this occurs in a patient who is otherwise terminally ill, with palliative goals, the treatment aims to reduce awareness and fear. Use dark towels (green or red) to cover blood. Being physically present with the patient continually is very supportive. Benzodiazepines (diazepam or midazolam) can be given parenterally to reduce panic and awareness, intravenous route is preferred if there is peripheral vascular shutdown.[56]

Stridor

Stridor is a harsh inspiratory wheezing sound heard due to the obstruction of the larynx or of major airways. Corticosteroids can be exceptionally beneficial in the initial stages. Dexamethasone can be given in high doses (8–16 mg/day). However, the symptom will progress and worsen if the primary cause is not reversible. Explanation to the patient and the carers is crucial. In the terminal phase, sedation can be used after discussion with the relatives.

The Last 48 Hours

During this period, patients may experience increasing weakness and immobility, loss of interest in food and drink, difficulty in swallowing, and drowsiness. This phase although usually anticipated can sometimes be rapid and sudden. It is important to identify the features of dying, such as increasing weakness, being sleepy, less interest in getting out of bed, in things happening around, confusion and occasionally features of agitated anguish. Confusion and restlessness are not uncommon. Haloperidol or benzodiazepines can be used to calm the patient.

Symptom control and family support should take priority. The drug chart should be studied with regard to the need and route of administration, as most patients may have difficulty to take by mouth. Only the essential drugs that would help in symptom control or patient comfort should be continued. Previously "essential" drugs like vitamin and iron supplements, antihypertensives, hypoglycemics, etc. may not be needed anymore. Analgesics, antiemetics, sedatives may form the new "essential" list.[58] The route of administration should be decided based on patient's ability to take orally. Drugs may need to be given parenterally, preferably by subcutaneous (SC) route. A microdrip set or a syringe driver can be used to give the drugs as SC infusions depending on its availability.

Various EOL care tools like the Liverpool care pathway, Gold Standards framework enable an optimised standard care to be delivered.[59,60] A customized EOL tool/pathway can be developed, based on the concepts in these various tools and modified to suit the local condition to ensure good EOL care.

Death Rattle

Death rattle is the noisy rattling breathing that occurs during the terminal phase. The secretions in the hypopharynx oscillating with every inspiration and expiration are responsible for the rattling noise.[61] This symptom can be very frightening and distressing to the carers. It is important to explain to the family/carers that the patient is unaware and not distressed. Positioning the patient semi-prone will help in drainage of secretions. Antimuscarinics reduce production of secretions and are hence helpful, if started early before the rattle is well established. The drugs commonly used include, hyoscine butyl bromide (20 mg SC q8h) or as infusion (maximum of 120 mg over 24 hours) or glycopyrronium (200 microgram stat and

600–1200 microgram over 24 hours) through subcutaneous infusion. Oropharyngeal suction should not be routinely used and should be reserved for unconscious patients.

EOL Care in the Intensive Care Unit (ICU)

Most patients who die in the ICU die as life-supporting measures are withheld or withdrawn.[62,63] Decisions surrounding life-sustaining treatments can be difficult, because they often involve complex ethical decision-making. Refusal of life-prolonging therapy may result in conflict of interests among medical professionals or between the medical professional and patient/family, over one-third of clinicians reported conflicts with families, of which 63% constituted EOL decisions.[64] Physicians may agree to the family's inappropriate demands for aggressive life prolonging therapy because they may be worried that angry families will sue if therapy is withheld (although this fear does not have any legal justification) or may not want to put the family through tough decisions or may not be fully convinced themselves.

In India, EOL decisions have additional challenges.[65,66] Discussion about patient's preferences on treatment during EOL or the use of advanced directives is not common. In such an instance it is the family members who decide the EOL issues for the patient. Often, family members are not well-informed or do not want to take any decision themselves. A vast majority is poor and many families end up selling all their property or take loans just to spend on their relative in ICU, often losing their assets and their loved one at the end.[67] A common cause of conflict with families is poor communication. Most conflicts can be avoided by facilitating communication through a formal family conference. Family meetings are an opportunity to foreshadow EOL discussions and allow family members to psychologically prepare themselves for the bad news. Effective communication improves family satisfaction, clinical decision-making and the psychological well being of family members.[68,69]

It is crucial to make the family feel that they are cared for and not abandoned at any stage. Non-abandonment (or fidelity) is also a central moral obligation of a physician.[69] Families need to be assured that the patient is not abandoned and will receive appropriate, competent care, regardless of the stage of his or her illness. It is also important to ensure that decisions to forgo a particular treatment are not seen as with drawing care.

Communication

Physician-patient communication about EOL decisions and treatment preferences is crucial. There is evidence that patients with chronic lung disease receive suboptimal palliative care largely due to insufficient communication with their physicians. It is important to note, that nearly all patients want information on EOL decisions and life support, less than 50% of patients had EOL care discussions and most patients felt that the physicians did not discuss about how long the patient had to live, what dying might be like or patient's spirituality.[70, 71] As accurate prognostication in an individual will remain difficult due to the variability inherent with chronic lung diseases, educating patients and families about the uncertainty in prognosis of lung diseases must be an essential feature of EOL care and decision-making.[72]

There are many patient and physician related factors that are barriers to effective communication and understanding them would be the first step towards better communication.[73,74] It is good to communicate with patients and their carers about prognosis and establish goals of care as early as possible. It is important to check with the patient about their willingness to know more about their disease status/prognosis. There are different steps in disclosing any bad news (Table 168.6) and the discussions can go over many visits, depending on each patient. During such communications, it is not uncommon to encounter denial, collusion or an angry patient/relative.[75,76] Further discussion with a colleague/team in dealing with the situation will be helpful.

Discussing EOL care or giving bad news can never make a clinician feel good. The most important principle is to do it in a sensitive manner and at the individual's pace. Most patients/caregivers want some discussion at the time of diagnosis of an advanced, progressive, life-limiting illness or shortly after.[77]

Support to the Caregivers

Anxiety and depression are common among caregivers of patients with terminal illnesses. The primary caregivers must be informed of the prognosis (with permission from the patient) and must be educated on the cause, importance and management of symptoms at home. They should also be warned of the likely ways the patient may deteriorate or die. Throughout the period, they should be provided with psychological and spiritual support. They should be informed of the support services which are available. Support to the caregivers should continue

TABLE 168.6: Steps in disclosing bad news (could be diagnosis or prognosis)

Preparation

1. Review in detail patient's medical record, including disease status, treatment options and prognosis prior to starting the discussion.
2. Review your own feelings and prepare yourself.

Physical setting

1. Ensure maximal privacy possible
2. Allow patient and key family members to be present

Disclose the information

1. Check with the patient if he/ she wishes to know
2. Elicit patient's understanding by asking the patient to say what he/ she already knows about their disease (listen and understand patients feelings/expectations)
3. Give a warning shot (e.g. *"I am afraid the tests are not good", "The situation is more serious than we think…")*
4. Pause….give time
5. Give small bits of information in lay language keeping in pace with the patient
6. Be honest always. (Be ready to say "I do not know" or "I will check and let you know")
7. Check outpatients understanding on the information given.

Following the disclosure

1. Be sensitive to patients emotions (sadness, anger, fear)
2. Respond to patients emotions, give non-verbal support and active listening (eye contact, touch when appropriate)
3. Follow patient-led agenda
4. Allow silence, give patient time to react
5. Give hope tempered with realism
6. Invite questions
7. Try to summarize the discussion and make a follow-up plan
8. Clarify your role in future medical care
9. Finally document the discussion, with details about the people present, content of discussion and future directions. This will help the others in the team to continue to provide the best care.

through bereavement.[78] Good support to the patient and family by a multidisciplinary team at the EOL will enable patients to spend their final days in their preferred places of care.

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APPENDIX 1: END-OF-LIFE CARE—RELIGIOUS BELIEFS AND PRACTICES IN INDIA

HINDUISM

SK Jindal

The traditional Hindus believe in the continuity of life after death. There is a great degree of sanctity attached to the pre-death worship, performance of last rites and to the rituals both before and after the death. It is strongly believed that the type and mode of death is an important determinant of the peace for the immortal soul ever thereafter. An easy and peaceful death is crucial to attain *nirvana* or *mukti*, i.e. liberation from the sufferings and miseries of the life and the death cycle.

The terminal care therefore essentially focuses to achieve the 'best possible' quality of life without interfering with the attempt to prolong the life. There is supreme importance of 'care beyond cure' and to 'dying with dignity'. Factually, the Hindu concept of life is centered around respiration and the length of life is measured by the 'limited' number of breaths which are fixed. Many a life-prolonging treatments, especially the artificial continuation of breathing with the help of ventilators are therefore in direct conflict with the traditional viewpoint. This, I believe is applicable only for artificial continuation of life in an otherwise dead (e.g. the brain-dead) individual than for assisted respiratory support as a mode for treatment.

Palliative treatment in Hinduism is quite in conformity with the existing concept of terminal care which involves the 'care beyond cure' philosophy. One aims to prevent, relieve or soothe the symptoms of disease without affecting a cure. The pre-terminal (and terminal) care is designed to offer symptomatic relief from the pain and suffering of approaching death. It is not a substitute or an alternative to curative treatment, but only an acceptance of the inevitability and of the limitations of life-prolonging treatments.

Rituals and Rites

Both the individual and the family are generally concerned with the last wish acts, and rituals near the death. Death in the bed is analogous to death of the sick which must be avoided. A dying individual is preferably moved to the floor—not for cardiac massage but to lie in the lap of mother-earth. Verses from the holy books such as the Gita or the Vedas are sung and the water from the sacred rivers, especially the Ganges is made available. The dying does like to bless the children as much as they like to be blessed. There is no better death for a Hindu elder than to die with everyone of the progeny around.

After-death handling of the body is both sacred and ceremonial. It must be properly cleaned and bathed. Nice and preferably new clothes, sometimes including the jewellary are worn before consigning the body to the flames.

Bereavement

Generally speaking, the degree of emotional attachment and inter-dependence is high in Hindu families. A sudden, or even a slow exit of a member of the family is mourned and remembered for long. The period required for resolution of grief is longer. It is possibly for this very reason that a number of sacred acts are undertaken afterwards. For example, the body remains and ashes are collected on the 3rd day or so and immersed in a sacred river. Several other functions are undertaken in the next two weeks and at fixed intervals in the following year.

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ISLAMIC RITES AND RITUALS
As per Islamic Principles
(Qur'an and Shariyat as Observed in India)

M Sabir

Prophet Mohammed(s) strongly advocated to take treatment for diseases till last in addition to prayers from the 'Allah Almighty'.

Death

- Separation of the material element from the non-material element (Soul).

The soul (Roohh) departs without being perceived or even felt at the time of death. Death *marks the end of the earthy life & the beginning of eternal life.*

Just before Death

- A Muslim is supposed to clear all his dues before death, which he might owe to others.
- Pray for forgiveness from God.
- Always wishes to utter last word Kalimah—L*a Ilaha Illa Allah ho Muhammadur Rasulallah,* e.g. solemn affirmation of his faith in one God and Prophet Mohammed(s) as is his messenger.
- Recital of Holy Qur'an by relatives.

Just after Death

- Dead body is kept at a clean and honorable place, wrapped in a clean cloth.
- All external tubes, needles, secretions, blood, pus etc on body to be cleaned.
- Eyes and mouth should remain closed. For closing mouth sometimes a strip of cloth is used to bring both jaws in approximation.
- Dead body is kept in supine position with both limbs kept straight (both big toes may be tied).
- Weeping and crying by relatives is not taken good as per Islamic teachings.
- Earliest cremation is preferred (even in the night).
- Before cremation, body is given bath with soap and water (plain/scented); dried up with a peace of clean cloth and wrapped in a clean cloth- Kaffan (traditionally white);
- Specific short prayer (Namaz-e-janaza) is offered for the peace of departed soul before burial in the grave.

Sura-ar-Rahman Al Qur'an

- He has created man.
- He has taught him an intelligent speech
- The sun and the moon follow courses (exactly) computed
- And the herbs and the trees both (alike) bow in the adoratives
- Then which of the favours of your Lord will ye deny?

THE SIKH TRADITIONS

KS Bhatia

First accept death and then life.
Even I and God incarnate die.

These 'sloks' from Shri Guru Granth Sahib define death that is end of life for all living beings.

In Sikh religion, death is transition from one world to the unknown other world; almost all the religions subscribe to this theory and have different rituals.

Once it is clear that a patient is going, a doctor should take steps to ease the anxiety of the patient and do his best to see that patient accepts the coming situation. The most important thing is that the patient should not be removed from his bed and all rites and rituals should be performed in a very subtle way and an atmosphere of divinity and peace be created around the patient.

In Sikh rituals, only very close friends and relatives remain with the dying person and try that the patient accepts what is happening—not all the dying patients accept his fate. Even when a patient is in coma, recitation of *Japji Sahib, Sukhmani Sahib* from Shri Guru Granth Sahib are recited. This sooths the body and soul of the dying patient and also stops the friends and relatives from crying and weeping. An Ardas to the Almighty *Waheguru* is performed with prayer to grant peace to the dying patient.

We all know that dying is very important part of life and we have to make it as peaceful and dignified as possible. Only the recitation in the name of *Waheguru* Akalpurkh can give that. Recorded tapes of Japji Sahib and Sukhmani Sahib be played in a low volume near the patient and prayer be offered till the end.

THE JAIN RITES

VK Jain

Jainism understands the process of dying as that of changing clothes.

Jains believe in reincarnation/rebirth and transmigration (movement from one life to another) of soul.

Jain leaders, relatives, family members visit the dying person to give the family solace (consolation), relief and support.

Monks and nuns if present in the vicinity may come to see the dying person. They sing hymns particularly the Namokar Mantra—a hymn for surrendering to the liberated souls.

They explain temporary nature for the physical body and all worldly attachments.

They encourage dying person to have noble thoughts, ask to think about forgiveness for anything they have done that was not life enriching during their life and to forgive all beings who have done wrong to them and have a peaceful death.

Scriptures like Kalpasutra, Samayasar and Uttaradhyan sutra are read for comfort and consolation.

Some Jains may choose to do a *santharo,* which is renunciation (giving up of all material possessions and attachments to people) and total acceptance of death for spiritual upliftment, where all life supports are removed including food and water.

This is a voluntary practice (willed death) one may choose when at the end-stage but must be conscious.

Prayers and Devotional Songs are Chanted

Audio-video cassettes may be used to accompany religious practices. The santharo is generally done away from the hospital. It is a personal choice done with the advice of a spiritual leader.

After Death

Family members participate in the process of preparing the body by washing and dressing the body in new clothes.

Prayers are continuously chanted.

A lit lamp burning with clarified butter may be kept in the room with a dead body.

Different Jains may or may not use flowers during this time

After death the body is cremated and the whole community may come to the cremation.

Family members and relatives usually take bath either at cremation place or at their homes.

Jains usually do not believe in sorting bone ashes at cremation place or surrender/immerse ashes in Ganga or any other rivers.

Usually third day of death after attending temple or religious leaders/

Feeling and Desires of a dying person:

- May afraid of death due to possible pain in dying process.
- Some deny for mortality.
- May be religious, non-religious and anti-religious.
- Desire to have place and funeral death.
- Feeling of helplessness, hopelessness, worthlessness, guilty, sadness, suicidal ideation, all are indication of depression.

CHRISTIAN RITUALS AND PRACTICES

George D'Souza

The Church does not support, euthanasia as life is a gift from God and He alone has a right to do what he pleases with it. But the Church is not for keeping a patient alive with extraordinary means when it is futile. It recognizes the ability of modern science to do so. It also recognizes the need that these resources may be better utilized for another with a better chance of living.

The Church also supports organ donation. Pope John Paul the II recognized its importance "man has found a way to give of himself of his blood and of his body, so others may continue to live". It does not compromise our beliefs. Instead it sees it as a true act of Christian charity.

The Church reminds us constantly of death and Ash. Wednesday is the day to take shock of ourselves and to remind us of the temporary nature of an individual's existence on earth—*dust thou art to dust thou returns*. But it also gives a hope in the resurrection of Christ.

There are certain sacraments, which are administered to the sick and the dying. The sacrament of reconciliation of penance remits all sins, however, grievous by sanctifying grace. The sacrament of anointing of the sick helps a patient cope with his suffering and gives him the strength to do so. The holy Eucharist is the sacrament, which unites one with Christ. The last sacrament is the sacrament of Viaticum, which prepares one for the final journey. A priest usually administers these. In his absence any Christian could say a prayer in place of the last sacrament.

Death for a Christian is meant to be an end of his travails on earth and the beginning of a new and glorious life in Christ our Lord. As written in the book of revelations "I heard, a voice from heaven saying Blessed are the dead who from now on die in the end. They will rest from their labors for their deeds follow them".

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Health Economics of Pulmonary Care

C Sudheendra Ghosh

INTRODUCTION

Cost-Effectiveness Analysis (CEA) is a technique of selection from amongst the competing wants, wherever the resources are limited. CEA was first applied to health care in the mid-1960s and was introduced with enthusiasm to clinicians in 1977 by Weinstein and Stason.[1] Since then, these approaches have been widely understood and accepted by the key decision makers in the health care sector, including the physicians. As a result, important health benefits or cost savings have been realized. This has altered the way we practice medicine and exchange information in the background of dynamic explosion of scientific knowledge. Science-based technology and availability of new therapies have provided us an opportunity to sustain life of many of our fellow human being.

Economic evaluation and deductive reasoning form the foundation for solutions to many clinical problems. We understand how subtle changes in many different genes can affect the function of cells and organisms. Uncertainty in clinical decision-making creates the need for probabilities and other quantitative tools like meta-analysis, decision analysis and cost-effectiveness analysis.[2] This is further facilitated by Evidence-Based Medicine (EBM). EBM refers to integration of best available research evidence with clinical judgment and experience in the care of patients.

A basic principle of economic analysis is that choices must be made between alternative uses of resources, and these decisions must consider for both the cost and the outcome. Trade-off and choices are inevitable since there are not enough resources to provide all the medical care that is technically possible or that patient prefers to receive. In the economic analysis of health care, there are three dimensions that need to be discussed:

1. The perspective of the analysis.
2. The type of costs involved.
3. The type of analysis considered.

The Perspective of the Analysis (Who Pays and Who Gains)

The costs, the outcomes, and the benefits can be differentially seen from the point of view of the society, the patient, the hospital authorities and the insurance agencies. For example, the cost to the insurance agency for critical care equals the charges that are allowed by that payer. The cost to the hospital is the true cost of providing critical care, regardless of the charge. The hospital's true economic cost can be found out only by carrying out a cost finding exercise. Cost to the patients is the amount they pay for the service plus the time missed from the work. The cost to the society is the total net cost of all of the different components of society, including the patient's productivity and the expenses involved in giving and receiving intensive care.

The Types of Costs Involved

Economist would define cost of critical care as the consumption of a resource that otherwise could have been used for another purpose. Since, the resource has been used for intensive care, the opportunity to use it for another purpose is lost. Therefore, its value in the next best use, which is no longer possible, is called "opportunity cost". Fixed cost is the investment required for setting up the intensive care unit. Variable cost is the expenditure required for the day-to-day management of the patient in the ICU.[4] This will vary with the volume of service.[3]

Resources used and their costs have been traditionally divided into direct and indirect costs. "Direct" generally refers to charges in resource-use attributable to the intensive care treatment, the term "direct" is used in economics to refer to productivity gains or losses related to illness or death.

i. *Direct cost:* Direct costs include the value of all the goods, services, and other resources that are consumed for the provision of intensive care treatment. These costs are often thought of as involving a monitory transaction. Direct cost involves physician time, nursing time, supportive staff time, equipment cost, procedure cost, lab cost, drug cost and costs for other consumables required for the ICU management. Direct non-health care cost includes increase in total costs required by a dietary prescription, and the cost of ambulance transportation, etc.
ii. *Indirect cost:* These are: (a) the cost associated with the lost or impaired ability to work or to engage in leisure activities due to morbidity and (b) lost economic productivity due to death.

The Type of Analysis

i. *Cost identification analysis:* It tries to find out the cost of providing Intensive Respiratory Care Unit (IRCU) care.[5] The result is expressed in terms of cost per service provided. Here, one may calculate the cost per case treated of IRCU. As an example, cost identification study may indicate the average daily cost of an ARDS patient in the IRCU as ₹ 5000, that of COPD patient as ₹ 4000 or that of pneumonia patient as ₹ 2000, it does not evaluate what these expenditure bring in terms of health outcomes.[6]
ii. *Cost-effectiveness analysis (CEA):* CEA is the structured process of evaluating the strength of evidence, incorporates both costs and effect of the treatment.[7] It measures the net cost of providing care as well as the outcomes obtained. Outcomes are reported in a single clinical unit of measurement such as a life saved. One may calculate the cost per year of life saved using noninvasive ventilation compared to ventilatory support in ICU setting. The cost-effectiveness of ICU management strategy needs to be compared with an alternative way of providing care. The reference case analysis is conducted from the societal perspective and accounts for benefits, harms, and costs to all parties. Although, CEA does not reflect every element of importance in health care decisions, the information it provides is critical to informing decisions about the allocation of health care resources.[8]
iii. *Cost utility analysis (CUA):* It is a form of cost-effectiveness analysis where the outcome measurement combines several outcomes on a common scale like Quality Adjusted Life Years (QALYs). Here, both duration and quality of survival are combined.[9] Measurement of QALYs weighs year of life by the quality of these years, which is determined by the presence of intangible outcomes such as pain and breathlessness. The QALY is a measure of health outcome which assigns to each period of time a weight, ranging from zero to one, corresponding to the quality of life during that period, where a weight of I corresponds to perfect health and a weight of 0 corresponds to a health state judged equivalent to death. The result is expressed as cost per unit of QALY.[10]
iv. *Cost-benefit analysis (CBA):* Cost-benefit analysis takes the analysis beyond measuring effectiveness in clinical terms or abstract concepts of utility. Cost-benefit analysis forces and explicit decision about whether the cost is worth the benefit by measuring both in the same units' viz. in Rupees. Cost-benefit analysis incorporate calculation of net benefit for net cost by subtracting cost from benefit. Program with larger net benefit is preferred. One may try to find out the net benefit of establishing an intensive critical care unit for the adults compared to neonatal intensive care unit.[11]

The Basics of CEA

Cost-effectiveness analysis is a technique for comparing the relative value of various therapeutic strategies. In its most simple form, a new treatment is compared with current practice (the "low-cost alternative") in the calculation of the cost-effectiveness ratio: It is also worthwhile to recognize that CEA is only relevant to certain decisions. There are various ways to how a new therapeutic strategy might compare with an existing approach (Table 169.1). Note that a CEA is relevant only if a new strategy is *both* more effective and more costly (or both less effective and less costly).

$$\text{CE ratio} = \frac{\begin{array}{c}\text{Cost of new strategy} -\\ \text{Cost of current practice}\end{array}}{\begin{array}{c}\text{Effectiveness of new strategy} -\\ \text{Effectiveness of current practice}\end{array}}$$

TABLE 169.1: Conditions under which CEA is relevant

Effectiveness	*Cost of new strategy high*	*Cost of new strategy low*
New strategy more effective	CEA relevant	Adopt new strategy
New strategy less effective	New strategy is dominated	CEA relevant

Estimating Cost-effectiveness of Self-management in COPD

There is emerging evidence that disease management with self-management education provided by a care-manager might benefit COPD patients. We evaluated the cost-effectiveness of Self-Management (SM) education among previously hospitalized COPD patients. The conventional treatment involved is inhaled medication with combination of long acting tiotropium and fluticasone; the other group received self-management education along with the conventional treatment. One year follow-up of study patients showed that the healthy days gained with conventional therapy were 289 days while that for SM therapy were 339 days. The estimated average cost for conventional therapy for one year was ` 6750.00 per patient and for SM patients it was ` 10555.00 (Table 169.2).

The result might be considered as the "price" of the additional outcome purchased by switching from current therapy to the SM treatment (e.g. ` 76 per disease free day). If the price is reasonable enough, SM can be considered "cost-effective" and a good value. Being cost-effective does not mean that the strategy saves money. Similarly, just because a strategy saves money does not mean that it is cost-effective. The very notion of cost-effectiveness requires a value judgment-what you think is a good price for an additional outcome, someone else may not.

Quality of Life and Outcome Assessment Measures

Quality of life (QOL) has been defined by the World Health Organization (WHO) as an individual's perception of his position in life in the context of the culture and value systems in which he lives and in relation to his goals, expectations, standards and concerns. It is a broad ranging concept incorporating in a complex way the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of the environment.

The WHO QOL group instrument is organized into six broad domains of quality of life. These are: Physical domain; psychological domain; levels of independence; social relationships; environment; and spiritual domain. Within each domain a series of subdomains (facets) of QOL summarize that particular domain of quality of life.[12]

With the cost utility analyses, the cost of an intervention is related to the number of quality adjusted life years (QALYs). A QALY is a year of full life quality. Poor health may reduce the quality of year (e.g. from 1 to 0.5). Here, each life-year is quality-adjusted with a utility value, where 1 is equal to full health. The utility value aims to reflect the health-related quality of life. Different types of interventions are then compared by calculation of costs per gained QALY.

Disability adjusted life years (DALYs) is a combined measure of years in disability and years of life lost due to premature death (from the disability).[13] Two mathematical equations are used to calculate DALY-Years of Life Lost (YLL) and Years Lived with Disability (YLD). YLL is the number of years of life lost due to premature death. YLD is the number of healthy years lost due to disability from the condition until remission or death. These are then summed together to provide years living with disability. The DALY scale range is the reverse of the QALY scale, with 1 indicating death and 0 indicating the best possible state of health. Unlike QALY, DALY reverse scaling would not allow for negative values because 0 is equivalent to perfect health. The calculations for DALY consider age and sex when calculating the burden of the disability; there is no consideration for economic status so that disability burden is measured globally for all.[14]

TABLE 169.2: CEA-examining conventional treatment and SM therapy in COPD

Strategy	*Cost in Rs*	*Incremental Cost Rs.*	*Effectiveness-(No of HDG)*	*Incremental effectiveness*	*CE RATIO*
Current	6750.00	-	289.00	-	-
Self-management	1055.00	3800.00	339.00	50.00	` 76/HD gained

TABLE 169.3: Common instruments to measure QOL in Pulmonary Medicine

Instrument	*Measure*
St. George's Respiratory Questionnaire (SGRQ)	3 aspects (activity, symptoms, impact)
Medical Outcome Study Short Form 36 (SF-36)	8 dimensions
World Health Organization Quality of Life (WHO QOL) assessment instrument	24 aspects of QOL
EuroQOL 5-D (EQ-5D).	5 dimensions

Health-related Quality of Life Instruments

Health status or health-related QOL assesses the influence of disease on physical, emotional, and social functioning. In contrast, the core of QOL is the person's perception of his or her life. QOL has a much wider scope than the physical, emotional and social domains.

There are several available instruments to measure QOL of patients with lung diseases (Table 169.3).

The St. George's Respiratory Questionnaire (SGRQ) measures three aspects (activity, symptoms, impact) and the medical outcome study short form-36 (SF-36) has 8 dimensions, whereas the World Health Organization Quality of Life (WHO QOL) assessment instrument measures 24 aspects of QOL. QOL encompasses the respondent's own perception of aspects of their life, while health status asks respondents about the presence or frequency of behavior and feelings.[2] However, in choosing between the SGRQ, the medical outcome study short form-36 (SF-36), and the WHO QOL, it will be important that researchers decide what domains are important in a particular study: Quality of life or health-related quality of life and generic or disease-specific. Furthermore, for studies in which both domains are important, it will be important to have head-to-head comparisons of the instruments measuring the reliability, validity, and responsiveness of each.

The difference between QALY and QOL measures is the dynamic of measurement. QALY attempts to provide a method of measurement for the impact of disease or treatment on an individual's ability to function and it can be equated to an economic scale. QALY measures differ from the QOL measures that provide subjective information describing individual's self-perception of their health status at a particular point of time.

Quality of Life with ILD

Chang et al.[15] studied the usefulness of four health-related QOL instruments, two generic and two respiratory-specific measures, in a group of interstitial lung disease patients [33 Idiopathic Pulmonary Fibrosis (IPF), 10 sarcoidosis, and seven miscellaneous], and concluded that the medical outcome study short scores from all four QOL questionnaires correlated significantly with 6 min walk distance and dyspnea score. Scores from the SF-36, QWB, and SGRQ showed significant correlation with FVC, FEV_1, and diffusing capacity as well. Patients with IPF appear to have similar impairments in HRQL to those with chronic obstructive pulmonary disease.

Other studies of HRQL in patients with IPF suggest that, in addition to the obvious effect on physical health, general health, energy level, respiratory symptoms, and level of independence are also impaired.[16] Variability in HRQL among patients is not fully explained by measures of dyspnea or pulmonary function, suggesting that HRQL measures provide unique information.[17]

CONCLUSION

The choice between the quality of care vis-a-vis its costs poses a persistent dilemma for the physicians. On one hand, they must serve as advocates for the individual patient and recommend the course of action most likely to be beneficial to the patient. On the other hand, physicians must understand the cost as well as the benefits of medical interventions so that they can choose amongst the wide range of options. Exponential growth in technology, the remarkable capability of modern pulmonology and its increasing availability (including in this country) have created many ethical and economic issues. Neither medical necessity nor expected medical benefit nor economic evaluations give us a decision procedure for resolving these distributive problems. Economic evaluation offers more complete information relevant to our decision.

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Section

23

SURGICAL ASPECTS OF RESPIRATORY DISEASE

SK Jindal

170

Surgery for Tuberculosis and Infective Lung Conditions

RK Dewan

Most of the thoracic surgery developed in the late 19th and early 20th century, specifically dealt with the management of Tuberculosis (TB) patients. The same challenges were also encountered while dealing with various other infective lung conditions. The management strategy for tuberculosis progressed from isolation and fresh-air sanatoria to various surgical collapse techniques and surgical resection. Surgical therapy was perfected in the mid-1950s, but subsequently declined with the emergence of effective antitubercular chemotherapy. Thereafter, reports of surgical intervention for tuberculosis have been extremely rare especially from the western countries. Most of the literature in thoracic surgery after 1960s dealt with carcinoma lung with occasional exception of tuberculosis and other infective lung conditions.

HISTORICAL ASPECTS

There is a fascinating history of development of surgery for lung diseases, which helps us to better understand their rationale and changing role in the present scenario. A Roman physician, Gorgio, in 1696, reported that a TB patient had improved dramatically after he suffered a sword wound in his chest, which produced a pneumothorax. This started the concept of collapse therapy. Carson, in 1822, suggested that something must be done in order to force the diseased lung to rest artificially by external means. Forlanini, an Italian physician, observed in 1890 that lung collapse tended to have a favorable impact on the disease outcomes. This ended the depressing era of helplessness in the face of advanced TB. Later, many other surgical procedures, e.g. artificial pneumoperitoneum, phrenic crush, plombage, thoracoplasty and resection followed. In the post-chemotherapy era, introduction of successful antitubercular chemotherapy decreased the need of surgical intervention. Most TB surgeons took toward developing cardiac surgery. The need for surgery in India, on the other hand, always remained considerable due to sheer number of cases. With Multidrug Resistant Tuberculosis (MDR-TB) and Human Immunodeficiency Virus (HIV), the west rediscovered interest in the subject. In the post-globalization phase, publications of interest are coming from former Soviet Republics, Japan, Italy, Hungary, Turkey, Argentina, Peru, Pakistan and elsewhere.[1-6]

There are several infective conditions of the lung that may warrant surgical management (Table 170.1). In all these conditions, the spectre of HIV [Acquired Immunodeficiency Syndrome (AIDS)] has added new dimensions, challenges and complexities in the past two decades. Tuberculosis with or without HIV remains the single most important challenge. Since there are no randomized prospective studies, surgical recommendations for surgery are based primarily on case reports, retrospective studies, experience and consensus.[7] The management of tuberculosis as well as of other infective lung conditions is primarily medical, surgery being resorted to only in occasional cases (Table 170.1).

There are three main categories of indications for surgery in TB (Table 170.2). These include the following: (1) Diagnostic procedures to confirm TB and to rule out other causes including cancer; (2) Excision surgery to remove worrisome disease in drug resistant cases; and (3) Emergent or urgent therapy to control life-threatening hemoptysis, or relieve a septic process.

TABLE 170.1: Infective diseases of lungs which may often warrant surgical management

- Tuberculosis, especially its complications and sequel
- Bronchiectasis
- Lung abscess
- Empyema
- Pleural complications of amoebic liver abscess
- Post-traumatic infective and inflammatory conditions in chest
- Latrogenic complications like esophageal perforation
- Lung abscess not responding to medical management
- Postoperative complications of thoracic and cardiac surgery
- Diagnostic problems in thorax

TABLE 170.2: Indications of surgery in tuberculosis

- Diagnostic
- Persistent sputum positive state despite therapy
- Complications and sequel:
  - Hemoptysis
  - Destroyed or bronchiectatic lungs
  - Empyema with or without bronchopleural fistula (BPF)

Indications in most of the series suggest that the evolving considerations are ruling out cancer, failure of chemotherapy, sequel/destroyed lung, failed operation, hemoptysis, MDR-TB, pleural disease and aspergilloma.[8]

TYPES OF SURGICAL PROCEDURES PERFORMED FOR TUBERCULOSIS

There have been many surgical procedures which had been used in the past or are being currently used for the diagnosis and management of tuberculosis. These can be classified as under:

Procedures of Historical Interest

1. Sandbag/diseased side down.
2. Pneumothorax, artificial.
3. Intrapleural pneumonolysis; apicolysis (injection of air, or paraffin-oleo thorax), utilizing open or thoracoscopic approach of Jacobaeus.
4. Pneumoperitoneum.
5. Multiple intercostal neurectomy to decrease costal excursions.
6. Scalenectomy to decrease upper costal excursions and to depress the lung apex.
7. Phrenic nerve crush or paralysis.
8. Transection of accessory muscles of respiration (scalenotomy).
9. Extrapleural plombage of pneumothorax (space between parietal pleura and endothoracic fascia); (injection of air, nitrogen, paraffin wax).
10. Subcostal and extraperiosteal plombage (bird cage) (periosteum stripped from upper five ribs). Lucite balls are most commonly used.
11. Caverostomy (Monaldi Procedure).
12. Thoracoplasty (staged).

Some of these procedures are still occasionally used, at least in the developing countries.

Diagnostic Procedures

1. Thoracocentesis.
2. Transthoracic needle aspiration.
3. Closed/open pleural biopsy.
4. Bronchoscopy (flexible/rigid), transbronchial needle aspiration.
5. Mediastinoscopy/anterior mediastinoscopy (Chamberlain procedure).
6. Thoracoscopy (Video-assisted thoracic surgery).
7. Exploratory/diagnostic thoracostomy-wedge biopsy.

Therapeutic Procedures

1. Decortication—with or without lung resection.
2. Drainage (closed/open) (temporary/permanent); pleurocutaneous window.
3. Thoracotomy with resection
   - Segment/wedge
   - Lobectomy
   - Pneumonectomy (transpleural; extrapleural; completion).
4. Chest wall/vertebral body-disc resection/ stabilization.
5. Muscle flaps (myoplasty).
6. Thoracoplasty (modified/tailored).
7. Omental transfer.

Persistently Active Disease

The decision about proper case selection is the most important in this situation. There is a justified indication for surgery in only some of the selected cases. These situations are:

1. The disease is sufficiently localized.
2. Adequate trial of antitubercular treatment (ATT) has been given.
3. Drug failure.
4. Patient is chronic secretor.

These are broad indications for surgery in patients of MDR-TB or persistent sputum positive status. There are

TABLE 170.3: Specific indications for surgical intervention in persistently active pulmonary tuberculosis

- When sputum smear or culture is positive for AFB, despite 4-6 months of appropriate and supervised Anti-Tuberculosis Treatment (ATT)
- When there have been two or more relapses
- One or more relapse while on therapy
- The organism has been shown to be resistant on culture and sensitivity
- When the patient is likely to relapse in the judgment of the physician
- Anticipated non-compliance in an admitted patient after discharge

a few other specific situations where surgery is a good adjuvant in the management plan of persistently positive active disease (Table 170.3).

Surgery plays an important role in the overall management of MDR-TB with acceptable mortality and morbidity.[9-13] Surgical interventions, in carefully selected cases, along with 2nd line ATT appear as the most favorable option since even the best available medical therapy alone provides bacteriological cure only in the order of 44 to 77% vis-à-vis more than 90% success rate with adjuvant surgery. Thoracoplasty is a useful approach for persistently positive cavitary disease (Fig. 170.1). Operative mortality is no longer a prohibitive issue, with most series reporting less than 3% early mortality. Though operative mortality has decreased, significant morbidity continues to remain a nagging problem, with Bronchopleural Fistula (BPF) in association with empyema formation being the most distressing manifestation. In cases of thoracic surgery, poor nutritional status and sputum positivity at the time of surgery are associated with a higher rate of complications.

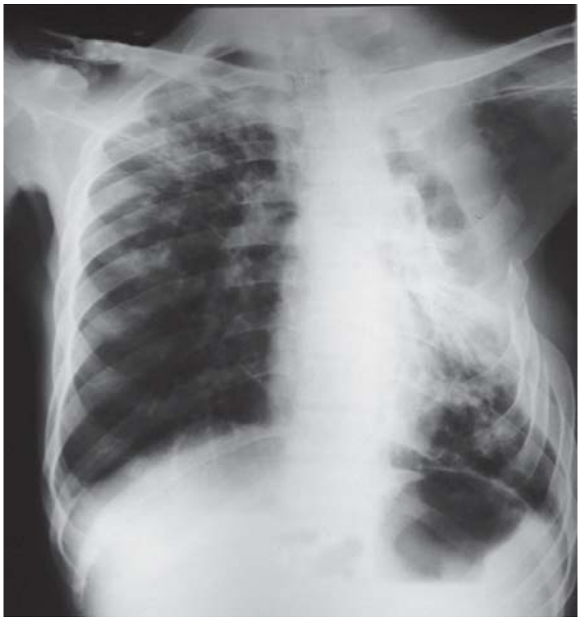

Fig. 170.1: Postoperative X-ray of a patient who has undergone thoracoplasty for persistent sputum positive status

Consensus lacks regarding the application of perioperative ATT. The rationale behind selecting the exact timing of intervention needs to be logical and scientific. Whereas it appears logical to use surgery after a defined induction phase of chemotherapy, a scientifically defined induction phase has yet to be worked out. Generally accepted timing of surgery is after 3 months of carefully prescribed 2nd line ATT, achieving optimal bacterial suppression at the time of surgery, yet avoiding delay to a point where the bacillary load is at a perilous high. Continuation of drugs for 18–24 months postoperatively seems reasonable by most authors, although given the economics involved, completion of this task is frankly daunting, if not utopian. Indications of surgery in MDR-TB remains to be a contentious issue, however, broad consensus is apparent now. Bacteriological cure in many series has been fairly impressive, with well over 90% success achieved with adjuvant surgery. Most such series are from the western world.[14, 15]

Hemoptysis

Surgery is not immediately required in a case of hemoptysis caused by pulmonary tuberculosis. Massive recurrent hemoptysis is the only justified indication in this setting. Conservative measures like positioning the good lung up after localizing the site, antibiotics, rest and sedation are almost always successful in controlling lung bleeding and surgery can be planned on an elective basis. Very often, post tubercular cavities are colonized by aspergillus fungus (aspergilloma) resulting in recurrent hemoptysis (Fig. 170.2). There are interventional measures other than surgery, which have their selected role in appropriate situations responsible for hemoptysis (Table 170.4).

TABLE 170.4: Different surgical interventions used for control of hemoptysis

- Endotracheal intubation to secure airway, suctioning and bronchoscopy
- Endobronchial tamponade with Fogarty catheter
- Laser photocoagulation (Nd-YAG or argon)
- Endobronchial hemostatic agents
- Selective bronchial artery embolization
- Surgical resection

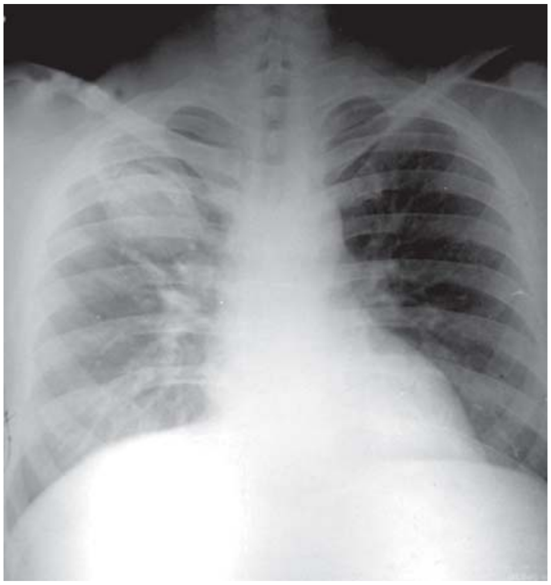

Fig. 170.2: X-ray chest of a patient with an aspergilloma in right upper lobe

Surgical resection of the involved portion of the lung is the most definitive and curative modality for treatment of massive and recurrent hemoptysis.[14] However in this technique, some points need to be emphasized. These include challenging surgeries involving careful dissection due to the presence of dense and unpredictable adhesions. A properly placed double lumen endotracheal tube, by which the anesthesiologist can collapse or inflate the lung depending upon the needs of the surgeon, is crucial. Position of this tube is confirmed with a pediatric fiber-optic bronchoscope and the time spent here is time well spent. This also protects the other healthy lung and ensures safety during surgery. The dissection of vascular structures at the hilum or in the fissure requires precise combination of sharp and blunt dissection. Adhesions are always a major challenge in this surgery. Use of a transfixation suture or double ligature on the proximal side while dividing arteries and veins is crucial to prevent deadly postoperative hemorrhage. Bronchus is closed with a bronchial stump stapler or with interrupted sutures. Equally good results have been shown by either of these techniques.

Empyema

Empyema continues to pose a challenge, and requires a common sense approach, for its management. The management depends upon the stage of presentation. Most of the cases are effectively managed with prolonged and expert intercostal tube management. In the subacute stage, drainage can be assisted by either vide-assisted thoracic debridement or instillation of intrapleural antifibrinolytic agents like streptokinase or urokinase. Decortication is indicated in the presence of persistent pleural infection in late fibrinopurulent stage. Thoracoplasty is partial decostalization of the thoracic cage to obliterate persistent pleural space. Whenever the lung is unlikely to expand due to an extensive disease or multiple bronchopleural fistulae, thoracoplasty is an appropriate intervention and is required quite often in our setting (Fig. 170.3). It is most suitable for management of postoperative empyemas. Results are quite gratifying.

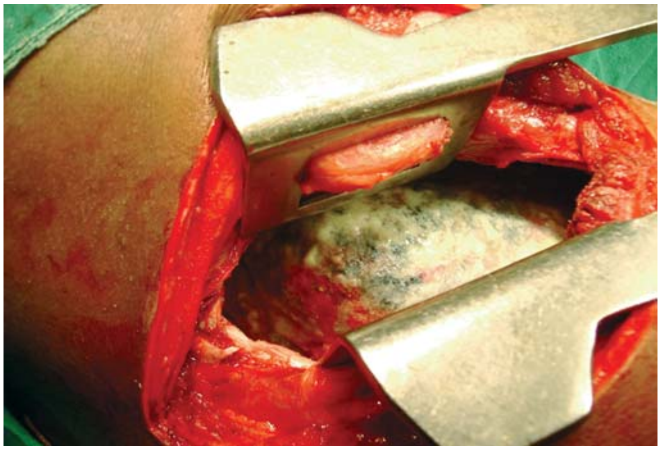

Fig. 170.3: Operative photograph of a case of tubercular empyema showing very little thickened pleura and diseased underlying lung—the reason why decortication is not suitable for most cases of tubercular empyema

Open Window Thoracostomy

Eloesser described a procedure to establish long-term open drainage of chronic empyema cavities in 1935. The procedure basically involves the creation of an open window thoracostomy in the chest wall for facilitating long-term open drainage without the need for an indwelling catheter. Various modifications of the procedure have been developed and described in the literature. It is an excellent procedure, the efficacy of which is matched by the beauty of its simplicity. Two to three ribs overlying the empyema cavity in the axillary region are partially resected, and the underlying pleura is stitched with the skin with the help of interrupted silk sutures. With good drainage being established, the empyema cavity slowly heals and closes over a period of months. Kohli and colleagues described complete expansion of the lung in 56% of 50 patients treated with open window thoracostomy over a period of 3 to 24 months after creating the flap.[16] A patient in the situation

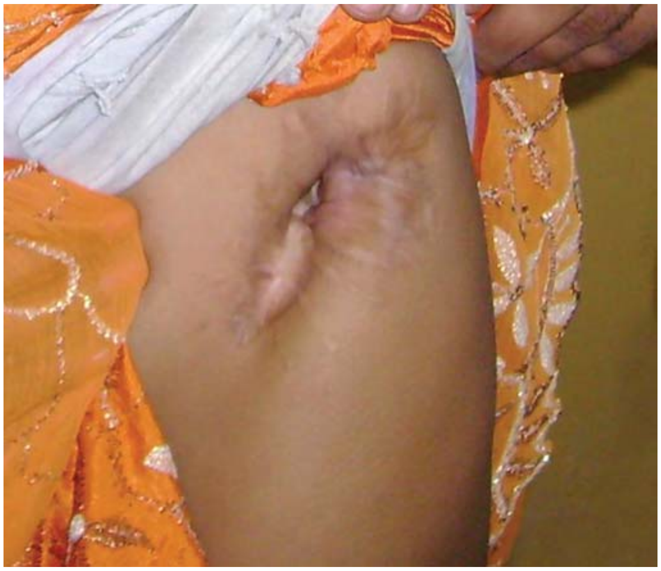

Fig. 170.4: Fully healed pleurocutaneous window, 8 months after the procedure

of chronic empyema, where the lung has not expanded after an adequate period of closed chest tube drainage and if the patient is judged to be not suitable for decortication because of diseased underlying lung, can be managed with this procedure. The results are generally excellent (Fig. 170.4).

Preoperative Work of a Thoracic Surgical Patient

There are some well-established prerequisites before a patient can be taken for surgery. It is of utmost importance that a detailed discussion is held with the patient and his relatives. This should include a frank talk about the natural course of the illness in the absence of any surgical intervention and the objectives of the proposed surgery in a given case. Risks of surgery and anesthesia are carefully explained along with the short-term and long-term results, if surgery is successful. It is of vital importance that a patient of pulmonary TB has taken an adequate course of ATT before the surgical decision is taken. Even an episode of massive hemoptysis as a presenting feature of pulmonary TB in a non-treated case is rarely an indication for surgical intervention. Patient's cardiorespiratory reserve to be able to withstand the surgery of this magnitude or proposed lung resection is carefully assessed. Various criteria have been laid down for different surgical indications and decision should be made jointly by the thoracic surgeons and the chest physician about the fitness of a given case after taking all the factors into account. Patients are urged to stop smoking for at least three weeks before surgery in order to ensure better postoperative results.

Postoperative physiotherapy, such as deep breathing, coughing and shoulder exercises, are taught to the patient in the preoperative period while forewarning him or her about a certain amount of expected postoperative pain. The patient should be as 'dry' as possible before surgery, meaning thereby that sputum or pus production (in cases of empyema) should be minimized by appropriate measures such as antibiotics, postural drainage, respiratory exercises, steam inhalation and nebulized bronchodilators, as appropriate. Some of these patients are quite weak and nutritionally depleted. Their nutritional status is built up before surgery, by rest and adequate diet, which may be sometimes ensured by hospitalization.

Bronchoscopy

Both rigid and fiberoptic bronchoscopies are excellent procedures and every thoracic surgeon should be able to perform them well. It is required for preoperative evaluation prior to all the surgical operations. Sometimes, bronchoscopy is also needed in the postoperative period to remove thick secretions or blood clots from the tracheobronchial tree.

Mediastinoscopy

It is required less often these days. However, mediastinal lymphadenopathy, which can be due to several diseases such as TB, sarcoidosis or lymphoma, is a perplexing clinical situation. If other measures fail to show a conclusive diagnosis, mediastinoscopy is a justified option for obtaining an adequate surgical biopsy.

Infective Conditions Other than Tuberculosis

Most of the indications and principles of surgery remain the same in all these conditions as for tuberculosis. Persistent septic foci in the lung or the pleura which do not resolve on medical management and remain a source of problems (like hemoptysis, empyema or other chest symptoms) warrant various kinds of surgical interventions, as described above. It may be mentioned that non-tubercular infective conditions generally do not cause significant lung destruction and hence the results of surgery are better. In cases of empyema of non-tubercular origin, good results can usually be obtained by intercostal tube management and decortication; open window thoracostomy and thoracoplasty are rarely required.

Postoperative Management

Results of surgery for TB and inflammatory lung disease improve if attention is given to detail in the postoperative period. Initial management is ideally done in an Intensive Care Unit (ICU). Antibiotics and painkillers are routinely given. Blood is transfused as per requirements. Respiratory exercises are encouraged and all measures to relieve pain should be taken. Incentive spirometry is a useful tool to achieve these aims. Care of the chest tubes is an essential ingredient of this management; these should be removed only when their output has completely stopped. Persistent air leak, development of bronchopleural fistula and residual pleural space are the most important issues to be carefully watched for, especially in the third postoperative week and onwards. These complications may require various kinds of intervention, including the open window thoracostomy and/or thoracoplasty.

Outcome of Surgery

Recent published series have demonstrated mortality of surgical interventions ranging from 0 to 3.1%.[17-21] The morbidity reported in most other series ranges from 3 to 53.7%. Postoperative empyema and BPF are best managed by prolonged tube drainage followed by open-window thoracostomy and thoracoplasty, if required. In the recent times, the use of good cardiac monitors, anesthesia support, pediatric fiberoptic bronchoscope to secure correct placement of the double-lumen endotracheal tube, liberal use of electrocautery, staplers for bronchial stump closure and adequate postoperative pain relief with epidural catheters have improved the results to the most optimum level. In the reported series, the operative aspects have been well addressed. Yet several issues such as the stapling versus suture techniques for lung and bronchus, air leak management and residual space problems need further debate and clarification. Pain relief, rehabilitation and long-term performance criteria are rarely discussed. All these issues require continued commitment from all the stakeholders to improve the results of this highly complicated and complex set of surgical patients.[22]

Surgery for inflammatory lung conditions like tuberculosis, whenever required, poses very special challenges. However, with adequate preparation, good case selection and optimal intraoperative and postoperative care, highly gratifying results can be achieved.

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Surgical Aspects of Obstructive Lung Diseases

Donald Ray Lazarus, Suryakanta Velamuri

INTRODUCTION

Obstructive lung diseases are characterized by airflow limitation which may be reversible or irreversible. The common obstructive lung diseases include asthma, Chronic Obstructive Pulmonary Disease (COPD) (both chronic bronchitis and emphysema), and bronchiectasis. The primary treatments for obstructive lung diseases are pharmacologic therapies, most notably bronchodilators and inhaled corticosteroids. Non-pharmacologic methods such as smoking cessation are important adjuncts.

Surgery has little to offer a patient with chronic bronchitis in the absence of emphysema. Aside from local resection for patients with focal disease, surgical treatment of bronchiectasis is largely limited to lung transplant, which is covered elsewhere in this text. Surgical techniques used to treat emphysema and asthma have been described, but not as commonly used, as widely available, and have benefits that are often not as clearly defined as commonly used medical therapies. The aim of this section is to describe currently used, investigational surgical and procedural treatments for emphysema and asthma to include both proposed indications and possible benefits.

LUNG VOLUME REDUCTION SURGERY

Emphysema is characterized pathologically by the permanent enlargement of air spaces distal to the terminal bronchioles with destruction of the alveolar walls.[1] In addition to impairment in gas exchange, this pattern of tissue destruction leads to a loss of elastic recoil and an increase in lung compliance. These in turn cause spirometric changes with increases in Total Lung Capacity (TLC), Functional Residual Capacity (FRC) and Residual Volume (RV), and a decrease in Vital Capacity (VC).[1] These pathophysiologic changes underlie the rationale for Lung Volume Reduction Surgery (LVRS) in patients with emphysema.

Lung volume reduction surgery for emphysema was originally described in the 1950s by Brantigan and colleagues. While a substantial proportion of their patients reported symptomatic improvement, the reported operative mortality of 18% in the absence of objective measures documenting benefit prevented LVRS from becoming commonly used.[2] In the 1990s, Cooper and colleagues revisited surgical lung volume reduction using more modern surgical techniques, including the utilization of bovine pericardium to minimize persistent postoperative air leaks.[3] Their initial successes and those reported by several others in small case series eventually led to the National Emphysema Treatment Trial (NETT), a randomized trial designed to prospectively evaluate LVRS patients with emphysema.[2] This trial and its offshoots have given us the best evidence to date on the indications and effectiveness of LVRS and will be referenced extensively throughout this section.

While the reasons for improvements in pulmonary mechanics and symptoms after LVRS are not definitively known, several mechanisms for the clinical and physiologic improvements seen after LVRS have been postulated. Removing portions of hyperinflated lungs should improve elastic recoil and increase air flow by decreasing the size mismatch between the hyperinflated lungs and the chest.[4,5] Reducing lung volume may also increase diaphragm curvature and length, leading to improvements in diaphragm strength.[6] Decreases in intrathoracic volume after LVRS may improve left ventricular diastolic function.[7] LVRS may also lower the central respiratory drive and ventilatory response to CO_2.[8]

Patient Selection and Prediction of Outcomes

In addition to standard preoperative risk assessment, patients who are candidates for LVRS should be assessed preoperatively using both physiologic and radiographic studies in order to predict the likely benefit of LVRS and also to identify those patients who are at high risk of poor postoperative outcomes. Physiologic assessment most often involves pulmonary function testing with spirometry, lung volumes, and Diffusion Lung Capacity of Carbon Monoxide (DLCO). Exercise capacity is also evaluated. Measurement of inspiratory lung resistance by esophageal balloon is less commonly performed. Preoperative radiographic evaluation typically includes chest radiographs as well as a Computed Tomography (CT) scan of the chest.[9]

Physiologic variables that have been shown to predict physiologic improvement after LVRS include measured inspiratory lung resistance and the ratio of Residual Volume to Total Lung Capacity (RV/TLC). Preoperative inspiratory lung resistance as measured with an esophageal balloon correlated inversely with postoperative improvement in Forced Expiratory Volume in one second (FEV_1).[10] This technique is not commonly available in the clinical setting, which may limit its utility. Fessler and colleagues later showed that the RV/TLC ratio correlated with improved Forced Vital Capacity (FVC) after LVRS.[11]

Radiographic criteria have also been shown to independently predict outcomes in LVRS. In one study, the presence of bilateral upper lobe pattern of heterogeneous pattern of emphysema was the only examined factor that was strongly associated with a good clinical outcome.[12] Correlation with postoperative improvement and upper lobe predominant-emphysema, presence of compressed lung, and percentage of normal or mildly emphysematous lung as assessed by CT was reported.[13]

While previous small randomized trials have shown improvement in physiologic parameters and symptoms after LVRS, they were not powered to detect differences in mortality.[14,15] The National Emphysema Treatment Trial (NETT), which began enrolling patients in 1998, is the largest controlled trial examining LVRS. It found that a combination of physiologic, clinical, and radiographic factors could be used to determine which patients were most likely to receive significant benefit or suffer serious harm from surgery. A total of 1218 patients with emphysema and severe airflow obstruction (defined as FEV_1 less than or equal to 45 percent of the predicted value) were enrolled. After initial screening, they were randomized to receive either LVRS or medical therapy. All patients underwent an initial period of pulmonary rehabilitation as well. Numerous prespecified substudies were also performed.[2] Interim analysis of the first 1033 patients enrolled in the NETT identified a group of patients at very high-risk of mortality after LVRS (Table 171.1). Patients who had FEV_1 less than 20 percent of the predicted value and either DLCO less than 20 percent of the predicted value or homogeneous distribution of emphysema on CT had a mortality of 16 percent at 30 days, as compared to no deaths in the medically treated group. Only 28 percent of the patients in this high-risk group reported improvement in health-related quality of life. Based on this initial data, NETT stopped enrolling patients in this high-risk group.[16]

TABLE 171.1: Predictors of mortality after LVRS

FEV_1 less than 20% predicted
and either
Homogeneous or non-upper lobe predominant emphysema
or
DLCO less than 20% predicted

Based on data from reference 16

The NETT investigators subsequently published results from the remaining 1078 patients who did not fall into the high-risk group described above. Overall, mortality at 90 days was higher in the surgical group than in the medical group (5.2 vs. 1.5%), equal between the two groups over the short-term (mean 29 months, RR 0.89, p-value 0.31), and lower in the surgical group than the medical group in the long-term(mean 4.3 years, RR 0.86, p-value 0.02).[17,18] PaO_2 was also significantly better in patients who were randomized to LVRS versus medical therapy at 24 months[19], and COPD exacerbations were less frequent.[20] A substudy of the NETT evaluated the change in exercise capacity in 238 patients. It found that exercise capacity was better in patients who had LVRS along with improvements in respiratory mechanics and dyspnea.[21]

Subgroup analysis of the non-high risk patients identified four subsets of patients who had differing outcomes after LVRS. The best outcomes after LVRS were obtained in patients who had both upper lobe predominant emphysema and low baseline exercise

TABLE 171.2: Predictors of benefit from LVRS

FEV_1 less than or equal to 45% predicted
Upper lobe predominant emphysema
Exercise capacity less than 40 watts (men) or 25 watts (women)

Based on data from references 2,17,18

capacity (defined as less than the sex-specific 40th percentile) (Table 171.2). These patients showed no difference in mortality between the surgical and medical groups at 90 days, and decreased short-term and long-term mortality. This group also was more likely to have improvement in exercise capacity and to report improvement in health-related quality of life.[17,18]

The second subgroup of patients had upper lobe predominant emphysema and high baseline exercise capacity. LVRS did not alter mortality in this group at 90 days or in the short-term and long-term analyses. Surgery did improve exercise capacity and health-related quality of life, these improvements were sustained at four years after randomization.[17,18]

The third subgroup of patients had non-upper lobe predominant emphysema and low baseline exercise capacity. Within this subgroup, patients who underwent LVRS had an increase in 90 day mortality but no significant difference in short-term or long-term mortality when compared to medically treated patients, and there was no significant improvement in exercise capacity with surgery in this subgroup. Surgery did produce a statistically significant improvement in health-related quality of life at 12 months, but this effect was no longer present at three years.[17,18]

The final subgroup had non-upper lobe predominant emphysema and high baseline exercise capacity. Surgery resulted in increases in 90-day and short-term mortality without a significant difference in long-term mortality. There were no significant differences in exercise capacity and health-related quality of life between patients who received surgery and those who were treated medically in this subgroup.[17,18]

Surgical Technique

While a complete discussion of surgical technique is beyond the scope of this section, a brief description of relevant developments in surgical techniques related to LVRS will be relevant. Cooper and colleagues revived LVRS in the 1990s using a technique of stapled excision with the staple line buttressed by bovine pericardium to reduce air leaks.[3] Since then, other techniques have also been investigated, most notably laser coagulation, which McKenna and associates compared to staple excision in a randomized controlled trial containing 71 patients. There were no significant differences between the groups in mortality, hospital length of stay, or air leak beyond seven days. The group undergoing staple excision had a significantly greater improvement in FEV_1 postoperatively as well as a higher probability of having no need for supplemental oxygen postoperatively as compared with the group treated with neodymium:yttrium aluminum garnet (Nd: YAG) contact laser surgery. Patients treated with laser surgery also had a significantly increased rate of delayed pneumothorax.[22]

Postoperative outcomes for both staple excision and laser volume reduction techniques are similar. Staple excision is the preferred technique, and there appears to be no benefit gained by adding laser to staple excision.[23-25] The staple line is frequently buttressed to reduce the occurrence of prolonged postoperative air leaks. Bovine pericardium has been used most commonly as buttressing material, but bovine collagen was equivalent in one trial and may be less expensive.[26]

Median sternotomy remains the most commonly utilized surgical approach, although Video Assisted Thoracoscopic Surgery (VATS) is also commonly used. Some experts suggest that VATS is superior for patients with apical or posterior adhesions, and for patients with posterior bullae.[22] Kotloff examined 120 patients undergoing LVRS, 40 via VATS and 80 via median sternotomy. He found similar outcomes in the two groups with the exception of a higher rate of postoperative respiratory failure in the patients undergoing median sternotomy.[27] One NETT substudy compared outcomes in patients undergoing LVRS via median sternotomy vs VATS. No difference in mortality, morbidity, or functional outcome was found between the groups except for a slightly longer length of ICU stay and higher cost associated with median sternotomy.[28] No consensus exists as to the preferred approach.

In summary, lung volume reduction surgery is an effective treatment for carefully selected patients with severe emphysema. It has been demonstrated to improve mortality, exercise capacity, and quality of life in patients with upper lobe predominant emphysema and low exercise capacity. Patients with upper lobe predominant emphysema and high baseline exercise capacity do not derive mortality benefit from LVRS, but may gain some symptomatic benefit. LVRS cannot be broadly recommended for these patients, but they can be considered for surgery on an individual basis if dyspnea is severe. LVRS has not demonstrated mortality benefit or significant durable symptomatic benefit in those patients with non-upper lobe predominant emphysema and low baseline exercise capacity and so is not recommended in this patient population. Patients who fall into the high-risk group described above (FEV$_1$ less than 20% predicted and DLCO less than 20% predicted or homogeneous emphysema) or who have emphysema which is not upper lobe predominant with high baseline exercise capacity have excess mortality from LVRS and should not undergo surgery.

Bronchoscopic Lung Volume Reduction

Despite successful outcomes in selected patients with severe emphysema, lung volume reduction surgery is a major procedure associated with a significant perioperative morbidity and mortality. For this reason, several bronchoscopic techniques intended to collapse areas of emphysematous lung without the need for median sternotomy or thoracotomy have been explored. This may provide many of the benefits of LVRS without the same degree of perioperative risk. Lung Volume Reduction (LVR) should be theoretically possible if the conducting airways to emphysematous areas of lung were blocked or closed endoscopically, causing the alveoli distal to the blockage to collapse. Several methods which may accomplish this are being examined, although none have been fully studied to date.[29]

Ingenito and colleagues initially reported bronchoscopic LVR (also called biological LVR) using a washout solution to collapse segments of emphysematous lung followed by sealing and scarring the collapsed segments with a fibrin-based sealant in sheep.[30] Reilly and associates subsequently published a small phase 1 trial evaluating the safety of this method in humans by treating two or four emphysematous lung subsegments in a total of six patients. No significant adverse effects were noted, but larger randomized trials are needed to confirm the safety and efficacy of this procedure.[31] Endobronchial plugs and blockers have also been described in preclinical studies, but no human trials of safety or efficacy have been published.[29] Several groups of researchers are investigating the use of endobronchial one-way valves that can be deployed bronchoscopially using at least two separate proprietary valves. An advantage of an endobronchial valve over an endobronchial blocker is the ability to clear secretions through the valve while still maintaining volume reduction. All published trials to date are unrandomized and open label. Initial results suggest promising improvement in symptoms and in some spirometric parameters, with generally acceptable rates of complications.[32-36]

Another method which remains in the early stages of investigation is bronchial fenestration with airway bypass. The rationale for this technique is based on the observation that patients with emphysema have elevated dynamic resistance in the small airways. This is accompanied by increases in collateral ventilation. If a direct connection between the bronchus and the collaterally ventilated lung can be made, the airway segments with high resistance can be bypassed, improving ventilation and reducing airway resistance.[29] The procedure itself involves using a radiofrequency ablation catheter to create fenestrations in the bronchial walls at the segmental or subsegmental levels. Then expandable stents are placed that connect the bronchus to the lung parenchyma.[37,38] To date results have only been published outlining the feasibility of the procedure in excised emphysematous human lungs.[37] The degree and duration of clinical benefit to be gained from this procedure remain unknown, as do the long term risks.[29] Clinical trials of all of these procedures are ongoing, and the future role of these bronchoscopic LVR techniques is not yet clear.

Bullectomy for Giant Bullous Emphysema

Bullae are defined as distended air spaces greater than one cm in diameter.[39] Giant bullous emphysema is a relatively uncommon form of emphysema. Patients who have bullous emphysema often develop progressive enlargement of bullae, worsening airway obstruction, and worsening dyspnea. Even with optimal medical therapy, dyspnea and severe obstruction can be very limiting for patients with giant bullous emphysema.[1] Spontaneous pneumothorax, often recurrent, is also reported, and bullectomy can be effective at preventing recurrence.[40] Resection of giant bullae in selected patients can result in reduction in airway resistance, improvement in elastic recoil, and a decrease in functional residual capacity. Dyspnea can also improve. Resection of bullae does not appear to cause those remaining to increase in size, and bullae do not typically recur after resection.[41] Reported operative mortality rates are between 0 to 22.5% in most case series, with a mean weighted mortality of around 8%. Durable improvement in symptoms and function can be expected in 60 to 90% of appropriately selected patients.[39]

Patient Selection and Prediction of Outcome

Even patients with severe emphysema do not commonly have bullae large enough that bullectomy would be beneficial. Careful preoperative evaluation and patient selection can identify the patients who are most likely to derive benefit from surgery and exclude those who are likely to have excessive morbidity or mortality. Typical preoperative assessment of a patient being considered for bullectomy includes chest radiographs and CT of the chest as well as spirometry with lung volumes and DLCO. Indications for bullectomy include the presentation of progressive dyspnoea and bullae occupying 30% or more of the hemithorax (Table 171.3).

Radiographic studies and physiologic tests can be used to predict the likelihood of improvement after bullectomy. In a series of forty six patients undergoing bullectomy for bullous emphysema, those who had bullae occupying more than one-third of the hemithorax had a significant increase in FEV_1 and FVC and concomitant decrease in TLC and RV at five years after bullectomy. While patients with bullae occupying less than one-third of the hemithorax also had reductions in TLC and RV, they did not demonstrate the improvements in airflow seen in patients with larger bullae.[40] Results of pulmonary function tests can also predict the likelihood of good outcome after bullectomy. The slope of the third phase of the single breath nitrogen washout curve and FEV_1 were shown to correlate with postoperative performance status in patients undergoing bullectomy. Third phase slope less than 5% and FEV_1 greater than 50% of the predicted value have better postoperative performance status.[42] Conversely, FEV_1 less than 500 mL and hypercapnia have been shown to predict poor prognosis, therefore, constitute a contraindication to bullectomy (Table 171.4).[43] Right ventricular hypertrophy and cor pulmonale also predict poor outcome.[41]

Several recent case series have examined physiologic and clinical outcomes after giant bullectomy. Schipper and colleagues evaluated 43 patients who underwent surgery for giant emphysematous bullae between 1994 and 2002 with mean follow up of over four years.[44] FEV_1 and DLCO were significantly improved over preoperative values at six months after surgery, and this improvement was sustained at three years. RV was significantly decreased at six months after surgery, and this improvement was maintained for two years. Improvement in six-minute walk distance was present out to one year postoperatively. Perhaps most importantly, dyspnea scores and quality of life measures improved significantly postoperatively, and these improvements were still present at three years postoperatively. The most common complication was prolonged air leak, which was present in 53% of patients. Mortality was low, at 2.3%.[44]

TABLE 171.3: Indications for bullectomy
Progressive dyspnea
Bullae occupying 30% or more of the hemithorax
FEV_1 greater than or equal to 50% predicted
OR
Large bullae and history of spontaneous pneumothorax ipsilateral to bullae

TABLE 171.4: Contraindications to bullectomy
FEV_1 less than 500 mL
Hypercapnea (relative contraindication)
Pulmonary hypertension with right heart failure

Another group prospectively identified 41 consecutive patients undergoing bullectomy and followed them with periodic clinical and physiologic evaluation for five years.[45] Dyspnea decreased markedly, continued to decrease through four years of follow up, and remained below the preoperative baseline level of dyspnea through the fifth year of follow up. FEV_1 also improved postoperatively and was still significantly better than the preoperative baseline through the fifth year of follow up, and resected bullae did not recur. Operative mortality was 7.3%, well within historical norms for bullectomy.[45] Neviere and associates prospectively evaluated pulmonary function, exercise testing, and dyspnea in 12 patients who underwent bullectomy. They observed significant improvements in FEV_1, DLCO, dyspnea score, and exercise capacity after bullectomy. These all remained significantly better than the preoperative baseline throughout the four year follow up period. All patients survived.[46]

Surgical Technique

A variety of surgical approaches are used to accomplish bullectomy, and no consensus exists as to the superiority of any one approach. For bilateral bullectomy, median sternotomy is typically used, but lateral thoracotomy may be preferred for unilateral procedures. Video assisted thoracoscopy is also used somewhat less often.[44-46] Multiple methods can also be used to excise the bulla. The most common are simple placation, stapler excision, and laser ablation. No controlled trials to date have compared the various methods.

Bullous emphysema is associated with progressive dyspnea and airflow obstruction. Resection of giant bullae has been demonstrated to be beneficial in reducing dyspnea and airflow obstruction in carefully selected patients. It is also indicated for patients with bullous emphysema and history of spontaneous pneumothorax. Multiple surgical techniques are used. Those patients with emphysematous bullae occupying greater than one-third of the hemithorax and who have FEV_1 greater than 50% predicted are likely to benefit from bullectomy. Those with smaller bullae or FEV_1 less than 40% predicted or 500 mL, significant hypercapnea, or right heart failure have excess operative mortality, so surgery should be avoided in these patients.

Bronchial Thermoplasty for Asthma

One of the hallmarks of asthma is airway hyperresponsiveness with bronchoconstriction. Despite the use of both antiinflammatory agents and bronchodilators, many patients with asthma continue to have recurrent exacerbations. Whatever the inciting event, bronchoconstriction results from contraction of smooth muscle in the bronchial walls. It has also been demonstrated that patients with chronic, poorly controlled asthma often have airway remodeling, hyperplasia of smooth muscle in the airway walls is an important component of this remodeling. It has, therefore, been postulated that by reducing the ability of airway smooth muscle to contract, the frequency of asthma exacerbations in patients who have been refractory to standard pharmacotherapy might be reduced. This constitutes the rationale underlying the investigational therapy for asthma called bronchial thermoplasty, although the full mechanism by which it works, remains unknown.[47,48]

The procedure itself involves the bronchoscopic access of the airways followed by deployment of an expandable basket with four electrode arms. These electrodes contact the airway walls, and the heat generated by radiofrequency energy is used to disrupt the epithelium at the points of contact. The technique can be used in the airways of three millimeters in size, or larger.[47] Initial studies in the canines indicate that the areas which are treated, fully re-epithelialize later with the exception of airway smooth muscle, which is replaced by loose connective tissue. In initial studies on dogs this had resulted in decreased airway constriction in response to methacholine up to three years after treatment. No stricture formation, generalized airway fibrosis, or mucus plugging were observed.[49] These promising results in animals have since led to trials in humans, some of which have been summarized here.

Evidence from Clinical Trials

Cox and associates evaluated sixteen patients with stable asthma in a nonrandomized prospective study to assess the safety of bronchial thermoplasty. All subjects underwent baseline spirometric evaluation as well as spirometry on the day of each treatment. The subjects were also given systemic corticosteroids around the time of treatment. The participants then underwent bronchial thermoplasty in three or four separate sessions, with all lobes treated except the right middle lobe. Treatments sessions were separated by three weeks, and patients were followed for two years after completing the treatments. The procedure was well tolerated, with 84% of procedure-related adverse events rated as mild, with the remainder classified as moderate. No severe adverse events or deaths were reported. All adverse events, occurred in the week after treatment, mostly cough, dyspnea, wheeze, and bronchospasm appeared to be related to airway irritation.[50]

The Asthma Intervention Research (AIR) trial was conducted to assess the affects of bronchial thermoplasty on asthma control. This multicenter randomized controlled trial enrolled 112 patients with asthma classified as moderate or severe persistent and who were taking daily Inhaled Corticosteroids (ICS) and Long-Acting Beta Agonists (LABA). Subjects also had to have objective evidence of airflow obstruction, positive methacholine challenge test for airway hyper-responsiveness, stable asthma (defined as unchanged use of asthma maintenance medication and rescue medication), and worsening of symptoms or peak flow during a required two week trial of abstention from LABA use prior to randomization. Patients were randomized to treatment and control groups. The control group was treated with ICS and LABA. The study was nonblinded, and no sham procedures were performed. The treatment group received bronchial thermoplasty in addition to continuing treatment with ICS and LABA. Bronchial thermoplasty was performed in the treatment group in three separate treatment sessions separated by approximately three weeks. Subjects were assessed at 3, 6, and 12 months after the last study treatment during a two weeks period in which LABA was withdrawn. The bronchial thermoplasty group showed a greater decrease in rate of mild exacerbations from baseline at 3 and 12 months after treatment than the control group. There was no difference at six months. There was no difference in the rate of severe exacerbations between the treatment and control groups. Patients in the bronchial thermoplasty group had a higher rate of adverse events, primarily exacerbations of asthma occurring in the first week after treatment. No change in FEV1 was shown. Post-hoc analysis suggested the greatest benefit was obtained by those patients who were on the highest doses of ICS at baseline.[51]

Pavord and associates performed a nonblinded randomized trial of 34 patients with severe, symptomatic asthma to evaluate the safety and efficacy of bronchial thermoplasty in this patient group. They included patients with asthma who were on high dose ICS as well as LABA, demonstrated airway hyperresponsiveness or reversible bronchoconstriction, and symptoms despite maintenance therapy. A significant number of patients were also on systemic corticosteroids as well. Patients in the bronchial thermoplasty group had a higher rate of adverse events in the treatment period, with most of these related to worsening asthma symptoms occurring within a day after the procedure and resolving within a week. Two patients experienced lobar collapse within two days of bronchial thermoplasty, and one required bronchoscopy with removal of a mucus plug to re-expand the affected area of lung. In both cases the collapsed portion of lung was the most recently treated lobe. During the post-treatment period there were no significant differences in adverse events. The group receiving bronchial thermoplasty had significantly greater reductions than the control group in the use of rescue inhalers and significantly greater improvements in the Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire at 22 and 52 weeks. The treatment group also had a significantly greater improvement in prebronchodilator FEV_1 at 22 weeks, but this difference was not sustained to 52 weeks.[52]

More recently, the AIR2 trial sought to evaluate bronchial thermoplasty for patients with symptomatic severe asthma in a blinded prospective randomized trial. The investigators randomized 288 patients who were on high dose ICS and LABA for asthma. Patients also had to have been on stable doses of asthma maintenance medication for four weeks prior to entry, have Asthma Quality of Life Questionnaire (AQLQ) scores less than 6.25, prebronchodilator FEV1 greater than or equal to 60% of the predicted value, evidence of airway hyperresponsiveness, and have had at least two days of asthma symptoms in the four-week baseline period. All subjects underwent three bronchoscopies at three week intervals. The results did indicate a greater change from baseline in AQLQ scores in the bronchial thermoplasty group, but the difference was not large. There were no significant changes in FEV1 or total symptom score. Both groups experienced a significant number of adverse events during the treatment period, with the bronchial thermoplasty group reporting more events, and also more serious adverse events. The most common adverse events were typical of airway inflammation, but 16 patients in the thermoplasty group required 19 hospitalizations compared to only two subjects in the sham group who needed two hospitalizations. During the post treatment period, the treatment group had a lower rate of emergency room visits and hospitalizations, but the number of emergency room visits and hospitalizations for respiratory events over the course of the entire study was no different between the groups.[53]

CONCLUSION

New and promising surgical interventions for both emphysema and asthma are being discussed. The field continues to evolve, particularly with regard to minimally invasive bronchoscopic methods. Bronchial thermoplasty shows promise as an adjunct treatment in patients with severe asthma who remain symptomatic despite optimal medical treatment. In addition to expense, it is limited by the need for multiple invasive procedures with a significant rate of adverse effects. Its role needs further elucidation before it can be recommended for widespread use. It is hoped that further assessment of their outcomes will justify the optimism that currently exists.

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Thoracic Trauma

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INTRODUCTION

Trauma is the leading cause of death, hospitalization and long-term disability for all the age groups from infancy to the old age. The earliest recorded reference to thoracic trauma is found in the "Edwin Smith Surgical Papyrus" written around 3000 BC. Much later, the closed chest tube drainage system, developed between the period of World War I and II in the 20th century had made marked impact on the treatment and outcome of chest injuries. Also during the World War II, thoracotomy became the most effective method to drain clotted hemothorax and to remove peel from the lung in case of empyema.

In multisystem trauma, chest-injury ranks third, after head injury and extremity (limb) fractures. Chest-injury is the cause of death in 25% of all deaths due to trauma.[1] Respiratory problems following chest injuries contribute significantly to 75% of deaths due to trauma. Blunt chest trauma is fatal in about 10% of cases, rises to 50%, if there are associated head and orthopedic injuries or abdominal trauma.[1]

In India, several factors such as the population explosion, marked increase in the number of vehicles, poorly regulated traffic control, driving under the influence of alcohol and drugs, and passion for speed are responsible for an alarming increase in the number of road traffic accidents. The situation is similar in several other developing countries. Road traffic accidents are the main causes of blunt chest and multi-system trauma. Increase in the domestic as well as the civilian violence due to activities of terrorism has lead to an increase in penetrating chest injuries caused by gun-shots, bomb blasts and stab injuries. Penetrating chest injuries have a mortality of 5% for simple stab-wounds to over 15% for gun-shot wounds. Less than 20% of patients with chest injuries require surgical intervention. Majority of chest injuries can be managed in small peripheral hospitals but a small number requires hospital admission and treatment in specialized cardiothoracic centers.[2]

The age of the patient plays an important role in the severity of an injury. In a pediatric patient, the chest wall is elastic and flexible, fractures are rare but intrathoracic injuries are common. In the elderly patients, the fragile bony thorax is highly susceptible to even the low impact-forces and offer poor protection to the underlying organs. Mortality is high even with minor injuries. Penetrating injuries are uncommon in both the elderly and the pediatric patients but they constitute the most common cause of death from trauma in persons of up to 50 years of age.

There is a desperate need of trauma-hospitals, rapid transportation of trauma-victims, improvement of road conditions, strict implementation of traffic-rules and knowledge of Cardiopulmonary Resuscitation (CPR) by paramedical persons and general public so that mortality and morbidity can be lowered in these patients.

PATHOPHYSIOLOGY[3]

The major visceral injury in chest trauma occurs due to three main mechanisms depending on the pattern of injury.

High Velocity Impact

This happens in high speed motor-vehicle collisions, when the chest wall suffers direct impact caused by rapid deceleration. The shearing force may cause transaction of bronchi or trachea, tear of the aorta and rupture of the diaphragm. There may be no or little injury to the chest wall, but the presence of bilateral-clavicular fractures or fractured-sternum should arouse suspicion for an internal organ injury. Anterior chest wall contusion may also be a warning for the underlying myocardial injury.

Low Velocity Impact

Low velocity force like direct blows to the chest wall cause damage to the bony cage with or without contusion of the underlying lung or myocardium. There may also be rupture of liver or spleen due to direct impact on the lower ribs.

Crush Injury

Crush injury may occur during industrial accidents, motor vehicular accidents and collapse of a building, where chest is crushed between two hard surfaces. Multiple bilateral rib fractures are common due to chest wall compression. The relatively low-velocity forces seldom damage the aorta or myocardium, but may rupture the diaphragm or lacerate the bronchi. The laceration is caused by widening of transverse diameter of chest-cage, pulling apart of the two lungs produces traction on the tracheobronchial tree.

EFFECTS ON LUNGS AND CHEST WALL

Chest injuries affect pulmonary functions adversely through three different mechanisms:

i. *Altered mechanics of respiration:* There is impairment of ventilation in majority of blunt and penetrating chest injuries that cause hemothorax and/or pneumothorax. Even simple rib fractures which cause sufficient pain may lead to hypoventilation, atelectasis, retained secretions, pneumonia, respiratory failure and septicemia in an elderly patient. More serious problems like tension pneumothorax, injury to major airways, multiple bilateral rib fractures with flail segment and ruptured diaphragm cause severe impairments in the mechanics of breathing. Multiple rib fractures may cause significant blood loss into chest wall and pleural cavity, which may further increase due to lung lacerations caused by sharp edges of the fractured ribs.

   There are two main types of chest wall derangements: A sucking chest wound and a flail segment. The flail segment is unstable, moves in during inspiration (paradoxical movement) and compromises ventilation by reducing the tidal volume. Following diaphragmatic rupture, the abdominal organs are sucked into the chest on inspiration causing lung collapse. If the pleural cavity is filled with air or blood, ventilation is compromised due to partial or complete collapse of lung. Injury of a major airway or inhalation of foreign material such as a loose tooth, stomach contents or road side debris may physically occlude the large (or small) airways leading to altered respiration.

ii. *Ventilation/perfusion imbalance:* Effective oxygenation of the blood and elimination of CO_2 depends on the fine balance between ventilation of the lung and its blood supply. Mechanical obstruction of the airway is an obvious cause of impaired ventilation, but in practice other mechanisms predominate. Normally, the inspired gases distribute preferentially to the areas of greater expansion which are the dependent portions of the lungs. If terminal alveoli are collapsed due to hemothorax or pneumothorax, inspiration results in preferential distribution of air to the already expanded areas. This maldistribution in the terminal airways due to external compression raises the intrapleural pressure. When a lobe or the whole lung collapses, there occurs a veno arterial shunt in the non-ventilated lung and systemic hypoxia results. Perfusion may be impaired due to thrombosis of vessels in the contused lung, due to fat embolism or platelet neutrophil microemboli in patients with Disseminated Intravascular Hemolysis (DIC) or ARDS.[4] Even a minor thoracic trauma may cause ventilation/perfusion imbalance causing severe hypoxia, recognized mainly by blood-gas analysis.

iii. *Impairment of gas transfer:* Passive diffusion of gases across the alveolar capillary membrane is dependent on the available surface area, the membrane-width, certain enzymatic factors and the partial pressure gradient between the alveolar and vascular compartments. In thoracic trauma, there is an adverse effect on gas exchange due to factors like pulmonary contusion, damage to the alveolar capillary membrane by inhalation of gastric contents or smoke, impaired cardiac output, interstitial pulmonary edema due to over transfusion of fluids or blood. The most serious process begins with the pathophysiological effects of shock. If unchecked, the condition progresses to Acute Respiratory Distress Syndrome (ARDS).[2] The mortality is quite high once

TABLE 172.1 Classification of chest injuries

Blunt Chest Injuries

1. Thoracic cage injuries
    - i. *Fracture Rib*
    - ii. *Flail Chest (multiple fracture ribs)*
    - iii. *First rib fracture*
    - iv. *Fracture of Sternum*
2. Injury to Pleura
    - i. Tension pneumothorax
    - ii. Open Pneumothorax
    - iii. Hemothorax
3. Surgical Emphysema
4. Lung parenchymal injury
5. Major airway injury
6. Diaphragm injury
7. Heart injuries
8. Rupture of aorta
9. Esophageal injury

Penetrating Chest Injuries

1. Pneumothorax / Hemothorax
2. Tension Pneumothorax
3. Pericardial tamponade
4. Cardiac injury
5. Tracheobronchial injury
6. Pulmonary parenchymal injury
7. Esophageal injuries
8. Great vessel injuries

ARDS occurs in a patient of thoracic trauma, especially after multiple injuries.

Classification (Table 172.1)

i. ***Blunt chest injury:*** It occurs mainly from automobile accidents; other causes being fall from height and crush-injury.

ii. ***Penetrating chest injury:*** In civilian violence, stab-injuries and low-velocity gun shots are the main causes. Marked increase in terrorism has introduced bomb-blasts and high-velocity guns-injuries which are far more damaging to the chest wall and the thoracic organs. In wars and military practice, high velocity missiles such as the gun shots and bomb blasts are the main cause of penetrating chest injuries.

BLUNT CHEST TRAUMA[2-4]

Thoracic structures get injured in varying degrees of severity in any combination. There may be little external evidence of the severity of the internal damage. If skeletal injuries are severe, the underlying parenchymal injuries are likely of the same proportion, except in the younger patients with flexible chest walls.

Patterns and Manifestations of Blunt Chest Injuries

Thoracic Cage Injuries

i. *Fracture rib* : This occurs mostly due to direct trauma. A simple rib fracture may be serious in the elderly individuals or in patients with chronic lung diseases with decreased pulmonary reserve. Chest X-ray is required to exclude pneumothorax. A routine chest X-ray may miss rib fractures. Uncomplicated fracture requires sufficient analgesia to encourage adequate ventilation and coughing. Oral analgesic drugs may suffice but intercostal nerve block with long acting local anesthetic drugs like bupivacaine may be helpful. Chest strapping is of little use, early ambulation and vigorous physiotherapy are encouraged. Oral antibiotics are required to prevent chest infection. Once pneumothorax and major internal organ injuries are excluded, the mainstay of management is control of local chest pain.

ii. *Flail chest*[5] *(Multiple fracture ribs):* Fracture of three or more ribs at two or more points, with or without associated fracture of sternum leads to flail chest. The flail-segment shows paradoxical movement, i.e. during inspiration, the chest is drawn inwards and on expiration it goes outwards, interfering with normal mechanism of respiration, resulting in hypoxia, atelectasis and hypercapnia. Associated pulmonary contusion aggravates the progressive respiratory failure.

If the segment is small which does not interfere with respiration and there are no associated major injuries, the patient should be observed in an Intensive Care Unit (ICU) with regular blood gas monitoring. Adequate analgesia and chest physiotherapy are required until the flail segment stabilizes. In a massive flail chest, the patient is ventilated for three to six weeks till the segment becomes less mobile or gets stabilized. Flail segment in itself is not an indication for assisted ventilation; it is the onset of respiratory failure due to the injury which necessitates ventilation. Thoracic epidural analgesia is also a good method in decreasing mortality in patients with multiple rib fractures without ventilatory support. The requirement for mechanical ventilation in patients with chest wall injury may reduce from 100 to 10% by epidural anesthesia.

Surgical fixation and chest wall stabilization are rarely done these days. Chest wall fixation may be done in case thoracotomy is required for excessive bleeding, laceration of lung or for clotted hemothorax. It may eliminate the need for ventilation in some patients and decrease the risk of pulmonary infection.

iii. *First rib fracture*[6]*:* It requires significant force to fracture the first rib which may be associated with injury to major neurovascular structures at the thoracic inlet. The mortality and morbidity are higher in patients of thoracic trauma having first rib fracture. Fractures of lower ribs can cause spleen-injury on the left side and liver-injury on the right side.

iv. *Fracture of sternum*[7]*:* Sternal fracture can occur due to sudden deceleration especially when driving fast. With seat belts in place, the steering wheel injuries are now much less common. The injury is quite painful even if only the external plate of the sternum is fractured. There is risk of an underlying myocardial damage, the patient should be observed in the hospital with Electrocardiogram (ECG) and cardiac enzyme monitoring. Most patients require only the analgesic drugs. If there is a marked paradoxical chest wall movement, it requires internal fixation of sternal segments by the wire or metal plates.

Injury to Pleura[8]

Injury to pleura may result in tension or open pneumothorax depending upon whether the visceral pleura is breached or a sucking chest wound is there. There may be associated hemothorax.

i. *Tension pneumothorax:* The injury to lung parenchyma which creates a flap valve mechanism allows air to enter the pleural cavity which can not get out during expiration via tracheobronchial tree or outside into the atmosphere. The air entrapment leads to the development of tension in the pleural cavity causing collapse of the lung and interference with the venous drainage to the heart. There occurs shift of mediastinum, and compression of large intrathoracic veins. Decreased cardiac output and sudden death can also happen.

The clinical diagnosis of tension pneumothorax can be made in a patient who had chest injury from the presence of marked respiratory effort, restlessness, cyanosis and dilated neck veins. Examination may reveal the presence of mediastinal shift, hyper-resonant note and absence of breath sounds on that affected side. Patient should not be sent for chest X-ray. The immediate treatment is required to release tension by insertion in the 5th intercostal space of an intercostal chest tube attached to an underwater seal.

ii. *Open pneumothorax:* It is more common in a penetrating chest injury. Usually, there is a wound in chest wall which is open to atmosphere, and it sucks air: "Sucking chest wound". Treatment consists of sealing of the sucking chest wound and an insertion of intercostal chest tube.

iii. *Hemothorax*[9]: In both blunt and penetrating injuries, the incidence of isolated hemothorax is 25 to 30%, in the remaining it may coexist with pneumothorax.

The pleural cavity has a potential capacity of 2 to 3 liters. On plain chest X-ray, a collection of up to 1 liter may be missed on a supine film. Slightly increased opacity of one lung field may be the only clue. A lateral decubitus film is useful to detect collection in the pleural cavity in a doubtful case.

In 80 to 90% of the cases, the source of bleeding is from the intercostal or the internal mammary arteries, pulmonary vessels are the source in 10 to 20% cases. Multiple rib fractures cause significant blood loss into the pleural cavity and the chest wall. Blood loss from lung lacerations is not much due to the low pulmonary pressure. In contrast, bleeding from aorta or big intrathoracic vessels is massive and usually fatal.

In majority of cases of hemothorax, insertion of a chest tube drain is the only required treatment. This encourages lung expansion which helps in arresting the bleeding. If hemothorax is neglected, it can lead to empyema and fibrothorax.

Surgical Emphysema

There is passage of air into the surrounding tissues when ever there is disruption of the respiratory tract at any level. Mediastinal emphysema occurs when air enters the mediastinum from a tracheobronchial tear or from perforation of the esophagus. The air moves inside the neck where it escapes from the deep tissue planes and enters the subcutaneous tissue. In case, the lung is stuck to the chest wall due to old tuberculosis or another infective lung disease, the injury to the lung parenchyma will lead to surgical emphysema, the lung does not collapse due to the adhesions with the chest wall and the air leaks into the subcutaneous tissue. Clinically, the patient's appearance is quite "distorted", but in most cases it does not require any treatment. More important is to treat the associated pneumothorax and to stop the air leakage.

Lung Parenchymal Injury[4]

Pulmonary contusion is caused by rapid deceleration against a steering wheel, fall from a height and from blast injuries. In young persons, there may not be any fracture of the ribs or sternum. There is capillary disruption causing intra-alveolar and interstitial hemorrhage, edema and obstruction of the alveoli and small bronchi by the exudates. Pulmonary contusion is often a part of a major chest injury that includes one or more fractures of ribs, pneumothorax and hemothorax. A large contusion may result in serious respiratory dysfunction. Pneumothorax or hemothorax can also develop later due to disruption of the contused pulmonary parenchyma.

Blood gas monitoring is important for treatment. A large number of patients with lung contusion require assisted ventilation for support. Continued hemorrhage and massive air leak require early thoracotomy and pulmonary resection, mortality is high in such cases. Small contusions usually resolve with physiotherapy, antibiotics and intercostal drainage.

Major Airway Injury[10]

Injuries to the major bronchi produce massive surgical emphysema, hemoptysis, pneumothorax and marked respiratory distress. Lung does not expand even after an intercostal chest tube when there is massive air leakage in the underwater seal bottle. Urgent thoracotomy and repair of the tear in the bronchi is needed. Lung resection is rarely required. Recovery is generally good after surgery.

Diaphragm Injury[11]

Injury to the diaphragm is more common on the left side, the right side is protected by liver. Tear is common on the posterolateral aspect. Abdominal contents such as the stomach, colon, and spleen may herniate into the chest, causing respiratory distress. Bowel sounds may be heard over the chest wall on the affected side. Chest X-ray in such a case may be confused with traumatic hemopneumothorax. Instances of perforation of stomach or colon with serious complications, while placing chest tube have been reported in these patients. Ryle's tube placement and chest X-ray examination are useful simple tests to diagnose this condition. Ultrsound, Computed Tomography (CT) scan and contrast study will confirm the diagnosis.

Cases missed during acute condition may present later with chronic diaphragmatic hernia. Patient coming in the acute stage should be explored by thoracotomy or laparotomy through thoracoabdominal incision. The abdominal organs are reduced back and the diaphragm is repaired after excluding/repairing injury to the liver, stomach or spleen.

Heart Injuries[12]

Major injuries to heart or great thoracic vessels are usually fatal, patient rarely reaches the hospital alive. Following types of injuries are generally encountered:

i. *Myocardial contusion*: Myocardial contusion is suspected, when sternum is fractured. The ECG pattern and enzyme changes are similar to those of myocardial infarction. Arrhythmias and cardiac failure are common. The patient should be kept under close observation in the ICU/Critical Care Unit (CCU) with full monitoring and resuscitation facilities being available. The risk of fatal arrhythmia decreases once enzymes and the ECG pattern become normal.

ii. *Heart chamber, valve or septum injury*: Rupture of a cardiac chamber is usually fatal, those who reach hospital alive are having small atrial or ventricular injury. Clinical picture is usually that of cardiac tamponade. Rupture of a cardiac valve or septum suspected from the presence of a loud murmur over the precordium causes heart failure. Open heart surgery is usually required for valvular or septal injury. Chamber-injury can sometime be repaired with a closed procedure, with standby heart lung machine. Results are dramatic in these very serious patients.

Rupture of Aorta[13]

About 15 to 20% of patients who die in the automobile accidents have some form of aortic injury. Aortic transaction is usually due to major deceleration force. Only 15% patients with aortic transaction survive long enough to reach the hospital alive. Of them, two-third will die of late rupture within two weeks and the remaining can develop false aneurysm. The most common location of this injury is just distal to the origin of the left subclavian artery. The classical finding in aortic transaction is the presence of normal or elevated B.P. in the right arm and low or absent B.P. in lower limbs. There may be radiofemoral pulse delay, infrascapular pain and an audible murmur at the back. Urine flow is decreased or absent. Patient may be completely asymptomatic. Chest X-ray is quite diagnostic in aortic transaction. CT scan is not of much help. Aortography is the confirmatory investigation of choice. Once the diagnosis is confirmed, immediate surgery should be undertaken. Left thoracotomy through 4th intercostal space is done. After proximal and distal control of aorta, the tear is repaired by direct suturing or interposition graft. There is risk of paraplegia after aorta is cross clamped, so some kind of aortic bypass shunt or atrio-femoral bypass should be used for spinal cord protection.

Esophageal Injuries

Esophagus is rarely injured in blunt chest trauma. The usual mode of esophageal injury is through endoscopy and esophageal intervention procedures.

PENETRATING CHEST INJURIES (PCI)[14,15]

The primary injury produces an open communication between the intrathoracic contents and the atmosphere. When examining the patient, the mode of PCI should be established, such as the position, the direction of entry and exit and the size of the wound to know about the intrathoracic organ injured.

The injury may be central or peripheral. The central area is bound superiorly by the sternal notch and clavicles, laterally by the midclavicular lines and inferiorly by the costal margin and the xiphisternum. Peripheral injuries lie on either side of these boundaries. The central and peripheral regions are further subdivided into superior and inferior regions by a line joining the two nipples. The path of the penetrating object can extend from central to peripheral areas and vice versa. Centrally located injuries are likely to be more serious since they involve the mediastinal structures. Chest injury below the level of diaphragm may extend into the liver, stomach and spleen.

Patterns and Manifestations of Penetrating Injuries

Pneumothorax/Hemothorax

Co-existing pneumothorax and hemothorax are the most common complications of PCI. Sucking wounds with size of more than two-third of tracheal diameter are hazardous since the air will enter the wound and into the pleural cavity more than it enters in the trachea. An open chest wound which is larger than laryngeal cross section area, will cause lung collapse, shifting of mediastinum, hypoventilation and reduced cardiac output. Sealing of the wound by dressing and placing an intercostal chest tube should be urgently done, followed by suturing of the wound or chest wall reconstruction.

Tension Pneumothorax

Diagnosis and management of the conditions due to PCI are similar to that of the blunt chest injuries.

Pericardial Tamponade

Tamponade is one of the major complications of PCI involving the central area. There is significant hemopericardium causing interference with the filling of the heart during diastole and a fall in the cardiac output. Classical signs of Beck’s triad are seen in 40% cases. Pulsus paradoxus may be present. Chest X-ray may show globular heart. The 2-D echocardiography has 96% accuracy, 90% sensitivity and 97% specificity for the diagnosis of cardiac tamponade in PCI. Unstable patient may require emergency thoracotomy. Diagnostic pericardiocentesis has a 33% false negative or false positive result due to the presence of clotted blood. Subxiphoid pericardiotomy as a diagnostic and therapeutic technique has been recommended by many authors. These should be done in the operation theater where facilities for immediate thoracotomy or midsternotomy are available since the release of tamponade may be followed by massive bleeding from the heart.

Cardiac Injury[15]

About 15 to 20% patients with cardiac injury may reach the hospital alive depending on the type of PCI, speed of the transport to the hospital and an early implementation of life support measures. Right ventricle, right atrium and left ventricle are the more common sites of cardiac injuries. Injuries to the valves, septum and coronary arteries are less common. Between the tamponade and frank hemorrhage, the former carries better prognosis than latter. Midsternotomy or left anterolateral thoracotomy is the common approach for cardiac injuries. Small tears can be controlled digitally or with vascular clamp and sutures. Facilities for cardiopulmonary bypass and auto transfusion/cell saver techniques should be available.

Tracheobronchial Injury[16]

The cervical trachea is usually injured due to neck wounds. Penetrating trauma to central chest may involve major airways like the bronchi and the intrathoracic trachea. There can also be an associated injury to the esophagus. Nonspecific symptoms include cough, dyspnea, voice-change, stridor and frothy bleeding from the wound. Injury distal to the main bronchi may produce pneumothorax or pneumomediastinum and subcutaneous emphysema. There is persistent air leakage and the lung does not re-expand after insertion of chest tube. Patient should be intubated if there is intrabronchial or tracheal bleeding. If this is not possible then tracheostomy should be done. Rigid bronchoscopy is very useful to clear the airways of blood and to diagnose the bronchial or tracheal injury. Anterior tracheal wounds of less than half the tracheal circumference should be primarily closed. Larger anterior and all posterior wounds require debridement prior to repair. Extensive tracheal injury may require resection of two to four rings and reanastomosis with absorbable sutures. The mortality of cervical injury is greater than that of intrathoracic injury. The overall mortality of tracheobronchial injury is around 30%.

Pulmonary Parenchymal Injury[17]

Parenchymal lung injury causes hemorrhage or hemopneumothorax. Ninety percent stab wounds and 70% of low velocity missile wounds are managed by insertion of an intercostal chest tube, analgesics and antibiotics. Thoracotomy is required whenever there is excessive bleeding or massive air leakages which are common with extensive lung laceration or hilar vessel injury in high velocity PCI. The lung tear may be either repairable or resection may be required.

Air embolism is one of the rare but dramatic complication of pulmonary and tracheobronchial injury. It occurs when there is combined airway and vascular injury and air enters the systemic circulation. The clinical manifestations may include confusion, unconsciousness, seizures, and cardiovascular collapse (due to air in the coronary arteries). Treatment consists of cardiopulmonary resuscitation and keeping the head lower than the chest. Rarely, surgery may be required to control the source of air embolism.

Esophageal Injuries[18]

Firearm injuries and stab wounds can cause esophageal injury especially in the cervical region. Associated injury to the adjoining vessels and trachea is fairly common. Clinical presentation includes the occurrence of subcutaneous emphysema, pneumo mediastinum and pleural effusion which may soon turn to empyema formation. Saliva and food particles are noticed in the chest tube drainage fluid. Diagnosis is confirmed by the contrast studies and esophagoscopy. After confirming the diagnosis, an intercostal chest tube should be placed. Treatment administered in the first 24 hours of injury gives the best results. There are a number of surgical techniques devised for this problem - repair of esophagus should be done in early esophageal injury (within 24 hours); in delayed injuries (beyond 24 hours) esophageal bypass procedures are done in view of the marked mediastinal inflammation. The over all mortality is around 15 to 50% depending mainly on the interval between the injury and the treatment.

Great Vessel Injuries[19]

Most of the patients with major thoracic vessel injuries do not reach the hospital alive. Penetrating injuries to the innominate-subclavian system have good prognosis with survival of up to 85%, if there is no cardiac arrest before reaching the hospital. Many of these patients may require immediate thoracotomy for massive bleeding. If patient is stable and diagnosis is not clear, angiography should be done. The surgical approach is done through median sternotomy except in cases of descending thoracic aorta injury when posterolateral thoracotomy is done. Primary repair is possible in majority of patients, otherwise graft interposition or bypass of damaged aorta is done.

MANAGEMENT OF THORACIC TRAUMA

Resuscitation: Practical Aspects

In developed countries, quick transportation of critical trauma patients by helicopters has dramatically changed the outcome of these patients. Similarly in those countries, knowledge of Cardiopulmonary Resuscitation (CPR) by the paramedical personnel and general public has done wonders in saving lives of these patients who otherwise would have died if on site CPR was not done. In most of the developing countries, including in India, such rapid transportation and CPR remain the distant goals.

The CPR of a seriously injured patient should follow the ‘ABC’ principle (Table 172.2).

Management of Blunt Chest Trauma

Most of the blunt chest injuries where heart is not injured, are conservatively managed with pain relief, chest physiotherapy and under water seal intercostal chest tube drainage. Thoracotomy is required in 15 to 20% of blunt chest injuries in the following conditions:

i. *Bleeding:* If after placement of intercostal chest tube, there is immediate drainage of 1500 ml of blood or continuous loss of more than 300 ml/hr for 3 hrs or

TABLE 172.2: The ABC of cardiopulmonary resuscitation

A. *Estabilishing a reliable AIRWAY*
   i. Oropharyngeal airway
   ii. Endotracheal tube
   iii. Tracheostomy
   iv. Bronchoscopy
B. *Restoration of mechanics of BREATHING*
   i. Artificial respiration
   ii. Evacuation of hemopneumothorax
   iii. Stabilize the unstable chest wall
   iv. Mechanical ventilation

C. *Resuscitation of CARDIOVASCULAR system*
   i. IV infusion of fluids—crystalloid, colloid or blood
   ii. Correction of acid-base status and electrolytes
   iii. Ionotropic support
   iv. External or internal cardiac massage
   v. Immediate thoracotomy to stop on-going bleeding

more, it calls for urgent thoracotomy. Similarly, continuous loss of more than 100 ml of blood for two or more consecutive days or continuous brisk bleeding of greater than 100 ml/15 minutes in the chest bottle needs an urgent thoracotomy.

ii. Rupture of bronchus, esophagus, diaphragm or aorta

iii. Cardiac tamponade or cardiac injury.

Mangement of Penetrating Chest injuries

The management includes measures for pain relief, chest physiotherapy, antibiotics and insertion of intercostal chest tube, if indicated.

Surgical intervention in the form of emergency thoracotomy is required later in 15 to 20% of the patients.

i. *Intercostal chest tube drainage:*[20] It is also called underwater seal chest tube drainage. Introduction of Intercostal Drainage (ICD) in the early 20th century was a very major step in the development of thoracic surgery, in the management of chest injuries and empyema. Intercostal drainage is indicated to continuously maintain an atmospheric or subatmospheric pressure in the pleural cavity (Table 172.3).

*Technique***:** Unless, there is tension in pneumothorax, a chest X-ray or ultrasound of chest should be done to decide the exact site for the chest tube.[21] The common sites of insertion are: (i) Apical: 2nd intercostal space in the axilla or infraclavicular area (for pneumothorax), and (ii) basal midaxillary line in 4th or 5th intercostal space (for blood or fluid in the chest cavity).

TABLE 172.3: Common indications for intercostal tube drainage

i. After opening chest— surgery
ii. Chest wall trauma with pleural space disruption
iii. Hemothorax
iv. Empyema
v. Pleural effusion
vi. Pneumothorax—tension or open
vii. Hemopneumthorax

After local anesthesia is infiltrated, an inch long incision is made in the skin and subcutaneous fat and a tract is made through the intercostal muscles along the upper border of rib and through parietal pleura. A chest tube of 28 to 32 F size is inserted in the pleural cavity and attached to a chest bottle or bag (under water seal). Application of negative pressure of 15 to 20 cms water is useful for re-expansion of lung. Chest X-rays should be done frequently to see the progress.

ii. *Management of stable patient:* In stable patients with central PCI, there is little time for investigations, 2-D Echo is a good tool for diagnosing or excluding pericardial tamponade or valvular or septal injuries of heart. Suspected great vessel injury should be confirmed or excluded by angiography. Bronchoscopy is indicated once there is clinical and radiological evidence of the major airway injury. In central penetrating chest injury, CT scan has very little significance but may be required for the associated head and abdominal injuries.

It is important to remember that a stable patient may suddenly deteriorate and will require urgent surgical intervention. A median sternotomy in all cases of central PCI with suspected vascular injury has been advocated without prior investigations because of the possibility of false negative angiograms.

iii. *Management of unstable patient:* Patients who remain serious or deteriorate despite resuscitative measures may require urgent thoracotomy for resuscitation in the emergency department itself.[22] This procedure is beneficial for those patients who arrive in the hospital with some signs of life. A patient who suffers cardiac arrest at the site of accident or en route to the hospital, has a very poor prognosis.

Indications for Thoracotomy (Table 172.4)[23]

Emergency room thoracotomy is required in about 5% cases of blunt chest trauma, more common in PCI

TABLE 172.4: Indications and contraindications for thoracotomy

A. *Emergency room*
   1. Acute pericardial tamponade
   2. Penetrating (stab wounds, gunshot injury) over the precordium.
   3. Cardiac arrest in the presence of fractured sternum or flail over precordium. .
   4. Exsanguinating, uncontrollable, intrathoracic hemorrhage
   5. Failed external cardiac massage requiring internal cardiac massage.
   6. Massive intra abdominal hemorrhage—intrathoracic aorta is cross clamped to control bleeding, this helps in preferential blood supply to brain and heart.

B. *Urgent thoracotomy*
   1. Hemothorax
   2. Large clotted hemothorax—to expand the lung and prevent empyema or fibrothorax
   3. Massive air leakage suggestive of major airway injury or lung parenchymal laceration
   4. Great vessel injury or thoracic inlet vascular injury proved by angiography
   5. Mediastinal traversing injury
   6. Proven esophageal injury
   7. Diaphragmatic injury/ hernia
   8. Chest wall defects
   9. Cardiac septal or valvular injury proved by echo/and cardiac catheterization and angiography
   10. Late cardiac tamponade due to blood or fluid

C. *Delayed thoracotomy*
   1. Clotted hemothorax
   2. Chronic Empyema
   3. Chronic traumatic diaphragmatic hernia
   4. Cardiac septal or valvular Lesions
   5. Missed tracheobronchial injury
   6. Traumatic AV fistula
   7. Delayed aneurysm
   8. Non closing thoracic duct fistula
   9. Infected intrapulmonary hematoma (Lung abcess)
   10. Treatment of various complications of PCI like pneumothorax, hemothorax and pericardial tamponade

D. *Contraindications to thoracotomy*
   1. Small volume hemothorax
   2. Pneumomediastinum
   3. Tension or simple pneumothorax
   4. Multiple pellets in chest wall or lung parenchyma or in a wall of major vessel

patients.[20] The mortality of emergency room thoracotomy is quite high (30 to 70%). Patients who become stable after intial resuscitation but deteriorate during observation, may also require urgent thoracotomy.

Surgical Techniques

The various incisions used for quick exploration of chest consist of the following:

a. *Midsternotomy:* It provides best access to all the chambers of heart and intra-thoracic parts of major vessels like the ascending aorta, the innominate artery, the carotid and the subclavian vessels. It can be extended into neck if required. One needs an electric sternotomy—saw for this procedure. A gigli saw can also do a good job.

b. *Left anterolateral thoracotomy (ALT):* It is an excellent approach in an emergency situation – quick and easy. All one needs is a knife and chest retractor. It is very good for internal cardiac massage. Depending upon the site of hemothorax right or left ALT can be used to drain.

c. *Posterolateral thoracotomy (PLT):* This is an excellent approach for esophageal, tracheobronchial, decending aorta and diaphragm injuries and for decortication in late empyema.

d. *Subxiphoid Pericardiotomy:* A small incision is made below the xiphisternum which is divided in the midline. Pericardium is opened between the two tendons of diaphragm. This approach is very useful in cardiac tamponade as a diagnostic and therapeutic procedure. The only danger is the precipitative massive hemorrhage in case of cardiac injury. This procedure should be done in the operation theater, so if there is need it can be converted into full midsternotomy to tackle the cardiac injury.

e. *Other incisions for chest injuries:* Trans-sternal bilateral thoracotomy, division or partial removal of clavicle and neck incision plus midsternotomy.

Miscellaneous Useful Measures

There are some useful techniques/measures which are of help in the management of chest injury patients:

i. **Autotranfusion:** The technique of auto transfusion of patient's own blood was started at the end of the 19th century for hemoperitoneum for ectopic pregnancy and blunt trauma abdomen. Blood banks were yet to come in that era, so autotransfusion was a life saving measure in those very sick patients.

   For chest injuries, the blood from the pleural cavity is collected in sterile chest bottles or bags and retransfused to the patient like the standard banked blood. This is especially useful in patients with a rare blood group or when there is shortage of that blood in the blood bank.

ii. **Thoracoscopy (Video Assisted Thoracic Surgery—VATS):** This is a useful technique for treating clotted hemothorax, loculated collection of blood, fluid or pus and for treating early empyema. It avoids major thoracotomy in a sick, injured patient.

iii. **Cardio pulmonary Bypass (Intra-aortic Balloon Pump—IABP), LVAD, RVAD:** In a cardiac injury when there is a large tear to a cardiac chamber or damage to a coronary artery, valve or cardiac septum, Cardiopulmonary (CP) bypass is required to treat the problems. Cardiopulmonary bypass is also needed in patients having injury to the ascending aorta or aortic arch or its vessels.

Intra-aortic balloon pump is a device which helps the heart to recover its function after any major cardiac injury leading to low output syndrome. It works on the principle of afterload reduction.

iv. **Extra Corporeal Membrane Oxygenation (ECMO):** If there is marked lung parenchymal injury or a large lung contusion as seen in flail chest, the standard treatment consists of prolonged ventilation. In some of these patients, blood gas reports show low PO_2 in spite of the use of high concentrations of oxygen and other treatments. In such cases, ECMO is a useful measure. In this method, patient's blood is oxygenated using venovenous extracorporeal membrane oxygenator system.

v. **Digital Exploration:** If there is a penetrating wound in the chest wall, one should not do digital exploration in the emergency department. This can lead to serious bleeding requiring emergency thoracotomy for which the place and conditions may not be suitable.

Complications of Chest Trauma

Chest trauma can cause a number of complications as follows:

1. **Lung atelectasis:** Lung atelectasis occurs commonly after blunt chest trauma. In the presence of fracture ribs, the pain causes restriction of respiration leading to alveolar collapse followed by segmental and lobar atelectasis. Retained secretions in the tracheobronchial tree will also lead to atelectasis.
2. **Infection:** Infection is fairly common after chest trauma:
   i. **Bronchopneumonia:** Due to pain after chest trauma, there is retention of secretions causing alveolar and segmental collapse of lung. In addition, the oropharyngeal secretions contain bacteria which migrate downwards in the lungs. Proper control of pain and chest physiotherapy are important for prevention. Appropriate antibiotics and other supportive measures are required for treatment.
   ii. **Empyema**: Hemothorax not properly drained, gets loculated and infected. In PCI, infection from outside can also enter the pleural cavity due to the entry of infected foreign object. Uncommonly, an infected intra-parenchymal hematoma may rupture into the pleural cavity. Treatment of acute empyema consists of proper drainage and antibiotics administration. Chronic empyema requires surgery such as decortication, rib resection with drainage and lung resection with decortication.
3. **Clotted hemothorax:** Hemothorax is common after blunt or penetrating chest injury. If hemothorax is not adequately and timely drained, it becomes a clotted hemothorax. Removal of clots is done through either thoracotomy or VATS. An infected hemothorax can turn to empyema or fibrothorax.
4. **Bronchopleural fistula (BPF):** Injury to a bronchus can lead to a BPF formation, more commonly after PCI than after blunt chest trauma. A BPF leads to partial or total lung collapse and empyema. A small BPF may close with proper ICD. A moderate or large BPF needs surgical treatment—closure of BPF or resection of part of lung containing fistula and decortication for empyema, if present.
5. **Bronchial stenosis:** There can be traumatic rupture of a lobar or main bronchus, usually following blunt chest trauma. If this injury is missed or not treated during the acute stage, bronchial stenosis may occur due to formation of fibrous tissue at the site of rupture. Patient may report with history of breathlessness while radiological investigations may demonstrate lobar or lung collapse on that side. Surgical exploratory thoracotomy is required for patch bronchoplasty or resection of stricture and end to end anastomosis. Results of surgery are generally good.

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Lung Transplantation

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Lung transplantation is an important therapeutic option for selected patients with advanced lung disease.[1] For such patients, transplantation offers the potential for improved quality of life and long-term survival. Currently, lung transplantation as a therapy for end-stage lung disease is limited by the availability of suitable donor organs, resulting in prolonged waiting periods with a substantial number of patients at an increased risk of dying before transplantation.[2,3] Despite advances in donor selection, surgical approach, and more effective immunosuppressive strategies, complications are frequent and result in constraints on long term preservation of graft function and patient survival.[2] Although the present indications and practice of lung transplantation allows only a selected few to benefit, especially in the developing countries such as in India, the future potential of lung transplant surgery is immense, and soon this form of therapy is destined to become a widely applicable treatment for diverse causes of lung diseases.[4-8]

HISTORY OF LUNG TRANSPLANTATION

The vascular experiments in animal models performed by Alexis Carrel at the University of Chicago in the early 1900s laid down the foundations of the surgical techniques for modern solid-organ transplantation.[9,10] In the late 1940s, the Russian surgeon Demikhov performed numerous heart-lung block transplantations without hypothermia or cardiopulmonary bypass in a canine model. By the end of the 1960s, there were three recorded attempts at heart-lung transplantation in humans, one in infant and the other two in adult recipients.[11] The adult patients survived for 8 and 23 days, which demonstrated the ability to breathe spontaneously, that suggested that humans could tolerate denervation.[12]

The advances in immunosuppressive therapy with cyclosporine in renal and heart transplant surgery contributed significantly to the successful introduction of lung transplantation in the early 1980s. In March 1982, the outcome of heart–lung transplantation (HLT) for pulmonary vascular disease in humans was described by the Stanford group.[1,13] After the successful introduction of heart-lung transplantation, single lung transplant was soon performed for interstitial lung disease,[14] followed by en bloc double-lung transplant for emphysema.[15,16] In 1989, bilateral sequential lung transplant (BSLT) was introduced.[17] By 2002, more than 3000 HLT and >20,000 LT operations had been performed worldwide.

GENERAL INDICATIONS

Since 1994, the yearly rate of lung transplants worldwide has remained constant at around 1,300 to 1,500.[18] Selection of lung transplant candidates requires an appreciation of the natural history of lung disease, and understanding of the impact of pre-existing medical co-morbidities on transplant outcomes. Selection is also influenced by the ability of the candidate to sufficiently handle peri and post operative complications associated with lung transplantation. The major indications for lung transplantation are Chronic Obstructive Pulmonary Disease (COPD), Idiopathic Pulmonary Fibrosis (IPF), Cystic Fibrosis (CF), and Primary Pulmonary Hypertension (PPH). Chronic obstructive pulmonary disease together with α-1 antitrypsin deficiency accounts for nearly half of all procedures performed worldwide. Other leading indications include, IPF (19%) and CF (17%). Idiopathic pulmonary arterial hypertension, now accounts for less than 5% of the procedures.[18]

Despite the recent advances, lung transplantation remains risky with a median survival among recipients of only 5 years. Because of the inherent risks involved, it is essential that this option be reserved for a time in the course of disease, when life expectancy is limited and quality of life is unacceptably poor. An individual assessment should be performed for every patient and careful counselling regarding risks and benefits is required. Specialist transplant team members should be consulted to undertake the detailed evaluation.

Selection Criteria for Individual End-Stage Lung Diseases

Disease-specific guidelines for selection and listing of patients have recently been updated and published by the International Society for Heart and Lung Transplantation (ISHLT) (Table 173.1).[19] Once inclusion and exclusion criteria have been met, the appropriate type of lung transplant needs to be considered. Options include heart-lung, single lung, double lung, and live donated lobar transplants. Heart-lung transplants are reserved for patients with Eisenmenger's syndrome with a non-correctable anomaly or a patient with lung disease with severe cardiac dysfunction. Isolated right heart failure due to pulmonary disease is not an indication for a heart-lung transplant, and severe dysfunction of the right heart has been shown to reverse after lung transplant. Double lung transplants are required for CF, bronchiectasis and other pulmonary diseases with secondary infections. Patients with pulmonary hypertension also usually receive a double lung transplant. A single lung transplant is the procedure of choice in most other types of transplant situations, including IPF and COPD.[20]

CONTRAINDICATIONS

Candidates for lung transplantation are thoroughly screened for any comorbidity that might adversely affect the outcome. Suitable candidates should have clinically and physiologically severe lung disease, otherwise they must be in reasonably good health. At most centers, the upper age limit for transplantation is generally set at 65 years.[21-23] Other absolute contraindications include, recent malignancy (other than non-melanoma skin cancer), active infection with the human immunodeficiency virus, hepatitis B or C virus with histologic evidence of significant liver damage, active or recent cigarette smoking, drug or alcohol abuse, severe psychiatric illness, documented and recurrent non-compliance with medical care, and absence of a consistent and reliable social support network.[4,18] Chronic infection with antibiotic-resistant *Pseudomonas*

TABLE 173.1: Disease specific guidelines for selecting candidates for lung transplantation

Chronic Obstructive Pulmonary Disease	BODE index of 7 to 10 or at least one of the following: History of hospitalization for exacerbation associated with acute hypercapnia (PCO_2 exceeding 50 mm Hg); pulmonary hypertension, cor pulmonale or both, despite oxygen therapy; FEV_1 < 20% and either DLCO < 20% or homogenous distribution of emphysema.
Idiopathic Pulmonary Fibrosis	Histologic or radiographic evidence of UIP and any of the following: DLCO < 39% predicted; 10% or greater decrement in FVC during 6 month of follow-up; a decrease in pulse oximetry < 88% during a 6-minute walk test; honeycombing on HRCT (fibrosis score > 2).
Cystic Fibrosis	FEV_1 < 30% of predicted, or rapidly declining lung function if FEV_1 > 30% (females and patients < 18 years of age have a poorer prognosis; consider earlier listing) and/or any of the following: Increasing oxygen requirements; hypercapnia; pulmonary hypertension.
Idiopathic Pulmonary Arterial Hypertension	Persistent NYHA Class III or IV on maximal medical therapy; low (350 m) or declining 6-minute walk test; failing therapy with intravenous epoprostenol or equivalent; cardiac index of < 2 L/min/m^2; right atrial pressure > 15 mm Hg.
Sarcoidosis	NYHA functional Class III or IV and any of the following: Hypoxemia at rest, pulmonary hypertension, elevated right atrial pressure > 15 mm Hg.

Source: Modified from International guidelines for the selection of lung transplant candidates: 2006 update–a consensus report from the pulmonary scientific council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745–55.

species, some *Burkholderia* species, *Aspergillus* species or non-tuberculous mycobacteria, is a matter of concern in some patients with CF or other diseases that have a component of bronchiectasis or chronic bronchitis.

WAITING LIST AND ORGAN ALLOCATION

At any given time, a large number of patients are waiting for a lung transplant. Due to the fragility of the lungs in brain-dead patients, only 7 to 22% of multiorgan donors are deemed suitable to become lung donors. Diminishing the donor pool even further, is the wide regional variability in donor organ acceptance rates. Consequently, only 800 to 900 lung transplants are performed yearly in the USA and waiting times for patients listed for a lung transplant continue to increase.[24] Approximately 10% of the patients on the waiting list died before transplantation, but the death rate, while waiting, was much higher for patients with IPF, PPH or CF than for those with COPD or α-1 antitrypsin deficiency emphysema.[3]

Lung allocation was first organized in 1990, under rules designated by the Organ Procurement and Transplantation Network (OPTN), the body which organizes the collection and distribution of solid organ transplants in the United States. The original rules governing lung allotment were simple. Donors were matched to recipients based on 3 criteria: Time spent on the waiting list, ABO blood type, and geographic area.[19] The new lung allocation policy, introduced in May 2005, allocates lungs on the basis of medical urgency and ''net transplant benefit'', defined as the difference between predicted 1-year survival with and without transplantation, so as to minimize the waiting time. Each lung transplant candidate over the age of 12 years would be scored from 0 to 100, with a score of 100 receiving the highest priority. The score was based on wait-list urgency, combined with an estimate of transplant benefit.[25, 26]

Donor Selection

The procurement of acceptable lungs for transplantation is quite difficult. During the first decade after the initial successes of lung transplantation in the early 1980s, the criteria used to select lung donors were quite conservative and stringent.[24] An ideal donor characteristics generally includes, age <55 years, insignificant smoking history, ABO compatibility, acceptable arterial oxygen tension (PaO_2 >300 mm Hg on 100% inspired oxygen with 5 mm Hg of Positive End Expiratory Pressure (PEEP)). There should be a clear chest radiograph and absence of purulent secretions at bronchoscopy. However, while some of these criteria have a sound scientific rationale; the others are controversial, based on small, center-specific reports from the early days of lung transplantation.[24,27] Acceptability criteria for lung donation were recently reviewed in an extensive consensus report from the pulmonary council of the ISHLT. The donor factors that were reviewed from the literature included age, graft ischemic time, blood type ABO compatibility, sex, organ size matching, cause of death, duration of mechanical ventilation, radiographic findings, microbial organisms, arterial blood gases, smoking exposure, and donor diagnoses of malignancy.

Donor Management

Because the process of potential donor identification, brain death certification, family consenting, and organ procurement may take 12 to 24 hours, it is important to focus on maintenance of body temperature via external warming, blood pressure, acid/base status, electrolytes, intravascular volume, and prevention of infection.[28]

Hemodynamic Management

Brainstem death is associated with autonomic crisis, the so called sympathetic storm, whereby a boost of noradrenaline is released in the circulation. This results in acute systemic vasoconstriction, and a rise in systemic vascular resistance that leads to increased pulmonary capillary hydrostatic pressure and deterioration in pulmonary function.[29] The sympathetic discharge is followed by a prolonged period of hypotension leading to a systemic inflammatory syndrome, whereby infiltration of activated neutrophils in the lung contributes to donor lung injury.[30,31] Vasopressors especially low dose vasopressin and iontropes may help stabilize the fluctuations in blood pressure to ensure optimal organ perfusion with the lowest possible myocardial oxygen demand. Patients with pulmonary hypertension undergoing single lung transplantation present particular difficulties, and cardiopulmonary bypass is usually required.[32]

Hormonal Resuscitation

As acute brain death also results in a substantial decrease of several hormones like cortisol, insulin, thyroid and antidiuretic hormone levels, replacement before organ recovery may increase graft viability and early recipient outcome. Administration of high-dose steroids to the donor in the hours after brain death has been advocated, as it is believed to reduce the systemic inflammatory response and thus lung injury.[33]

Postoperative Care

A multidisciplinary team manages the patients in the post-transplant period including, but not limited to, the transplant surgeons, the critical care nursing staff, the transplant coordinators, the transplant pulmonologist, physical and respiratory therapists, nutritionists and infectious disease specialists. Routine early postoperative care includes careful monitoring of vital signs, accurate documentation of intake and output, daily chest-radiographs, and laboratory analysis, including cyclosporine or tacrolimus levels. The serum creatinine must be monitored particularly closely as keeping the patient with relative intravascular volume depletion, together with the use of nephrotoxic immunosuppressive agents, and antibiotics increases the risk for acute kidney injury.[34]

Mechanical Ventilation

A ventilatory strategy with high tidal volumes is potentially harmful and may exacerbate donor lung injury, already triggered by the systemic inflammatory response. The use of low tidal volume ventilation was shown to be beneficial in the ARDS population and is believed to be of help in post-transplant lung due to similar shared pathophysiological mechanisms.[35] Recruitment maneuvers, along with high PEEP are important components of donor ventilatory strategies to prevent atelectasis and achieve adequate oxygenation.[36]

Bronchoscopy

Bronchoscopy should be performed on all potential lung donors to assess for airway damage and visible signs of infection. Examination of the airways is performed in the operating room and again before extubation to evaluate the anastomoses. Regular suctioning of retained secretions through a closed ventilator circuit may be beneficial to improve gas exchange. In patients requiring prolonged mechanical ventilation after transplantation, frequent bronchoscopy may be required to clear secretions, and to obtain microbiologic specimens.[37]

Antimicrobial Therapy

Standard infection prophylaxis are routinely utilized for bacterial, Cytomegalovirus (CMV), *Pneumocystis jirovecii* and *Toxoplasma gondii* infections, and in some centers for fungal infections as well. Patients with cystic fibrosis should undergo periodic preoperative sputum culture analysis for specific antibiotic coverage against *Pseudomonas* species, based on susceptibility data. The incidence of CMV infection after lung transplantation is related to the preoperative CMV status of both the donor (D) and the recipient (R).[38] Transplantation of CMV-seropositive donor lungs transmits a significant viral load to recipients. A discordant CMV status between donor and recipient may result in a higher incidence of acute and chronic rejection, and the mortality rates are even higher compared to patients in whom CMV status is concordant. Therefore, it is recommended to match D and R status.[39] The use of ganciclovir prophylaxis has been shown to eliminate the incidence of primary disease, and to improve the outcome of CMV-disparate lung transplants.[40]

IMMUNOSUPPRESSIVE TREATMENT

The discovery of cyclosporin A (CsA) has been a corner stone for the success of clinical lung transplantation. Lung transplantation performed before the CsA era invariably failed due to inadequate immunosuppression.[41-43] Worldwide, the standard protocol advocates the use of a three-drug regimen for immunosuppression (a calcineurin inhibitor, cell-cycle inhibitor and steroids), with the aim of obtaining additive effects in terms of immune suppression, while limiting drug toxicities. Recently cytolytic therapies such as Campath (anti-CD52), OKT3, daclizumab, basiliximab (anti-CD25) and anti-thymocyte globulin have also been used for this purpose. These therapies are generally initiated within 24 hours of transplantation and are combined with the standard triple-drug regimen. Adverse effects of these immunosuppressive agents include nephrotoxicity, hypertension, hypertrichosis, gastrointestinal disturbances, neurotoxicity, gingival hypertrophy, hyperglycemia and hyperkalemia.[41, 42, 44]

COMPLICATIONS

Lung transplantation has emerged as an effective option in treating a variety of end-stage lung diseases by prolonging life expectancy and by substantially improving quality of life. Unfortunately, the lung transplant recipient is at risk for developing numerous complications that threaten these objectives. Although, early surgical complications and mortality have been minimized due to improvements in lung preservation and surgical techniques, medical complications have become the main rate-limiting factor for long term survival.[45]

Surgical Complications

The airway is the most common location for anastomotic complications after lung transplantation, because of ischemia. Major dehiscence of the bronchial anastomosis was once a major cause of perioperative mortality. Fortunately, refinements in surgical technique, tissue preservation, and immunosuppression have significantly reduced the risk of this life-threatening complication. Focal dehiscence is seen more commonly (in 1 to 6% of cases). Narrowing of the bronchial anastomosis caused by excessive granulation tissue, fibrous stricture or malacia is seen in 5 to 14% of patients.[46] Phrenic nerve injury should be suspected in patients who are difficult to wean from mechanical ventilation, demonstrate paradoxical diaphragmatic movement on examination, and have unexplained persistent atelectasis or an elevated hemidiaphragm on radiographic studies.[47] Pleural complications, especially pneumothorax, air leak and pleural effusion, are common after lung transplantation. Approximately 10% of air leaks are persistent and require prolonged placement of a thoracostomy tube.[48]

Medical Complications

Medical complications of lung transplantation can be categorized into two groups: Pulmonary and non-pulmonary complications (Table 173.2).

TABLE 173.2: Medical complications after lung transplantation

Pulmonary Complications
Complications affecting the allograft(s)
1. Rejection - Acute and chronic
2. Primary graft dysfunction (PGD)
Complications affecting the allograft and native lung
1. Infection
2. Post-transplantation lymphoproliferative disorder (PTLD)
3. Pleural complications
4. Thromboembolic disease
Non pulmonary complications
1. Renal failure
2. Gastrointestinal: Gastroesophageal acid reflux, peptic ulcer disease, ileus, bowel perforation, cholecystitis, appendicitis
3. Endocrine: Diabetes mellitus, hyperlipidemia, obesity, osteoporosis
4. Musculoskeletal: Osteonecrosis, myopathy
5. Neurotoxicity: Tremors, seizures, cerebrovascular accident, blindness, coma
6. Metabolic: Hyperammonemia, electrolyte disturbances
7. Hematologic: Thrombotic microangiopathy, immune hemolysis, cytopenias, hypogammaglobulinemia

Acute Allograft Rejection

Acute lung rejection is defined as perivascular mononuclear cellular infiltrates on histological analysis of lung allograft tissue. The Lung Rejection Study Group (LRSG), under the banner of the ISHLT, has revised a working formulation for grading acute allograft rejection incorporating acute cellular rejection (A-grade), airway inflammation (B-grade), chronic airway rejection, or bronchiolitis obliterans syndrome (BOS C-grade) and chronic vascular rejection (D-grade).[49] Despite the recent development of many new immunosuppressive agents for use in transplantation, acute rejection occurs with much greater frequency in lung allografts when compared to all other solid organ transplants.[50] Why lung allografts are more susceptible to acute rejection is not entirely clear, although it is speculated that lung tissue is more immunogenic. As many as 55% of lung transplant recipients are treated for acute allograft rejection in their first year post transplantation, and only 50% of lung recipients are alive 5 years post transplant.[2] The degree of Human Leukocyte Antigen (HLA) mismatch between donor and recipient, genetic variations in the recipient's innate response, and environmental factors including both the nature and intensity of immunosuppression, as well as local allograft exposures and infections have been identified as risk factors for acute lung rejection.

The precise immune mechanisms and their complex interactions, that ultimately lead to the stimulation of adaptive cellular immunity and lung rejection remain to be fully elucidated. The common pathway of acute cellular rejection involves the recruitment and activation of recipient lymphocytes (predominantly effector T cells) to the lung allograft, which can result in allograft injury and loss of function. In addition, some lung transplant recipients appear to mount a humoral response to the allograft after transplantation.[51,52] Most evidence suggests that this humoral response occurs to donor Major Histocompatibility Complex (MHC) antigens, although other endothelial or epithelial antigens expressed in the lung may become antibody targets as well.

The diagnosis of acute cellular rejection relies on the identification of lymphocytic perivascular or bronchiolar infiltrates in lung tissue. When symptomatic, acute rejection presents with dyspnea, cough or sputum production. However, in view of non-specific clinical symptoms and the poor specificity of non-invasive studies, bronchoscopy with transbronchial biopsies is the most important modality in the diagnosis of acute allograft rejection, and should be considered in any lung transplant recipient with allograft dysfunction. It allows acute rejection to be distinguished from other potential etiologies of allograft dysfunction, such as airway stenosis or infection and routinely includes Bronchoalveolar Lavage (BAL) with cultures and transbronchial biopsies for histopathological analysis. A common schedule consists of bronchoscopy at 1 month, 3 months, 6 months and then annually. The main rationale for surveillance biopsies includes the occurrence of clinically silent acute rejection. Multiple studies demonstrate that acute rejection is associated with the development of chronic airflow obstruction as well as increased risk for BOS.[50]

Treatment of acute lung allograft rejection consists of pulse methylprednisolone intravenously for about three doses followed by an oral prednisone taper. Several studies have found tacrolimus useful for treatment of persistent acute rejection.[53,54] Other rescue therapeutic modalities include pulse treatments with a polyclonal Antithymocyte Globulin (ATG), anti-interleukin-2-receptor antagonists, or muromonab-CD3 (OKT3), and recently alemtuzumab, an anti-CD52 monoclonal antibody. Plasmapheresis is the mainstay for antibody removal from the circulation with humoral rejection in lung transplant recipients and in patients with pulmonary capillaritis unresponsive to steroids.[55]

Chronic Allograft Rejection: Bronchiolitis Obliterans Syndrome (BOS)

Bronchiolitis obliterans syndrome remains the major limiting factor to long-term survival after lung transplantation, and is the leading cause of death after the first year. Approximately 30% and 75% of patients develop BOS by 2.5 and 10 years after transplantation, respectively.[18] The histological pathognomonic lesion of chronic rejection is, Obliterative Bronchiolitis (OB) characterized by an inflammatory/fibrotic process affecting the small non-cartilagenous airways (membranous and respiratory bronchioles) causing partial or complete luminal occlusion. Bronchilolitis obliterans syndrome affects all lung transplant recipients irrespective of donor and recipient's characteristics. The time between transplantation and BOS onset, ranges from a few months to several years. The presentation may be acute and imitate a respiratory infection. In most patients, however, BOS is an asymptomatic process that produces an insidious decline in lung function. As the disease progresses, permanent airway colonization with pathogens such as *Pseudomonas aeruginosa* and *Aspergillus fumigatus* frequently develops.[51]

Classically, BOS is considered to be the end-stage consequence of repeated alloimmune-dependent and -independent mechanisms acting alone, or in combination to the lung allograft.[56] There are a number of factors that are strongly correlated with the development of OB. These include the frequency of acute rejection, particularly in the first three months after transplant. Also, the finding on transbronchial biopsy of a lymphocytic bronchitis or bronchiolitis is strongly associated with the subsequent development of OB. The occurrence of CMV infection or other significant pneumonias does not seem so clearly associated with the development of OB.[57]

The diagnosis of BOS is defined by a sustained (≥ 3 weeks) decline in the FEV_1 provided alternative causes of pulmonary dysfunction (e.g. anastomotic stricture/complications, infection, acute rejection and recurrent or progressive native disease) have been excluded.[58] The syndrome was classified according to the degree of FEV_1 reduction.[58]

Treatment options for BOS generally remain disappointing. Augmentation of immunosuppression or changing immunosuppressive medications within therapeutic classes has been a mainstay of therapy. In light of limited availability of donor lungs, the role of re-transplantation remains controversial.

Primary Graft Dysfunction (PGD)

Primary Graft Dysfunction (also known as primary graft failure, severe ischemia-reperfusion injury or re-implantation response) is a severe, acute lung injury syndrome after lung transplantation, that is characterized by diffuse radiographic infiltrates in the allograft and increased alveolar–arterial oxygen gradient.[59,60] Primary graft dysfunction affects 10 to 25% of all lung transplants and is a leading cause of early morbidity and mortality.[18,61,62] Primary graft dysfunction likely represents a form of ischemia-reperfusion lung injury occurring within the first three days of lung transplantation in a variety of clinical presentations. In 2004, the International Society for Heart and Lung Transplantation (ISHLT) working group on PGD after lung transplantation developed a classification system upon which to grade the severity of allograft dysfunction based on the degree of hypoxemia ($PaO_2:FiO_2$ ratio) and chest radiograph appearance.[62]

On lung biopsy, the histological pattern is one of acute lung injury with reactive type II pneumocytes.[63] Additional histological findings in severe cases can include hyaline membranes along the alveolar ducts, neutrophil infiltration and detachment of endothelial cells from the basement membrane. Many steps involved in the lung transplant procedure contribute to the development of PGD, including changes in donor homeostasis related to brain death prior to harvesting, aerobic hypothermic preservation during organ transit and intraoperative organ reperfusion. Central to this process is ischemia-reperfusion injury with the generation of harmful and damaging Reactive Oxygen Species (ROS). Donor acquired risk factors, that potentially contribute to the development of PGD include prolonged mechanical ventilation, aspiration pneumonitis/pneumonia or ventilator-associated pneumonia, trauma, and hemodynamic instability, and the systemic inflammatory response following brain death. Elevated recipient pulmonary artery pressures are also associated with increased risk of PGD.[64] Studies on the impact of prolonged graft ischemic times have yielded conflicting results.[65]

There is no specific treatment for PGD that has proven efficacious. Several principles underlying the supportive care of patients who have acute respiratory distress syndrome may be helpful. However conventional mechanical ventilation using low tidal-volume strategies to reduce the risk of ventilator-induced lung injury is recommended. Although, inhaled nitric oxide or prostacyclin may improve oxygenation transiently, studies have not shown clinically significant benefits.[66] PGD is a major cause of perioperative death, with studies reporting mortality rates over 60%. These patients require prolonged duration of mechanical ventilation and extended hospital stay. In addition, patients who have PGD, who recover from respiratory failure and survive beyond the first transplant year continue to be at higher risk for death and on average have poorer functional outcomes, than patients who do not have PGD.[67,68]

Malignancy

The incidence of malignancy is higher in patients who have undergone lung transplant than in those who have undergone other solid-organ transplants.[69] The prevalence of malignancy in patients who have undergone lung transplant is reported to be 3.7% in 1-year survivors and 25% in 10-year survivors. Beyond the first year, malignancy accounts for 9.3% of deaths.[45] Post-Transplantation Lymphoproliferative Disorder (PTLD) being the most common cancer in the first 2 years after transplantation and skin cancers the most common malignant after the second year.[69,70] PTLD comprises a spectrum of disorders that arise in post-transplant patients that are due to abnormal lymphoid proliferation.[71] The reported incidence of PTLD ranges from 2 to 8%.[72] The pathogenesis of PTLD is related to reactivation of the Epstein-Barr Virus (EBV) and usually involves B cells (76 to 95%).[73] Clinically, early cases of PTLD generally present with constitutional symptoms, infectious mononucleosis, like illness and thoracic manifestations, which may include pulmonary nodule(s) or infiltrate(s) usually located in the allograft, and at times mediastinal lymphadenopathy.[74,75] Immunotherapy with rituximab has been used with success for PTLD in solid-organ transplants and in lung transplants.[76,77]

Bronchogenic Carcinoma

Lung transplant recipients are at risk for bronchogenic carcinoma due to several factors, including older age, prior smoking exposure, underlying chronic obstructive or fibrotic pulmonary disease, and the effects of immunosuppressive regimen.[78-80] Bronchogenic carcinoma diagnosed after lung transplantation has a very aggressive course with a poor prognosis. The incidence of bronchogenic carcinoma after lung transplantation ranges between 2 and 4% in recipients with COPD and IPF.[78, 80]

Thromboembolic Disease

Venous thromboembolism disease, which includes deep venous thrombosis and pulmonary embolism, has an increased incidence in lung transplant recipients, with a reported incidence of 8.6 to 29%.[81-84] The etiology for the increased incidence of thromboembolism in patients who have undergone lung transplant is unclear but risk factors may be advanced age, diabetes, concomitant pneumonia, greater immobility, and a higher incidence of indwelling catheter placement.[85, 86] Treatment consists of standard heparin followed by warfarin for long-term anticoagulation.

Infectious Complications

Infectious complications following lung transplantation are associated with significant morbidity and mortality.[87] The pulmonary allograft is the most common infection site.[88] Distinctive infectious complications such as *Mycobacteria*, *Stenotrophomonas*, *Burkholderia*, and *Pseudomonas* have unique clinical features that impact the post-transplant survival and medical management of these complex patients.[89] The highest risk of pneumonia is during the first month after lung transplantation and this risk reduces after 6 months and of those in which an etiology was found (67%), *Pseudomonas* is the most common (25%) isolated organism.[89,90] The incidence of *P. aeruginosa* in the post-transplant lungs is significantly higher in patients who underwent transplant for CF compared with other indications (60.3% vs 38.2%).[91] Colonization with pan-resistant bacteria was associated with a slightly decreased survival following lung transplantation. Later in the time course, after lung transplantation, the frequency of *P. aeruginosa* colonization in airways increases and can be associated with chronic graft rejection, the BOS.

Burkholderia cepacia complex may cause multi- or pan-resistant invasive infections in patients with CF, and is associated with a pre-transplant mortality of up to 50%. However, the virulence factors of *B. cepacia* complex are still poorly understood and differ between the strains of each genomovar. Whether colonization with *B. cepacia* is an absolute contraindication to transplant remains controversial.[92] Infection with *M. tuberculosis* may occur due to reactivation, occult disease in the remaining native lung after single lung transplantation, transmission by transplantation or nosocomial infection.[89,93] Infections with non-tuberculous mycobacteria are infrequent.[94]

Cytomegalovirus is one of the most important pathogens after lung transplantation. Transplantation of CMV-seropositive donor lungs transmits a significant viral load to recipients.[95] Recipients with evidence of previous/latent CMV infection (seropositive recipients) are at risk, while seronegative recipients transplanted with a seropositive pulmonary graft (D+R-) are at highest risk of developing CMV infection and disease after lung transplantation (primary infection).[96] The incidence is reported to range from 30 to 86%, with an associated mortality range of 2 to 12%.[38,95,97,98] With prophylactic treatment, the presentation of CMV infection occurs later after transplantation. Without prophylaxis, the symptoms of CMV reactivation occur typically between the first and fourth month after transplantation. Newer quantitative molecular techniques for detection of CMV antigens allows for early and more sensitive detection of active viral replication, and may correlate with CMV disease, which is defined as symptomatic end-organ involvement attributable to active infection. Quantitative PCR, hybrid capture assays and the semi-quantitative pp65-antigenemia assay, have shown to be effective in diagnosis of CMV infection, however quantitative methods are most predictive of disease severity.[99] The most serious manifestation of CMV disease is CMV pneumonitis, a relatively common manifestation of either primary or reactivation of chronic pulmonary viral infection in immunocompromised hosts. Commonly used protocols vary from 90 days of prophylaxis with IV ganciclovir in high-risk recipients only (D+R-), to indefinite prophylaxis with CMV immunoglobulin, followed by daily oral valaciclovir in all transplant recipients.[100,101] Beside direct effects of CMV disease leading to organ damage, CMV provokes additional alteration of the immune system, referred to as indirect effects of CMV infection such as acute and chronic rejection.[96] The Gamma herpes viridae including HHV 8 and EBV, are oncogenic viruses. HHV 8 causes Kaposi sarcoma. EBV is strongly associated with PTLD.[77]

Fungal infections occur in 15 to 35% recipients after lung transplantation. *Aspergillus* species, together with *Candida*, are responsible for early fungal colonization of the airways.[102] The mortality rate of fungal infections can be over 80%.[103] The diagnosis of invasive aspergillosis is difficult. The airways of up to 55% of lung transplant recipients can be colonized with *Aspergillus* species. Nodular opacities and areas of consolidation observed on computer tomogram that may indicate invasive pulmonary *Aspergillus* infections may also represent other diagnoses.[102,104] Other emerging rapid laboratory methods are diagnostic tests for 1/3-beta-D-Glucan. Invasive infections with *Candida* species include candidemia, mediastinitis and necrotic infections of the anastomosis.[105,106] Zygomycosis as an invasive fungal infection with saprophytic fungi, including *Rhizopus*, *Rhizomucor*, *Mucor* and *Absidia* are also seen infrequently. The overall mortality is approximately 50%.[96]

Renal Failure

Renal dysfunction is one of the most common long-term complications of lung transplant, occurring in 25.5% of cases at 1 year after transplant and 37.8 at 5 years after transplant.[2] The most common cause of renal failure is due to calcineurin inhibitor nephrotoxicity. Other factors are hypertension, hyperlipidemia, and diabetes. Additional insults to the kidney at the time of transplant due to hypotension, hypoperfusion and aortic cross-clamp, and aggressive diuresis contribute to the assault.[107-109] Management of kidney disease include lowering the levels of calcineurin inhibitor if the lower levels of immunosuppression can be tolerated. Associated comorbidities such as hypertension, diabetes and hyperlipidemia should be aggressively treated. The progression of chronic renal failure ultimately leads to renal replacement therapy in the form of dialysis or renal transplantation.[73]

Diabetes Mellitus

The development of diabetes is a relatively common in patients who have undergone lung transplant, with incidence of 33.5% at 5 years after transplant.[2] Risk factors leading to the development of diabetes are due to glucocorticoid use and calcineurin inhibitor use, with tacrolimus having a much greater likelihood than cyclosporine of inducing diabetes.[110] Other risk factors include older age of recipients, obesity, and frequent acute rejection requiring high dose steroids. Guidelines for treatment of diabetes for solid organ transplants recommend intervention, when patients have fasting glucose levels greater than 126 mg/dl and hemoglobin A1C levels greater than 6.5%.[111]

Cardiovascular Complications

Cardiovascular cause of death accounts for less than 5.3% of deaths in patients who survive longer than 1 year.[2] Hypertension, hyperlipidemia, diabetes and renal disease contribute to the heightened risk. Use of statin may lower the risks associated with these cardiovascular comorbidities in addition to lowering the risk of rejection and BOS.[73]

Osteoporosis

Osteoporotic bone loss appears to be accelerated in the first 3 to 6 months after transplant for all solid-organ transplants, as measured by decreases in BMD scores.[112-114] Within the first year of lung transplant, the post-lung transplant fracture rate ranges from 6 to 18% and a loss in BMD of 4 to 12% is reported.[115] Estrogen and hormone replacement therapy, in combination with calcium and vitamin D supplementation and bisphosphonates, have been shown to prevent decreases in BMD.[73]

Neurologic Complications

The majority of complications were due to calcineurin inhibitor toxicity or infections.[73] Manifestations of calcineurin inhibitor toxicity include confusion, tremor, paresthesias of hand and feet seizure, blindness and encephalopathy.

OUTCOMES

Lung transplants are expensive procedures and are associated with a continued cost of care that involves not only the immunosuppressive treatments but also the monitoring of lung function and diagnostic procedures. With careful candidate selection using current criteria, overall results of LT have improved over the decades. The current 1-, 5- and 10-year unadjusted survival outcomes are 79%, 52% and 29%, respectively.[18] Another observation that possibly impacts on survival is the type of transplant performed. In the recent analysis of data from the ISHLT registry, there appears to be a small survival advantage for patients who have received DLT compared with SLT procedures.[18] Despite improvement in the peri-operative survival, over the long-term the slope of the survival curve continues to show the same slow attrition rate reflecting the problem of chronic rejection, for which there remains no effective therapy.

Pulmonary Function and Gas Exchange

When performed in patients with obstructive or restrictive lung disease, both single-lung and bilateral transplantation dramatically improve lung function. The peak effect of transplantation on lung function is typically achieved within three to six months. Exercise capacity improves sufficiently to allow the majority of transplant recipients to resume an active and unencumbered lifestyle.

Quality of Life

Despite the availability of highly reproducible tools to assess the quality of life, information on the effect of lung transplantation on this outcome measure is limited.[116] Important improvements in QOL are reported after lung transplantation. Recent studies show that heart and lung transplant patients benefit from the transplant procedure with respect to HRQOL improvements for at least 5 years post-transplant; however, their trajectories during this time interval differ.[117] Lung transplant recipients generally were satisfied with their decision to have undergone transplantation.[118]

THE FUTURE OF LUNG TRANSPLANTATION

Lung transplantation has reached its current clinical plateau largely through refinements in the selection of patients, operative techniques and postoperative care. Two major hurdles must be overcome to increase the applicability of lung transplantation and improve long-term results: The supply of donor organs must be increased to meet the demand and chronic rejection must be more effectively prevented. There are a number of emerging therapies like stem cell therapy and xenotransplantation that may offer alternatives to human organ transplantation. However, as of now, the supporting data is too meagre to recommend them as a standard of care rather than experimental therapy.

LUNG TRANSPLANTATION IN INDIA

The burden of chronic respiratory diseases in India is on the rise, accounting for nearly 1 in 10 deaths. Improved access to healthcare and better imaging modalities have led to an increase in the diagnosis of advanced chronic lung diseases like IPF and pulmonary artery hypertension in India. For these end-stage lung diseases, lung transplantation is an effective and established treatment option in the developed world. However, this expensive form of treatment coupled with lack of infrastructure and the expertise involved, makes lung transplantation programmes in India currently out of reach of most of the population. The first heart-lung transplant in India was performed on May 3, 1999 and subsequently, two more patients have undergone this procedure. The initial experience is encouraging and heralds a new era of thoracic organ transplantation in India.[119]

SUMMARY

Lung transplantation has emerged as a viable therapeutic option in treating a variety of end-stage lung diseases by prolonging life expectancy and by substantially improving quality of life. Since the advent of the first lung transplant there has been substantial progress made in surgical techniques, lung preservation, immunosuppression and management of infections thereby improving the short-term mortality. However, there are numerous problems and complications that limit the long-term success of this vital treatment modality. Chronic allograft rejection in the form of BOS continues to be the common cause of morbidity and mortality and, threatens to shorten the long term survival of the lung transplant recipients. There is still a scope of much research in transplantation immunobiology so as to cross this hurdle before lung transplantation fulfils its potential as an effective and definitive treatment option for patients with advanced lung disease.

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